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Incidence of Carotid Atherosclerosis in Ischemic Stroke Detected by Duplex Ultrasound

Asmaa Abd Al-Aziz Saad*[1], Samir Mohamed Attia[2], Mohamed Said Gomaa[3], Hesham Khairy Ismael[4]
Departments of [1]Emergency Medicine, [2]Vascular Surgery, [3]Neurology and
[4]Critical Care Medicine, Faculty of Medicine, Mansoura University
***Corresponding author:** Asmaa Abd Al-Aziz Saad, **Mobile:** (+20) 01092980099, **E-Mail:** smsmsaaad27@gmail.com

ABSTRACT
Background: Carotid artery atherosclerosis is one of crucial pathogenetic factors of cerebrovascular disease, such ischemic stroke. The degree of artery stenosis has been regarded as one of the most effective criteria to assess carotid atherosclerotic severity. Color Doppler ultrasound (CDUS) acts as an easy and noninvasive technique to research the characterization of carotid atherosclerotic lesion through echogenicity, which is referred to as the reflectance of the ultrasound signal.
Objective: To evaluate the incidence of extracranial carotid atherosclerosis in patients presenting with ischemic stroke using the noninvasive CDUS.
Patients and methods: This was a cohort prospective observational clinical study conducted on a total of 80 patients with ischemic stroke, divided into two groups (no atherosclerosis n=12 and atherosclerotic cases=73). The study was conducted at Mansoura University Emergency Hospital through one year period from December 2018 to December 2019.
Results: A statistically significant higher median right carotid artery intimal medial thickness among atherosclerotic than non-atherosclerotic group. A statistically significant higher median right carotid artery intimal medial thickness was detected among atherosclerotic than non-atherosclerotic group with median thickness was 0.82 and 0.515, respectively. Median plaque index was 4 ranging from 1.6 to 5.9 and incidence of left carotid artery stenosis was 78.1%.
Conclusion: Multiple risk factors like age, sex and high mean arterial blood pressure are strongly associated with carotid artery atherosclerosis, so we suggest that high risk patients should be screened by Doppler ultrasonography in order to plan out medical and surgical intervention for primary and secondary prevention of ischemic stroke.
Keywords: Carotid atherosclerosis, Ischemic stroke, Duplex ultrasound.

INTRODUCTION

Atherosclerosis is the major cause of cerebrovascular diseases. Reduction in the risk factor burden can decrease the risk of cerebrovascular events and atherosclerosis progression. Initially, atherosclerosis is asymptomatic disease that may progress silently for decades before clinical manifestations that generally appear in middle and late adulthood**.** Therefore, an early identification of subclinical atherosclerosis and interventions may prevent or delay the onset of CVD **(1).**

Stroke is the major cause of long-term disability in adults, and the second leading cause of death worldwide. Thirty-day mortality rate of ischemic stroke has been estimated at around 15% in high-income countries. Stroke carries a major morbidity concern in terms of quality of life, health care maintenance and cost. More than 80% of strokes are ischemic, with the rest being hemorrhagic **(2).**

Atherosclerotic carotid stenosis of the extracranial carotid artery accounts for 15% to 20% of ischemic strokes. Asymptomatic carotid artery stenosis is very commonly encountered in daily clinical practice. Its prevalence ranges from 0.1 to 7.5% in the general population and is highest in older men. Carotid disease can become symptomatic because of plaque thrombosis, atheroembolism or, less commonly, a hemodynamic mechanism and it represents a significant proportion of anterior circulation strokes **(3).**

Carotid duplex ultrasound (CDUS) is an imaging method that has been widely used to detect and measure carotid plaques (CP) and carotid intima-media thickness (cIMT), which are arterial markers integral to the development of atherosclerosis independently associated with future cerebrovascular events (stroke). These two arterial markers are correlated; however, they show differing patterns of association with risk factors and different predictive value for CVD **(4).** CDUS is a noninvasive imaging modality that can safely and accurately estimate subclinical atherosclerotic carotid stenosis to improve cardiovascular risk assessment. However, the cost-effectiveness of using CDUS to screen for atherosclerotic carotid stenosis has long been debated. CDUS is not recommended for screening asymptomatic individuals in the general adult population. Symptomatic individuals or adults with high risk factors for carotid atherosclerotic disease are recommended to undergo CDUS screening **(5).**

The purpose of this study was to evaluate the incidence of extracranial carotid atherosclerosis in patients presenting with ischemic stroke using the noninvasive carotid duplex ultrasound (CDUS).

