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Assessment of Extracranial Carotid Arteries in Acute Ischemic Stroke: Correlation with Risk Factors

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Abstract **Background:** Acute ischemic stroke (AIS) is one of the major causes of death worldwide. An estimated 80% of strokes are thromboembolic in origin, often with carotid plaque as an embolic source. Carotid Doppler study is valuable to assess the cause, localization, extent and severity of extra cranial arterial stenosis**. The aim** of our work is to investigate the relation between Doppler findings in carotid artery disease and vascular risk factors in acute ischemic stroke patients. **Methods**: We prospectively analyze 64 consecutive patients with first-ever ischemic stroke admitted within 24 hs of the onset of stroke symptoms. Carotid doppler ultrasonography was performed to all subjects. Carotid intima-media thickness (CIMT) measurement of both right and left sides of the common carotid arteries and internal carotid arteries were taken and degree of stenosis was calculated. **Results:** 53.1% of our patients were males and 46.9% were females with the mean Patient's age were 66.5(±10.0) years. The mean CIMT of our patients were 1.4±0.86 while stenosis was present in 50% of our patients. The vascular risk factors showed positive association with stenosis of carotid arteries, with the hypertention showed the strongest association. Also, the CIMT was significantly high in hypertensive ($p < 0.05$) and diabetic patients ($p < 0.04$) which demonstrated that there was a significant association between them. **Conclusion:** carotid artery stenosis and CIMT was significantly correlated with the vascular risk factors of ischemic stroke.

Keywords: *acute ischemic stroke, risk factors, extracranial carotid arteries, carotid stenosis, carotid intema media thickness*

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1. Introduction

Acute ischemic stroke (AIS) is one of the leading causes of mortality and long term disability all over the world [1]. Thromboembolic stroke accounts about 80% of the strokes, with the carotid plaque as an embolic source [2]. Arterial atherosclerosis results into many vascular accidents including cerebrovascular, ischemic heart disease and peripheral vascular diseases [3]. Intimal thickening, fibrous cap atheroma and plaque formation, all are consequences from Progressive atherosclerosis. Early detection allows controlling the disease in risky patients [4].

Carotid Doppler study is valuable to assess the cause, localization, extent and severity of extra cranial arterial stenosis [5]. B-mode ultrasound has been considered as the ideal modality for carotid intima media thickness (CIMT) evaluation [6].

2. The Aim of the Work

The aim of the work is to investigate the relation between Doppler findings in carotid artery disease using non invasive high resolution B mode and other risk factors e.g: hypertention (HTN), diabetes mellitus (DM), dyslipidemia and smoking in AIS patients.

3. Patients and Methods

Between March 2016 and February 2017, we prospectively analyze 64 consecutive patients (34 males and 30 females) with first-ever ischemic stroke admitted within 24 hours of the onset of stroke symptoms to the intensive care and stroke units, Neurology Department, Zagazig University Hospitals, Egypt. The patients who qualified WHO definition [7] of stroke as "rapidly

developing clinical signs or focal (or global) disturbances of cerebral function lasting for more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin", presented within 24 h of first symptoms and diagnosed cerebral infarction by either computed tomography (CT) scan or magnetic resonance imaging (MRI) were included in this study. Exclusion criteria were Transient ischemic attack (TIA), previous history of cerebro or cardiovascular events (cerebral ischemia or hemorrhage, ischemic heart disease or acute myocardial infarction), renal failure, valvular heart disease, atrioventricular block, atrial fibrillation (AF) and patients on drugs like statins, aspirin, angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARBs). Also, patients of vertebro-basilar insufficiency were not included in the study. Cerebral infarction was diagnosed on the basis of history, neurological examination, and neuroimaging (CT or brain MRI). CT scan was performed within 12 hs of admission to exclude patients with stroke mimic or primary intracerebral hemorrhage. All subtypes of ischemic stroke were included. Clinical history, examination and medications were recorded at baseline.

3.1. Defining Risk Factors

The risk factors included hypertension (receiving medications for hypertension or blood pressure ≥140/90 mmHg on two occasions (at least one week a part) [8], diabetes mellitus (receiving medications for diabetes mellitus, fasting blood sugar ≥126 mg/dL or HbA1c ≥6.5%, or a casual plasma glucose >200 mg/dL) [8], hypercholesterolemia (receiving cholesterol-reducing agents or an overnight fasting cholesterol level ≥240 mg/dL, ≥200 mg/dL triglycerides, or Low density lipoprotein (LDL) cholesterol ≥160mg/dL) [8], A "current smoker" was defined as a person who self reported smoking within the calendar year prior to the year of diagnosis [9].

