Original Article

Association of Carotid Plaque Echogenicity with Recurrence of Ischemic Stroke

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Abstract

Background: Atherosclerosis is related to various cardiovascular and cerebrovascular events like cerebral infarction. Recurrence of ischemic stroke is specifically related to atherosclerotic load as determined by the presence of carotid atheromatous plaques and its echogenicity. **Aim:** This study was to evaluate the association of recurrence of stroke with echogenic characteristics of carotid plaque in ischemic stroke patients. **Materials and Methods:** Carotid sonography using high-resolution 7.5 MHz along with gray-scale technique was done in each ischemic stroke patient to find the occurrence of plaque and its echogenicity according to Mannheim Carotid Intima-Media Thickness Consensus (2004-2006). Followup of patient done to know the recurrence of stroke during 6-month duration and its association with plaque echogenicity. **Results:** A significant association found between the presence of plaque and known cerebrovascular risk factors. Also significant association found between recurrence of stroke and echolucent character of carotid plaque in bivariate analysis ($P = 0.0028$). **Conclusions:** Recurrence of stroke is related to advanced stage of atherosclerosis that is specified by carotid plaque and its characteristics. It will help us to identify groups of patients at different risk for stroke and planning better strategies to prevent such events.

Keywords: Carotid ultrsonography, Cerebrovascular diseases, Echogenic plaque, Ischemic stroke

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Introduction

A stroke, or cerebrovascular accident, is defined by the abrupt onset of a neurological deficit that is attributable to a focal vascular cause. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurological symptoms manifest within seconds because neurons lack glycogen; hence, energy failure is rapid. If the cessation of blood flow lasts for more than a few minutes, infarction or death of brain tissue results, leading to prolongation of neurological symptoms causing stroke if symptoms persist even after 24 h.[1]

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TOAST classification that was based on clinical symptoms as well as results of further investigations; classified stroke due to (1) thrombosis or embolism due to atherosclerosis of a large artery, (2) embolism of cardiac origin, (3) occlusion of a small blood vessel, (4) other determined cause, and (5) undetermined cause (two possible causes, no cause identified, or incomplete investigation).[2,3]

Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries.[4] The early lesions of atherosclerosis consist of subendothelial cholesterol-engorged macrophages called foam cells. More advanced lesions are characterized by the accumulation of lipid-rich necrotic debris and smooth muscle cells. Fibrous lesions typically have a fibrous cap consisting of smooth muscle cells and extracellular matrix that surrounds and encloses the lipid-rich necrotic core. As the plaque progresses, it may exhibit calcifications, ulcerations at the luminal surface and hemorrhaging that is presumed to result from small vessels growing into the lesion from the media of the blood vessel wall.[5-7] Hyperlipidemic obese

patients are particularly at risk of deposition of fats in arteries and other tissues.[8,9]

Although carotid ultrasound imaging was used primarily to detect and characterize focal lesions of carotid artery, it may also have an important role in evaluating diffuse changes that involve the arterial wall. This is based on reports from the late 1980s that indicate diffuse thickening of the intima and medial layers of the aorta and carotid arteries are associated with atherosclerosis.[10,11] In this study, we utilized its role for determination of atherosclerotic burden.

The main mechanism of stroke related to pathology of the carotid artery is thought to be embolism from a fissured or ruptured plaque. Recent pathological studies of postmortem and arterectomy specimens have shown that plaque vulnerability is related to the size of the atheromatous core, the thickness of the fibrous cap, and inflammation within the cap. Unstable plaques usually have a thin fibrous cap with a necrotic core situated near the surface. The position of the core and the local thinning of the cap may therefore predispose to rupture, which then exposes the thrombogenic atheroma to circulating blood, thus initiating thrombus formation possibly leading to thromboembolism and subsequent ischemic stroke.[5]

Recurrent stroke is frequent and responsible for major stroke morbidity and mortality. The immediate period after a stroke carries the greatest risk for early recurrence; rates range from 3% to 10% during the first 30 days as suggested by different studies.[12] Thirty-day recurrence risks varied by infarct subtypes; the greatest rates were found in patients with atherosclerotic infarction and the lowest rates in patients with lacunar infarction. The immediate period after an ischemic stroke carries the greatest risk of death, with fatality rates ranging from 8% to 20% in the first 30 days.[12]