PATIENTS AND METHODS

This was a cohort prospective observational clinical study conducted on a total of 80 patients with ischemic stroke, divided into two groups (no atherosclerosis n=12 and atherosclerotic cases=73).

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The study was conducted at Mansoura University Emergency Hospital through one year period from December 2018 to December 2019.

Inclusion criteria: Age group >18 years old, both genders, and patients with ischemic stroke.
Exclusion criteria: age group <18 years, patients with hemorrhagic stroke, recurrent stroke, and patients who refuse to be included in this study.

All Patients were subjected to the following:

1) **Resuscitation:**
   Primary survey and resuscitation: A = Airway opening and maintenance of airway. B = Breathing and ventilation. C = Circulation. D = Disability: neurological status and Glasgow coma scale (GCS). E = **Exposure**: segmental exposure.
   Secondary survey: from head to nail examination (head, neck, chest, abdomen, pelvis, lower limb, upper limb) and vital signs (pulse, blood pressure, respiratory rate).
2) **Clinical examination:**
   A. Continue to monitor: Mental state, airway, respiratory rate, oxygen saturation, heart rate, blood pressure, capillary refill time and temperature of extremities.
   B. Full clinical examination of all body especially neurological examination by NIHSS score, which is a systematic assessment tool that provides a quantitative measure of stroke-related neurological impairments [(6)] and FAST score [(7)].
3) **Investigations:**
   - **Non-contrast CT brain:** At the moment of admission has the possibility to show the location, age and size of lesions or unspecific images like diffuse cerebral edema
   - **Carotid Duplex Ultrasound (CDUS):** All patients who proved to have ischemic stroke by clinical examination are subjected to extracranial CDUS examination for evidence of atherosclerosis: CP or Cimt. According to degree of carotid artery stenosis: Significant carotid artery stenosis: ≥ 50%, and insignificant carotid artery stenosis: < 50% [(8)].

Ethical consideration:

An approval of the study was obtained from Mansoura University Academic and Ethical Committee. Informed written consent was obtained from each participant sharing in the study. Confidentiality and personal privacy were respected in all levels of the study. Collected data were not be used for any other purpose. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS Corp. released 2013 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) Qualitative data were described using number and percent. Quantitative data were described using mean, standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at 0.05 level. Chi-Square test was used for comparison of 2 or more groups. Parametric tests for student t-test was used to compare 2 independent groups. The Spearman's rank-order correlation was used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables. P value ≤ 0.05 was considered significant.

RESULTS

Table (1) demonstrated that there was no statistically significant difference of age, sex and smoking. Mean age of atherosclerotic group was 56.07 years versus 50.5 years for no atherosclerotic group. Among atherosclerotic group, 57.5% are males versus 75% among normal group.

Table (1): Sociodemographic characteristics of the studied cases

	C (n=12)		**Atherosclerotic cases=73**		**Test of significance**
Age (years) Mean ± SD	50.50±11.02		56.07±9.69		t=1.81 p=0.07
	n	**%**	**n**	**%**	
Sex					
Male	9	75.0	42	57.5	χ^2=1.31
Female	3	25.0	31	42.5	p=0.252
Smoking					
+ve	10	83.3	63	86.3	χ^2=0.075
- ve	2	16.7	10	13.7	p=0.784

There was statistically significant higher mean blood pressure and LDL among group with atherosclerosis than the group without atherosclerosis (Table 2).

Table (2): Clinical, laboratory and medical history distribution among studied cases

	No atherosclerosis n=12		Atherosclerotic cases=73		Test of significance
SBP (mmHg) Mean ± SD	125.83±14.58		140.03±17.39		t=2.67 p=0.09*
DBP (mmHg) Mean ± SD	79.33±7.56		87.14±8.57		t=2.97 p=0.004*
HDL (mg/dl) Mean ± SD	49.16±5.21		48.71±10.19		t=0.130 p=0.987
LDL (mg/dl) Mean ± SD	65.59±3.32		93.38±3.63		t=2.91 p=0.005*
	n	**%**	**n**	**%**	
DM	3	25.0	13	17.8	χ^2=0.349 p=0.824
Anti-HTN	3	25.0	19	26.0	χ^2=0.006 p=0.940
Controlled by antihypertensive	3	25.0	19	26.0	χ^2=0.006 p=0.940
Lipid lowering drugs	3	25.0	11	15.1	χ^2=0.739 p=0.39

