



## Original Research Article

## Carotid plaque morphology-An indicator for brain infarcts

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## ABSTRACT

**Background:** Cerebrovascular adverse events are one of the most common causes for morbidity and mortality worldwide. Thromboembolism being the culprit behind a significant number of such events. An attempt has been made to ascertain the association of carotid plaque morphology in the occurrence of ischemic stroke. Heterogeneous plaques (Type 2 & 3) were mostly observed to be ipsilateral to the side of brain infarct, as compared to the contralateral side. Detection of heterogeneous plaques and plaque ulceration in patients may indicate future development of stroke.

**Materials and Methods:** This study included 75 consecutive patients having anterior circulation infarct in MRI of the brain and atherosclerotic changes in extra cranial carotid system on Carotid Duplex scan. Plaque morphology ipsilateral to the brain infarct was compared to that on the contralateral side.

**Result:** Significantly higher number of heterogeneous plaques (Type 2 & 3) were present ipsilateral to the side of brain infarct, as compared to the contralateral side (p-value 0.004). Plaque ulceration was also observed to be present more frequently on the side of infarct (22.6% on the ipsilateral side and 5.4% on the contralateral side). Moreover, Diabetes mellitus and dyslipidemia were the most prevalent risk factors (78.2% and 65.2%, respectively) in patients with these types of plaques.

**Conclusion:** Detection of heterogeneous plaques and plaque ulceration in patients may indicate future development of stroke, necessitating prompt and appropriate management protocols. Periodic screening of such patients with Carotid Duplex Ultrasonography is expected to be very helpful.

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## 1. Introduction

Stroke is defined as a sudden onset of focal neurologic deficit due to vascular cause.<sup>1</sup> It is one of the leading causes of mortality in India and accounting for about 11.8% of total deaths worldwide.<sup>2,3</sup> An Indian study observed that almost 70% of stroke related death was from the primary stroke and about 19.27% from a recurrent event. This indicates that secondary preventive measures are more in effect than primary prevention in our country.<sup>4</sup>

Data shows that about 68-80% strokes are of ischemic etiology among which almost 41% are of large vessel pathologies.<sup>5</sup> Carotid artery atherosclerotic plaque with luminal stenosis constitute a little more than one-fourth of these large vessel diseases.<sup>6,7</sup> Atherosclerotic changes of the extra-cranial carotid arteries usually involve the internal carotid artery within 2cm from the common carotid bifurcation. This site can be easily evaluated by ultrasound.<sup>8</sup>

There is a significant recurrence rate of ischemic stroke. If the aetiology of the primary stroke can be determined followed by appropriate interventions, occurrences of secondary stroke can be reduced to a considerable extent.<sup>8,9</sup> Moreover, such interventions might even have a role in

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preventing primary ischemic stroke attacks in high risk individuals.<sup>10–12</sup>

Selection of different management protocols are largely determined by the amount of carotid stenosis that is present. The plaque morphology has not been considered as a primary determining factor for carotid interventions in any of the large scale clinical trials till date.<sup>8–12</sup>

The combined use of gray scale imaging, colour flow Doppler and Doppler spectral analysis, is highly accurate for detecting plaque morphology.<sup>6</sup> Moreover, ultrasound of carotid artery can predict haemorrhage within plaque which is an independent risk factor for stroke.<sup>13,14</sup>

This study determines the association of ischemic brain stroke with carotid plaque morphology using Doppler ultrasonography.

## 2. Materials and Methods

A single center cross-sectional observational study was done in a tertiary care hospital in Odisha state of India. Seventy five consecutive patients from the medical and neurological wards presenting within two weeks of symptom onset having anterior circulation infarct in MRI brain and atherosclerotic changes in extra cranial carotid system were included in the study. The duration of study was for 2 years from September 2018 to August 2020. GE Signa HDxt 1.5T MRI (GE Healthcare<sup>®</sup>) MRI with head coil, was used for performing MRI brain. Carotid artery evaluation was done with GE Voluson S6 Ultrasound machine, using high frequency linear array transducer (4–12 MHz). Patients with posterior circulation stroke or other organic brain disease were excluded.