The pathophysiologic mechanism of the relationship between plaque echolucency and increased recurrence risk of ischemic stroke is not completely understood. El-Barghouty *et al*.[13] found that the content of soft tissue (i.e., lipid and hemorrhage) was associated with plaque echolucency. Conversely, a highly fibrous tissue content was associated with echo-rich plaques, and this has been confirmed by few studies.[14,15] Plaques rich in lipids or with a necrotic core are thought to be most prone to rupturing and causing clinical events.[16,17] This fact seems to be a potential explanation for recurrence of ischemic events in patients having echolucent plaques. In addition, inflammation as a trigger for endothelial dysfunction and plaque growth is an important pathophysiologic substrate in the process of generalized atherosclerosis and has also been linked to echolucent carotid plaques. [18,19]

We conducted this study to assess the prevalence of carotid plaques in symptomatic ischemic stroke patients admitted in our wards along with evaluation of echogenicity of plaque. During the follow-up phase we assessed the recurrence of stroke confirmed by imaging and tried to find out a relation between recurrence of stroke and echogenicity of plaque.

Materials and Methods

Study population

The study was conducted on patients admitted to the Medicine Department of King George's Medical University over a period of 2 years with follow up of patients up to 6 months. The study comprised of 206 consecutive (more than 30 years of age) patients of ischemic stroke admitted in our wards but proper evaluation and regular follow up occurred only in 154 patients. Informed consent was taken from all the patients or their relatives before inclusion in this observational study.

Identification of ischemic stroke patient was difficult as was confused with few other congener cerebrovascular diseases. Hence, both imaging modalities and clinical assessment were used to select patients for this study. This included full detailed clinical current and past history as well as imaging modalities to rule out other diseases. Ischemic strokes were defined as focal neurological symptoms lasting for more than 24 h (with or without persisting disabilities) for which magnetic resonance imaging (MRI) showed corresponding ischemic infarction and ruled out cerebral hemorrhage.

Following patients had been excluded from the study, isolated transient ischemic attack, stroke as a result of apparent cardio-embolic origin, vasculitis syndromes causing stroke, stroke caused by coagulation disorders, subarachnoid hemorrhage, and intracerebral hemorrhage. This criterion was applied to rule out causes other than atherosclerosis.

After patient selection they underwent a thorough evaluation for various risk factors along with carotid sonography. Detailed history taking including both present and past history (history of diabetes, hypertension, and other risk factors), clinical examination, routine blood chemistry, electrocardiography, lipid profile, color Doppler of carotids, and MRI Scan of the brain were done.

Carotid sonography

The patient was kept supine with slight hyperextension and rotation of the neck in the direction opposite the probe. A linear array transducer with a multiple

frequency (7 to 12 MHz) attached to a high-resolution B mode ultrasound system (Toshiba Xario XG ultrasound machine Tokyo - Japan, GE Logic PS ultrasound Instrument) was used to acquire images by a single-sonographer blind to clinical data of subjects equipped with a 7.5 MHz linear array transducer. The far wall and near wall of the right common carotid artery, bifurcation (bulb), and internal carotid artery (six locations) were scanned for the presence of plaques. Generally atherosclerotic plaques occur predominantly at the sites of nonlaminar turbulent flow in the carotid artery typically in the bifurcation and the proximal internal segment. According to Mannheim Carotid Intima-Media Thickness Consensus (2004-2006),[20] a plaque was defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding intramural thickness (IMT) value, or demonstrates a thickness 1.5 mm as measured from the media–adventitia interface to the intima–lumen interface.

The assessment of plaque echolucency was based on the modified version of the Gray–Weale classification.[21] The vessel lumen was used as the reference structure for defining echolucency, and the bright echo zone produced by the media–adventitia interface at the far wall was used as the reference structure for defining echogenicity. Plaques were graded as (1) dominantly echolucent with a thin echogenic cap, (2) substantially echolucent with small areas of echogenicity, (3) dominantly echogenic lesions with small areas of echolucency, and (4) uniformly echogenic lesions. Because of the very low prevalence of type 1 and type 4 plaques in our study population, groups 1 and 2 and groups 3 and 4 were merged into two groups defined as predominantly echolucent or predominantly echogenic lesions [Figure 1].

End points

Every patient with the presence of carotid plaque was followed for 6 months for new neurological symptoms through telephonic interview, outpatient visits, and readmission. In the case of onset, new neurological symptoms brain imaging was performed to see newer infarcts. The primary end point of the study was taken as new ischemic stroke developing ipsilateral to the relevant carotid plaque.