There was a statistically significant higher median right carotid artery intima medial thickness among atherosclerotic than non-atherosclerotic group with median thickness was 0.83 and 0.485 respectively. Median plaque index was 3.7 ranging from 1.6 to 5.9 and incidence of right carotid artery stenosis was 71.2% (Table 3).

Table (3): Sonographic results of right carotid artery

	No atherosclerosis cases n=12		Atherosclerotic cases=73		Test of significance
Sonography	**n=12**	**%**	**N=73**	**%**	
Right carotid artery intimal media thickness Median (min-max)	0.485(0.25-0.76)		0.83(0.45-1.32)		z=4.05 p<0.001*
Right carotid artery plaque index Median (min-max)	NA		3.7(1.6-5.9)		
Right carotid stenosis	0	0.0	52	71.2	

There was a statistically significant higher median left carotid artery initial medial thickness among atherosclerotic than non-atherosclerotic group with median thickness is 0.82 and 0.515 respectively. Median plaque index was 4 ranging from 1.6 to 5.9 and incidence of left carotid artery stenosis was 78.1% (Table 4).

Table (4): Sonographic results of left carotid artery

	No atherosclerosis cases n=12		Atherosclerotic cases=73		Test of significance
Sonography	**N=12**	**%**	**N=73**	**%**	
Left carotid artery initial medial thickness Median (min-max)	0.515 (0.39-0.60)		0.82 (0.24-1.21)		Z=4.35 P<0.001*
Left carotid artery plaque index Median (min-max)	NA		4.0(1.6-5.9)		
Left carotid stenosis	0	0.0	57	78.1	

From this table, it was demonstrate that median stroke score was 5.0 ranging from 1.0 to 9.0 and median NIHSS score was 13 ranging from 5 to 20 (Table 5).

Table (5): Stroke and NIHSS scores distribution among studied cases

	No atherosclerotic	Atherosclerotic	Test of sign
Stroke score Median (min-max) mean±SD	 4(1.0-5) 2.25±0.85	 5.0(1.0-9.0) 4.95±2.55	 z=1.98 p=0.04*
NIHSS score Median (min-max) mean±SD	 9.0(5.0-11.0) 9.58±1.58	 13.0(5.0-20.0) 12.18±4.93	 z=2.0 p=0.02*

z: Mann Whitney U test

There was statistically significant positive correlation between NIHSS score and stroke score (r=0.377, p=0.001) and between NIHSS score and left carotid artery initial medial thickness (r=0.234, p=0.047). Stroke score have statistically significant positive correlation between left carotid artery plaque index and stroke score (r=0.248, p=0.035) (Table 6).

Table (6): Correlation between NIHSS score, stroke score and left carotid artery initial medial thickness and plaque index

		NIHSS score	Stroke score	Left carotid artery initial medial thickness	Left carotid artery plaque index
Stroke score	r	**.377***	1.000		
	p	**.001**	.		
Left carotid artery initial medial thickness	r	**.234***	-.117	1.000	
	p	**.047**	.326	.	
Left carotid artery plaque index	r	.052	**.248***	.099	1.000
	p	.662	**.035**	.404	.

r: Spearman correlation co-efficient *statistically significant if p<0.05

There was statistically significant positive correlation between NIHSS score and stroke score (r=0.377, p=0.001) and between NIHSS score and Right carotid artery initial medial thickness (r=0.699, p=0.001). Stroke score had statistically significant positive correlation between right carotid artery initial medial thickness, plaque index and stroke score (r=0.734 & 0.499). Right carotid artery initial medial thickness illustrated statistically significant positive correlation with right carotid artery plaque index (r=0.366).