Informed written consent was taken. Risk factors related to atherosclerotic pathology as well as brain stroke like hypertension, Diabetes mellitus, dyslipidemia and prolonged history of smoking were noted. Smoking history was considered positive if the patient smoked more than 10 cigarettes per day for last 5 years or more. The cumulative amount of smoking would have varied largely according to the age of the participant, if Brinkman Index was calculated. Hence, it was not considered in this study. MRI brain protocol included T1, T2, T2 FLAIR, DWI, ADC and SWAN sequences.

Participants were positioned supine with their head tilted at about 45 degrees opposite to the side being examined, during carotid sonographic examination. Care was taken to keep the neck of the patient relaxed as a contracted sternocleidomastoid muscle would result in poor sonographic penetration and difficulty in placement of probe. Different transducer positions were used (transverse, antero-lateral, postero-lateral and far postero-lateral) for adequate visualisation.

Transverse & longitudinal scans of the Common Carotid Artery (CCA), the carotid artery bifurcation, the Internal Carotid Artery (ICA) & External Carotid Artery (ECA)

were done using B-Mode and colour Doppler ultrasound mode. Entire course of the extra-cranial carotid arterial system caudally from the supraclavicular notch, cephalad up to the angle of mandible was scanned.

Plaque morphology was noted and classified as follows (Figure 1):<sup>15</sup>

1. Type 1 – Anechoic plaque
2. Type 2 – Predominantly hypoechoic heterogeneous plaque
3. Type 3 – Predominantly hyperechoic heterogeneous plaque
4. Type 4 – Homogenous plaque
5. Type 5 – Calcified plaque

Plaque ulceration was defined as a focal breach in the luminal surface of the plaque with anechoic area extending from the vascular lumen into the body of the plaque.<sup>6</sup>

Prior to the characterisation of the plaque, gain adjustment was done in a manner so that the flowing blood in the lumen appears completely black (anechoic) and the tunica media adventitia interface appears bright white (echogenic).

All parameters were documented in the common patient proforma. After completion of data collection, correlation of carotid artery ultrasound findings was done with those of MRI brain.

All the data were tabulated, compared and analyzed using software STATA version 15.1, Statacorp, Texas, USA. Fischer exact test was applied for Non-numerical data analysis and association. A p-value < 0.05 was taken as statistically significant considering 95% confidence interval.

## 3. Results

### 3.1. Demography

In the present study 79% of patients were male and 21% female. Maximum number of cases (29% of the total) belongs to the age group 61–70 years followed by the age group 71–80 years (23% of total) and followed by 51–60 years (21%). Bulk of cases (73%) comes in the age bracket of 51–80 years. All female patients in our study population is above the age of 50 years (Figure 2). The age groups of 51 to 60 and 71 to 80 years each represent 37.5% of the females in the present study.

### 3.2. Risk factors

Hypertension and Diabetes mellitus were both equally prevalent (47%) in our study population of ischemic brain stroke patients (Figure 3). However, in patients with predominantly hypoechoic and heterogeneous carotid plaques, Diabetes mellitus was the most prevalent risk factor being present in 78.2% of those patients (Figure 4). It was followed by dyslipidemia which affected 65.2% of this

group of patients. Hypertension ranked third among this group (60.8%) followed by smoking habit (56.5%).

### 3.3. Carotid duplex analysis

Total number of plaques found in our study was 129 (Table 1). Bilateral carotid arterial involvement was seen in 32(43%) patients of ischemic stroke. In terms of vessels involved, out of total 150 vessels examined, 107 were found to be harbouring atherosclerotic plaques. The most common plaque morphology found in our study was Type 3(50%), followed by Type 2(35%), Type 4(9.3%), Type 5(5.4%) and Type 1(0.78%).