3.2. Carotid Doppler Ultrasonography

Sonography examination of extra cranial carotid arteries was done by using a high frequency 6-10 MHZ linear array transducer with subject lying in the supine position and the head slightly tilted to opposite side. Examination was done by using Siemens Acuson X 300 colourdoppler machine. Before performing Doppler ultrasonography, informed consent was obtained from the patients. The examination was performed with a Doppler angle of less than or equal to 60 degree and sample volume of 1 to 5 mm. CIMT is anechoic zone between two echogenic lines, first echo is lumen-intima surface, and the second echo is caused by media-adventitia interface. The IMT measurement of both right and left sides of the common carotid arteries and internal carotid arteries was taken. The mean value of above four sites was used for analysis. A CIMT more than 1 mm was almost indicative of atherosclerosis.

The diameter of the residual lumen and the external diameter of the artery at the same level were measured and the degree of stenosis was calculated using the following relationship: Percent stenosis = D-d.100/D, where D is vessel wall-to-wall diameter and d is patent vessel diameter. All carotid stenoses were included in the analysis, irrespective of the laterality to the symptomatic hemisphere or its unilateral or bilateral presence, or the presence of solitary or multiple stenoses in one or more vessels.

The systolic and diastolic velocity of blood flow, presence of atheromatous plaque and thrombus were looked for and then the percentage of stenosis of the affected patients was assessed.

Carotid Doppler study was graded as follow **[10]**: Normal; ICA/CCA PSV ratio<2 and ICA EDV<40, mild stenosis <50%; ICA/CCA PSV ratio<2 and ICA EDV<40 with presence of atheromatous plaques, moderate stenosis 50-70%; ICA/CCA PSV ratio= 2-4 and ICA EDV=40-100, sever stenosis >70%; ICA/CCA PSV ratio>4 and ICA EDV> 100.

All findings were included in the carotid Doppler study of common carotid arteries and internal carotid arteries of both sides.

Ethical consideration: A written informed consent was obtained from every patient or his/her relative to be included in the study. This study was approved by the institute research board of Faculty of Medicine, Zagazig University.

4. The Sample Size

The sample size of this study was calculated using the percentage of hyperlipidemia was 90.3 % in carotid artery stenosis >50% and was 59.1% in carotid artery stenosis < 50% in a study of Carotid Doppler and lipid profile findings in ischemic stroke patients A hospital based study [11]. A sample size of 64 was found to achieve a power of 80% at 95% Confidence interval. The calculation was performed using Epi Info 7 (CDC, 2015).

5. Statistical Analysis

Statistical analysis Data were coded and analyzed using SPSS 22 statistics (*IBM 2013*) [12]. Quantitative variables were expressed as mean ± SD, whereas qualitative variables were expressed as numbers and percentages. Group comparison was performed using the Chi- square ($\chi 2$) and t-test for qualitative and quantitative variables, respectively. Spearman's rank correlation coefficient was calculated between carotid duplex findings and vascular risk factors of ischemic stroke. We consider (+) sign as indication for direct correlation and (-) sign as indication for inverse correlation. P-value of 0.05 or less was considered significant and less than 0.001 as highly significant.

6. Results

Our study included Sixty four AIS patients, 53.1% of our patients were males and the mean Patient's age was 66.5(±10.0) years. Demographic and clinical characteristics results of the patients are presented in Table 1. The mean CIMT was 1.4±0.86 mm in our patients. Among the 64 AIS patients, carotid stenosis was present in 50% of them (32 patients). Regarding the

relation between vascular risk factors of ischemic stroke and carotid artery stenosis, we found that carotid artery stenosis was associated with hypertension, smoking, diabetes mellitus, dyslipidemia and hyperuricemia.

Table 1. Baseline Characteristics and Potential Baseline Factors of the studied group

Baseline Characteristics	All patients (N= 64)
Age [a]	66.5±10 (30-90)
Male sex [b]	34 (53.1%)
GCS, median (IQR)	
SBP [a]	147.2±20.7 (110-200)
DBP [a]	88.9±12 (70-120)
Glucose, mg/dL [a]	196.7±92.6 (93-450)
Hypertension [b]	49 (76.6%)
Diabetes mellitus [b]	31 (48.4%)
Dyslipidemia [b]	35 (54.7%)
Coagulopathies [b]	2 (3.1%)
Smoking [b]	25 (39.1%)
Hyperuricemia [b]	29 (45.3%)
CIMT [a]	1.4±0.86
PSV [a]	66.6±23.9
EDV [a]	35.1±7
PSV/EDV [a]	2.25±0.95
Stenosis [b]	32 (50%)
Atheromatous plaque [b]	17 (26.6%)
Thrombosis [b]	3 (4.7%)
Normal [b]	32

[a] mean (±SD); [b] number (%); CIMT, carotid intima media thickness; DBP, Diastolic blood pressure; EDV, End Diastolic Velocity; GCS, Glasgow coma scale; PSV, Peak Systolic Velocity; SBP; systolic blood pressure.