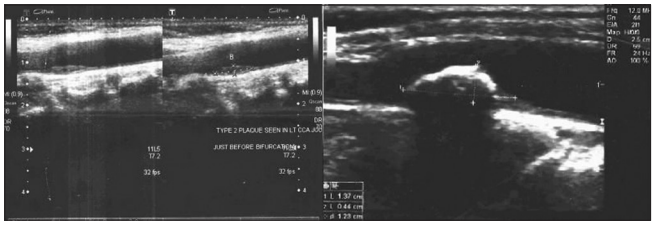

Figure 1: Carotid sonography showing type-2 plaque (echolucent) in left common carotid artery just before bifurcation and echogenic plaque at bifurcation in two different patients

Statistical analysis

The results were presented in mean ± SD (standard deviation) and percentage. Chi-square test was done to compare the dichotomous and categorical variables. The unpaired *t*-test used to compare two means. The $P < 0.05$ was considered as significant. All the analysis was carried out by using Statistical Product and Service Solutions (SPSS) 15.0 Versions.

Results and Observation

Characteristics of the study subjects

The study was conducted on 206 patients out of which 52 were withdrawn due to various reasons (including death due to reasons other than recurrent ischemic stroke and leaving against medical advice); hence, only 154 patients were finally included in the study. Age distribution of the study was > 70 years in 37.66%, 61-70 years in 33.76%, 51-60 years in 20.12%, and 13 (8.4%) were less than 50 years. More than half (61.69%) of the patients were males. In our study hemiparesis was seen in 81.81% of the patients and cranial nerve involvement in 25.97%. Aphasia was present in 35.71% patients. Of all the patients in our study, previous history of hypertension was present in 54.54% and diabetes in 33.37% of patients. More than one-third (35.06%) were tobacco chewers, 29.8% were smokers, and about 14.28% were alcoholic. The average values of the risk factors such as serum fibrinogen, homocystiene, triglycerides, total cholesterol, low density lipoprotein, and high density lipoprotein cholesterol were found to be higher than normal average values.

Carotid sonographic evaluation

The Carotid Plaque was present in 44.1% patients. 61.76% patients had right sided plaque where as 38.23% patients had left-sided plaque. Echogenic plaque was present in 44.11% and echolucent plaque was present in 55.88% patients. The biochemical values and risk factors were compared between patients with and without carotid plaque. Diabetes, hypertension, serum fibrinogen, serum homocystiene, serum triglyceride, and serum low density lipoproteins were found to be significantly associated with the presence of plaque [Table 1]. At the end of 6 month followup, a total of 32 patients in the plaque group had recurrence of ischemic stroke out of which eight were in echogenic group and 24 were in the echolucent group. The association between echolucent type of carotid plaque and recurrence of ischemic stroke was found to be statistically significant in this Bivariate analysis (*P* value-0.0028) [Table 2 and Figure 2].

Table 1: Distribution biochemical and risk factors in ischemic stroke patients with the presence and absence of plaque

Risk factor parameters Dichomatous variables	Plaque present (*n*=68) Number of patients (%)	Plaque absent (*n*=86) Number of patients (%)	*P* value
Male sex	40 (58.82)	44 (51.11)	0.343
Hypertension	52 (76.47)	30 (34.88)	<0.0001
Diabetes	56 (82.35)	34 (39.53)	<0.0001
Smoking	24 (35.29)	28 (32.55)	0.397
Alcoholism	14 (20.58)	22 (25.58)	0.467
Continuous variables	**Mean±SD**	**Mean±SD**	***P* value**
S. Fibrinogen (g/l)	3.90±0.81	3.20±0.76	<0.0001
S. Homocystiene (µmol/l)	9.27±1.06	7.42±0.54	<0.0001
S.Triglycerides (mg/dl)	162.93±21.11	148.34±20.65	<0.0001
S. high density lipoprotien cholesterol (mg/dl)	33.32±6.06	31.88±5.86	0.137
S. low density lipoprotien cholesterol (mg/dl)	106.15±39.13	90.51±20.34	0.001

Table 2: Ischemic stroke recurrence in patients with echogenic and echolucent carotid plaques

Plaque echogenicity	Recurrence at 6 month follow up (Yes) (%)	Recurrence at 6 month follow up (No) (%)
Echogenic plaque	8 (26.6)	22 (73.4)
Echolucent plaque	24 (63.1)	14 (36.9)

P=0.0028

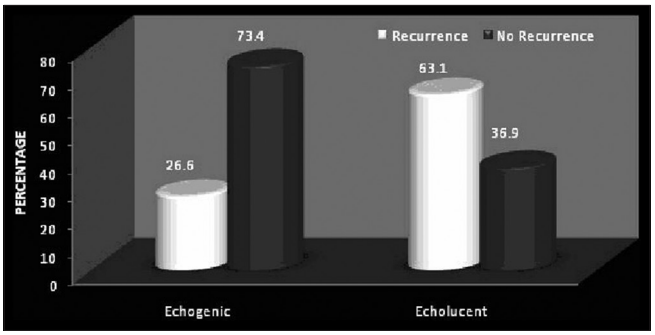

Figure 2: Comparison of ischemic stroke recurrence in patients with echogenic and echolucent carotid plaques