### 3.4. Association between plaque morphology and occurrence of ischemic brain stroke

The present study found that heterogeneous plaques (Type 2 & 3) are more prevalent on the side of brain ischemic stroke compared to the opposite side (Table 1, Figure 5) and a statistically significant correlation existed in this regard (p-value 0.004). Around 23% of ipsilateral plaques showed plaque ulceration whereas, about 5.4% showed similar finding in the plaques of contralateral arteries (Table 2).

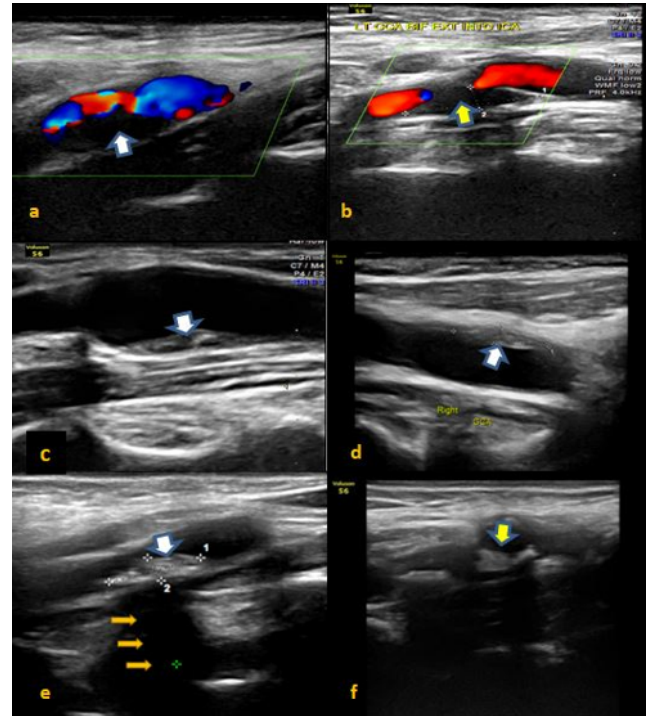
## 4. Discussion

The present study was done on 75 patients, referred for MRI brain, with provisional diagnosis of stroke. Only those patients were considered for the study whose initial MRI confirmed the diagnosis of acute or sub-acute ischemic stroke in the anterior cerebral circulation. They were then evaluated for carotid artery disease with Color Duplex Ultrasonography.

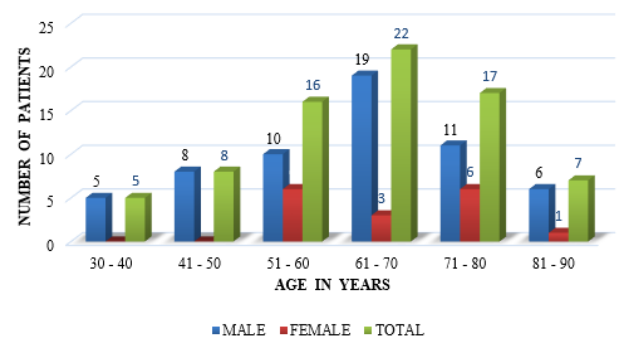
Study conducted by Fernandes et al on ischemic stroke patients showed 72% male and 28% female with highest number of patients within the age group of 60 to 69 years.<sup>16</sup> In the present study 79% of patients were male and 21% female. Almost 29% of the total study group were in the age group 61-70 years, which is the highest.

### 4.1. Risk factors

Hypertension, dyslipidemia and smoking are responsible for arterial wall remodeling, endothelial dysfunction and producing a state of increased oxidative stress by increased production of Reactive Oxygen Species (ROS) all of which promote atherosclerosis.<sup>17</sup> Hyperglycemia leads to the glycation of serum proteins (like haemoglobin) and ultimately forms Advanced Glycation End-Products (AGEs). These products act as catalysts in the atherosclerotic cascade thereby accelerating the process.<sup>17</sup> In the present study, hypertension and diabetes were the most prevalent risk factors among ischemic stroke patients being present in 62.7% of the study population. It was closely followed by dyslipidemia (57.3%) which