Table (7): Correlation between NIHSS score, stroke score and right carotid artery initial medial thickness and plaque index

		NIHSS score	Stroke score	Right carotid artery initial medial thickness	Right carotid artery plaque index
NIHSS score	r	1.000			
	p	.			
Stroke score	r	**.377***	1.000		
	p	**.001**	.		
Right carotid artery initial medial thickness	r	**.699***	**.734***	1.000	
	p	**.001**	**.001**	.	
Right carotid artery plaque index	r	.148	**.499***	**.366****	1.000
	p	.210	**.001**	**.001**	.

r:Spearman correlation co-efficient *statistically significant if p<0.05

DISCUSSION

The current study illustrated the sonographic characteristics of both carotid arteries. According to normal intimal media thickness which is ≤ 0.8 mm [9]. There was a statistically significant higher median right carotid artery intimal media thickness among atherosclerotic than non-atherosclerotic group with median thickness was 0.83 and 0.485, respectively. Also There was a statistically significant higher median left carotid artery intimal media thickness among atherosclerotic than non-atherosclerotic group with median thickness is 0.82 and 0.515, respectively. According to definition of carotid plaque, which is a localized thickening of > 1.5 mm [10]. Median plaque index was 3.7 ranging from 1.6 to 5.9 and incidence of right carotid artery stenosis was 71.2%. Median plaque index was 4 ranging from 1.6 to 5.9 and incidence of left carotid artery stenosis was 78.1%. In harmony to our results, **Polak *et al.*** [11] found that the severity of internal carotid artery stenosis was associated with thickening of the intima-media layer of the common carotid artery wall (r = .37, P < .0001) which is statistically significant.

The current study reported that there was no statistically significant difference in age, sex and smoking, with mean age of atherosclerotic group was 56.07 years versus 50.5 years in normal non-atherosclerotic. Among atherosclerotic group, 57.5% were males versus 75% among normal non-atherosclerotic group which are in concordance with many studies, **Atif *et al.*** [12], **Hadi *et al.*** [13] and **Fernandes *et al.*** [14]. The explanation is that hormonal factors such as estrogen have been observed to play a significant role in slowing the progression of atherosclerotic lesions in females. Also, there was significant relation between male gender and severe atherosclerosis (p = 0.005). According to literature, male gender is also risk factor for extracranial atherosclerosis in Asia [15, 16]. **Razzaq *et al.*** [17] evaluated the role of carotid Doppler ultrasonography in the diagnosis and management of carotid stenosis in young stroke patients. A total of 118 patients between the ages of 15-45 years were admitted with a diagnosis of ischemic infarct over a five-year period. The mean age was 38 years and males were pre-dominant with a sex ratio of 1.8:1.

The current study evaluated the clinical and laboratory data of studied cases showing that there was statistically significant high mean blood pressure and LDL among the group with atherosclerosis than the group without atherosclerosis, but there was no significant difference as regards smoking, HDL, DM, Anti-HTN drugs and Lipid lowering drugs. High mean blood pressure was also found to be the major risk factor of extracranial carotid atherosclerosis in other studies [13, 18, and 19].

Among the cases with atherosclerosis in the current study, DM was detected in 17.8%. The frequency of DM in our study is similar to **Dabilgou *et al.*** [20] who showed that diabetic patients represent 15.3% of the cases in their study. DM is an important risk factor for extracranial carotid atherosclerosis [16, 18, and 19].

Among the atherosclerotic cases, the current study showed that the median stroke score was 5.0 ranging from 1.0 to 9.0 and median National Institutes of Health Stroke Scale (NIHSS score) is 13 ranging from 5 to 20. While, among the non-atherosclerotic cases, the median stroke score was 4.0 ranging from 1.0 to 5.0 and median National Institutes of Health Stroke Scale (NIHSS score) is 9 ranging from 5 to 11. This demonstrates that cerebral stroke is more severe in patients with carotid atherosclerosis. **Klarin *et al.*** [21] performed a study to assess the atherosclerotic risk factor profiles, anatomic features, and clinical outcomes of previously asymptomatic patients admitted with stroke of carotid etiology. Stroke severity was assessed using the National Institutes of Health stroke score (NIHSS) recorded by the neurology team on admission. Individuals were then classified as having either a minor stroke (NIHSS 1-4) or a moderate to severe stroke (NIHSS ≥ 5). Of the 219 patients, 156 (71%) presented with a moderate or severe stroke (≥ 5 at admission).