Discussion

Atherosclerosis remains the main culprit of ischemic stroke in countries all over the world. With the advent of carotid sonography we got a tool by which we assess the load of atherosclerosis in individuals and predict the outcome. Ultrasound assessment of carotid arteries is a simple and noninvasive method to accurately evaluate early carotid atherosclerosis by measuring intima media thickness or by direct visualization of an atherosclerotic plaque.

While carotid intima media thickness describes early changes, carotid plaque specifies more advanced stage of atherosclerosis. In India and other developing countries, various studies correlating CIMT as a marker of atherosclerosis-related diseases have been conducted but carotid plaque is neglected generally.[22-24] It is still controversial whether carotid plaques merely reflect generalized atherosclerosis or are directly related to subsequent stroke by release of thromboemboli. This study included the assessment of the prevalence of plaque and its characteristics in ischemic stroke patients. Carotid plaque was found to be present in 44.1% patients in stroke population of this cohort. Various cerebrovascular risk factors were found to be significantly associated with the presence of plaque. Many studies showed such association and it denotes that carotid artery atherosclerosis is itself influenced by various factors such as age, sex, lipid profile, and diabetic or hypertensive status of patients.

We know carotid plaques are frequently found in subjects who suffered from a stroke.[25,26] Few studies have quantified the association between carotid plaques and risk of subsequent stroke in asymptomatic subjects.[27] A higher rate of recurrence within the first year from an initial ischemic stroke is well recognized.[28,29] We investigated the association between carotid plaque echogenicity, measured at six locations in the carotid arteries and the recurrence of subsequent stroke in a population-based cohort of ischemic stroke patients. Certain echomorphologic characteristics of carotid artery plaques, largely echolucency and heterogeneity, have been consistently associated with symptomatic disease in cross-sectional studies,[25,30] and increased incidence of cerebrovascular events in large cohorts.[31-33] Similar inferences came out in our study with the recurrence of ischemic stroke at end of 6-month follow-up. A significant association between echolucent type of carotid plaque and recurrence of ischemic stroke was found in this study (*P* value: 0.0028).

The mechanism behind the association between plaque echolucency and increased stroke incidence is not completely resolved. It is generally considered that unstable plaques are likely to have a tissue with hypoechoic lesions and these are considered to be vulnerable. On the other hand, plaques with higher echogenicity are likely to have much fibrous component and these are considered to be stable.[29,33] Thus, because echolucency is associated with lipid-rich carotid plaques[13,15,19,34] and coronary plaques rich in lipid are thought to be most prone to rupture and causing clinical events,[35] it seems possible that carotid echolucent plaques are those most prone to rupture and thus cause embolic stroke.

The significance of this study is to confirm the regulating and causal factors so that we are able to accurately stratify patients according to their risk of recurrent stroke. This could help with planning targeted secondary prevention strategies, facilitate the design of future clinical trials and, ultimately favorably affect stroke morbidity and mortality.

Although we demonstrated that echolucent plaques were a significant predictor of the recurrent stroke in symptomatic ischemic stroke patients we did not take various independent risk factors affecting the rate of recurrence in consideration, and also we did not show that characteristics of the plaque was a better predictor than traditional cerebrovascular risk assessment for the prediction of future events. Even though we excluded the cardioembolic cause of the ischemic stroke, we could not absolutely rule out other causes of ischemic stroke other than carotid atherosclerosis. Other characteristics of carotid plaque were not taken in consideration while eliciting association with recurrence. Our study was a single centre study with doubt in reproducibility of ultrasonographic measurements.

Conclusion

In this study, we found a significant association with recurrence of stroke and the echolucent type of carotid artery plaques in symptomatic ischemic stroke patients in bivariable analysis suggesting the importance of echogenicity of carotid plaques in generation of such catastrophic event recurrences neglecting various confounding factors. It might be interesting to apply these methods of determining carotid plaque echogenicity to prospective natural-history studies involving asymptomatic patients also with carotid plaques and study the development and progression of stroke attributable to carotid atherosclerosis. Such studies might identify groups of patients at different risk for stroke. The result will be better refinement of the criteria for defining risk factors associated with recurrent stroke and planning strategies to halt such events in future.

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