**Fig. 1:** Different types of plaques and plaque ulceration found in the study, **a.** Longitudinal Colour Doppler image shows a Type 1 plaque in the left CCA bifurcation (white arrow). **b.** Longitudinal Colour Doppler image showing a Type 2 plaque extending from left CCA bifurcation to left ICA (yellow arrow). **c.** Longitudinal Gray scale image shows Type 3 plaque in distal CCA (white arrow). **d.** Longitudinal Gray scale image shows Type 4 plaque in CCA (white arrow). **e.** Longitudinal Gray scale image shows Type 5 (calcified) plaque in CCA casting posterior acoustic shadow (orange arrows). **f.** Longitudinal Colour Doppler image shows an ulcerated plaque in CCA (yellow arrow)



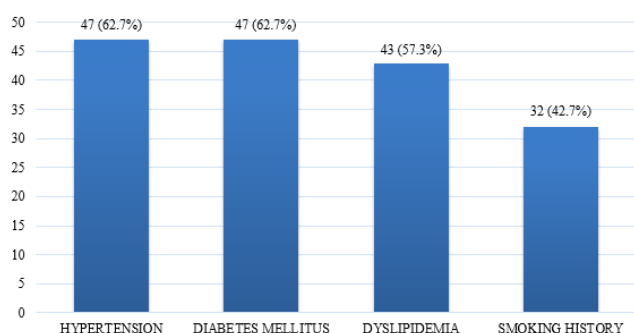
**Fig. 2:** Age and gender distribution of study population (N = 75)

**Table 1:** Carotid plaques according to their occurrence in ipsilateral or contralateral to the side of infarct

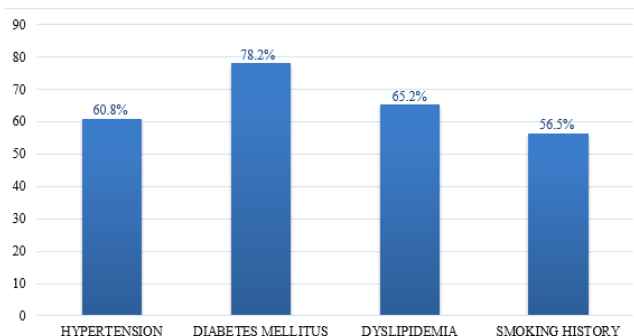
| Type of Plaque | Ipsilateral To Brain Infarct | Contralateral To Brain Infarct | Total |
|----------------|------------------------------|--------------------------------|-------|
| Type 1         | 1 (100%)                     | 0 (0)                          | 1     |
| Type 2         | 40 (87%)                     | 6 (13%)                        | 46    |
| Type 3         | 44 (68%)                     | 20 (32%)                       | 64    |
| Type 4         | 5 (42%)                      | 7 (58%)                        | 12    |
| Type 5         | 3 (43%)                      | 4 (57%)                        | 7     |
| Total          | 93                           | 37                             | 129   |

**Table 2:** Intra-plaque haemorrhage according to their occurrence in ipsilateral or contralateral to the side of infarct

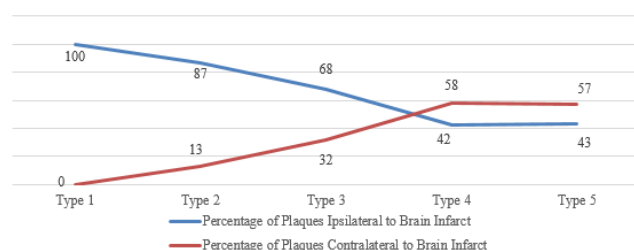
| Plaque Ulceration | Ipsilateral To Brain Infarct | Contralateral To Brain Infarct |
|-------------------|------------------------------|--------------------------------|
| Number            | 21                           | 2                              |
| Percentage        | 22.6                         | 5.4                            |