The current study evaluated the stenosis type distribution among studied cases. As regards right carotid artery, 59.6% of the right carotid artery stenosis was significant. As regards left carotid artery, 52.6% of the left carotid artery stenosis was significant. **Fernandes *et al.*** [14] reported that 39 (78%) patients had plaques in the carotid artery of which 9 patients had plaques on the right side, 7 patients had plaques on the left side and 23 patients had bilateral involvement. Carotid bifurcation is commonly involved by the atherosclerotic plaque located distal to the origin of the carotid arteries.

The current study discussed the relation between the carotid arteries stenosis type and NIHSS score among studied cases. As regards right carotid artery, there was statistically significant higher mean NIHSS score among cases with significant carotid artery stenosis than cases with insignificant stenosis (14.97& 8.81) respectively. As regards left carotid artery, the current study illustrated that there was statistically significant higher mean NIHSS score among cases with significant left carotid artery stenosis than cases with insignificant stenosis (16.63 & 9.4 respectively).

Regarding the relation between right carotid artery stenosis type and stroke score among studied cases, there was statistically significant higher mean stroke score among cases with significant carotid artery stenosis than cases with insignificant stenosis (6 versus 3.9). However, the left carotid artery showed no

statistically significant relation between stroke score and type of stenosis and side of stenosis ($p > 0.05$).

Interestingly, the current study evaluated the relation between carotid arteries stenosis and the scores. There was statistically significant higher NIHSS score and mean stroke score among cases with left carotid artery stenosis than cases without (12.82 versus 9.87 respectively). However, there was no statistically significant relation between incidence of right carotid artery stenosis and NIHSS, stroke score among studied cases ($p > 0.05$). Denoting that severity of stroke, by stroke scores, could be more associated with left carotid artery stenosis.

The current study illustrated correlation between NIHSS score, stroke score, left carotid artery intimal medial thickness and plaque index. There was statistically significant positive correlation between NIHSS score and stroke score. Stroke score had statistically significant positive correlation between left carotid artery plaque index and stroke score.

As regards right carotid, there was statistically significant positive correlation between NIHSS score and stroke score and between NIHSS score and right carotid artery initial medial thickness. Stroke score have statistically significant positive correlation between right carotid artery intimal medial thickness, plaque index and stroke score. Right carotid artery intimal medial thickness illustrated statistically significant positive correlation with right carotid artery plaque index.

Ebrahim *et al.* [22] showed that focal carotid plaques are more strongly associated with cardiovascular risk than a diffuse increase in IMT. For the quantification of such plaques, **Handa *et al.*** [23] used a scoring system, which is currently known as the "plaque score" (PS). PS is defined as the sum of all plaque heights in bilateral carotid arteries. Because PS increases in parallel with the height and number of atheromas, it may allow for the quantification of later stages of carotid atherosclerosis. PS has been associated with cardiovascular risk factors and diseases, suggesting its potential utility as a reflection of systemic atherosclerosis [24].

Sun *et al.* [25] showed that, after adjusting for sex and age, positive correlations were found between ulcerated plaque and luminal stenosis, carotid plaque volume and hypoechoic plaque volume. However, there were no correlations between ulcerated plaque and hyperechoic plaque volume (P ¼ 0.07). In addition, after adjusting for age, sex, and carotid luminal stenosis, ulcerated plaque was also positively associated with carotid plaque volume and hypoechoic plaque volume but was negatively associated with hyperechoic plaque volume.

About 30–60% of strokes are caused by atherosclerotic disease involving the extracranial carotid arteries usually within 2 cm of the carotid bifurcation. Sonography is unique among vascular imaging procedures in that it can assess plaque composition. Sonographically detected plaque characteristics may have prognostic value and may be useful for selection of medical and surgical therapy [24]. The discrepancies in findings of the above mentioned studies can be explained by a number of factors including the differing interval between stroke onset and vascular imaging, the methods to evaluate occlusive lesions, the etiology of stroke, dissimilar populations, selection of patients and limited sample size.

CONCLUSION

The carotid artery atherosclerosis is a well-known cause of ischemic stroke and there is positive correlation between its degree and severity of stroke scores. Our study showed that multiple risk factors like age, sex and high mean arterial blood pressure are strongly associated with carotid artery atherosclerosis, so we suggest that high risk patients should be screened by Doppler ultrasonography in order to plan out for medical and surgical intervention and for primary and secondary prevention of ischemic stroke.

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