**Fig. 3:** Association of risk factors in ischemic stroke patients



**Fig. 4:** Risk factors in patients with predominantly hypoechoic and heterogeneous carotid plaques



**Fig. 5:** Types of Carotid plaques as found in ipsilateral and contralateral sides of brain infarct

in turn was followed by history of smoking (42.7%). Multiple previous studies have also observed hypertension and Diabetes as predominant risk factors for ischemic stroke.<sup>16,18–20</sup>

However, the present study revealed that the association of diabetes mellitus (78%) is higher than that of hypertension (60.8%), in patients having predominantly hypoechoic and heterogeneous carotid plaques. Dyslipidemia (65%) is the second most prevalent risk factor in this group. Lipid rich cores within the plaque are represented by the hypo and anechoic areas in sonographic examination. Different studies have shown the association between diabetes and dyslipidemia with lipid rich cores within atherosclerotic plaques. Yahagi K et al found in their study that coronary atherosclerotic plaques with larger lipid rich areas was more commonly associated with diabetic patients than non-diabetic controls.<sup>21</sup> Wasserman BA et al observed that hypercholesterolemia was associated with plaques having lipid rich cores.<sup>22</sup>

**4.2. Duplex evaluation of carotid artery**

Total number of plaques found in our study was 129. Around 43% of patients showed bilateral carotid arterial plaques. A study conducted by Fernandes M et al also showed 46% of ischemic stroke patients as having bilateral carotid involvement.<sup>16</sup>

Most common type of plaque found in this study is Type 3 (~50%) which is predominantly hyperechoic (Table 1) whereas, echogenic plaques were the commonest variety in previous study.<sup>18</sup> In our study it was difficult to analyse the exact nature of calcium laden plaques which remained hidden to some extent, under the posterior acoustic shadow from the calcifications.

Out of total 129 plaques, 70 were found on the right and 59 on the left side. Plaque was seen only in CCA bifurcation in 66 carotid arterial systems and another 22 arteries showed plaques both in CCA bifurcation and proximal part of extra-cranial ICA. Hence, total number of plaques present at CCA in our study population is 88 (68.2%), making it the

commonest affected site. Available literature and previous studies of corroborate with this finding.<sup>6,18,19</sup> Rest of the 41(32%) plaques were found in the proximal ICA.

In general, it was seen that Type 2 and Type 3 (heterogeneous) plaques were more prevalent ipsilateral to the side of infarct (Table 1, Figure 5) which was statistically significant (p-value 0.004). Close to 90% of Type 2 and about 70% of Type 3 plaques were found on the side of infarct. Type 4 and Type 5 plaques did not show any definitive prevalence pattern on ipsilateral or contralateral side in relation to infarct. Percentage of plaques showing evidence of plaque ulceration was found to be much higher on the side of brain infarct (~23%) as compared to that on the opposite side (Table 2). Multiple previously conducted similar studies also had similar observations.<sup>13,15,23–25</sup>

## 5. Conclusion

In conclusion, carotid plaque morphology is an important determinant for the occurrence of ischemic brain stroke.

Type 3 was the most common plaque morphology encountered overall. However, more number of Type 2 and 3 plaques as well as plaque ulceration were seen ipsilateral to the side of brain infarct as compared to those in the contralateral carotid arteries.

Hence, Carotid Sonography is a useful screening modality which can be used in evaluating atherosclerotic disease of the extra-cranial part of carotid arteries, especially in diabetic and dyslipidemic patients, who are at higher risk of developing ischemic stroke in the future. Early identification of high risk plaque characteristics in such individuals may pave the way for appropriate management for the prevention of future ischemic cerebrovascular events.

## 6. Limitations and Future Directions

We had several limitations in this study. The population size was relatively small. Moreover, in patients having high carotid artery bifurcation, the proximal part of ICA was difficult to evaluate by Doppler ultrasound study. Some of the plaques found in the current study were heavily calcified. It was difficult to search for hypoechoic areas in those plaques. Hence, the exact nature of these plaques remained hidden to some extent under the posterior acoustic shadow from the calcification.

## 7. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

## 8. Source of Funding

None.

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