Table 2. Degree of carotid stenosis in patients with ischemic stroke

Degree of stenosis	N (%)
Mild <50%	20 (62.5%)
Moderate 50-70 %	9 (28.1 %)
Sever > 70%	3 (9.3%)

Table 3. Relation between vascular risk factor and carotid stenosis

Risk factor	No stenosis		Stenosis		P value
	No.	(%)	No.	(%)	
1-HPN					
Yes	21	9.37 %	28	35.93%	0.03
No	11	40.62%	4	14.06%	
Total	32	50%	32	50%	
2-DM					
Yes	11	26.56%	20	25%	0.02
No	21	23.43%	12	25%	
Total	32	50%	32	50%	
3- Smoking					
Yes	8	31.25%	17	29.68%	0.02
No	24	18.75%	15	20.31%	
Total	32	50%	32	50%	
4- Dyslipidemia					
Yes	13	25%	22	20.31%	0.02
No	19	25%	10	29.68%	
Total	32	50%	32	50%	
5- Hyperuricemia					
Yes	10	23.43%	19	21.87%	0.02
No	22	26.56%	13	38.12%	
Total	32	50%	32	50%	

DM, diabetes mellitus; HTN, hypertension.

Table 4. Comparison of CIMT values of patients with presence or absence of different risk factors for ischemic stroke

Risk factors	CIMT (mm) Mean ±SD	P value
1-HPN		
Yes	1.63 ±1.4	0.05 *
NO	0.86 ±0.3	
2- DM		
Yes	1.79±1.7	0.04 *
NO	1.1± 0.5	
3- Smoking		
Yes	1.5 ± 1.5	0.43
NO	1.3 ± 0.6	
4- Dyslipidemia		
Yes	1.6 ± 1.6	0.14
NO	1.2 ± 0.4	
5- Hyperuricemia		
Yes	1.5 ± 1.5	0.55
NO	1.3 ± 0.8	

DM, diabetes mellitus; HTN, hypertension.

Table 5. Correlation between vascular risk factors and size of infarction with carotid stenosis and CIMT

	Carotid stenosis		CIMT	
	r	p	R	p-value
Systolic BP	0.720	0.001**	0.354	0.004**
Diastolic BP	0.593	0.001**	0.254	0.04*
DM	0.405	0.001**	0.297	0.02*
Dyslipidemia	0.400	0.001**	0.289	0.02*
Hyperuricemia	0.308	0.01*	0.201	0.11
Infarction size	0.716	0.001**	0.450	0.001**

BP, blood pressure; DM, diabetes mellitus.

In the current study, the risk factors for stroke affecting CIMT were analysed and it showed that the CIMT was significantly high in hypertensive ($p < 0.05$) and diabetic patients ($p < 0.04$) which demonstrated that there was a significant association between them. Regarding the correlation between vascular risk factors and size of infarction with CIMT and stenosis, we found a highly significant positive correlation between them.

7. Discussion

Stroke had been found to be responsible for More than two-thirds of the global burden in developing countries [13]. Ischemic stroke is a polyetiologic disease with the risk factors includes non-modifiable, modifiable and potentially modifiable risk factors. Well documented risk factors that can be controlled include HTN, DM, AF, dyslipidemia, cigarette smoking, and asymptomatic carotid stenosis [14].

Many different mechanisms can be accused for causing arterial occlusion, including in-situ atherosclerosis with superimposed occluding thrombosis. Consequently, CIMT is considered as one of the non-invasive markers for evaluation of sub-clinical and clinical atherosclerosis. A CIMT more than 1 mm is indicative of atherosclerosis and higher risk of cardiovascular disease [15].

This study presents data on the carotid artery parameters and their relations to the vascular risk factors in ischemic stroke patients.

In the current study, Mean CIMT of our patients group was 1.4 (±0.86) mm, which is almost similar to other Italian study by Cupini et al [16] who reported that mean CIMT in lacunar stroke and non lacunar stroke patient was 0.91 mm and 1.04 mm respectively. Also, Sau et al [17] detected that the CIMT is increased among dyslipidemic group (1.71 ± 0.57 mm) compared to non-dyslipidemic group (0.77 ± 0.10 mm) in patients with type 2 diabetes mellitus.

Other asian studies reported lower CIMT values such as, Sahoo et al [18] (0.792 mm), Mukherjee et al [19] (0.66 mm) and Das et al [14] from India who stated that the mean CIMT was 0.8 mm in ischemic stroke patients which is higher than healthy controls 0.6 mm.

Carotid Doppler examination can help in identification the occlusive lesions in the carotid vessels. Patients with significant stenosis (≥ 70%), are more risky of developing cerebral infarction. In our study, half of our patients (32 patients) have carotid artery stenosis. This was in similar to Hadi et al [10] who found that about 56% of their ischemic patients had carotid artery stenosis. Also, the same percent was showed by Ahmed [20] (44%) and Atif et al [21] (48.5%) of their patients. In 32 patients with stenosis on doppler study, 62.5% had mild stenosis while significant stenosis (>70%) was noted only in 9.3% patients. Wasay et al [22] reported mild stenosis in 78% and severe stenosis in 12% and total occlusion in 1% in a study with 672 patients undergoing bilateral carotid doppler ultrasound. This correlates with Mitchell el al [23] who found that out of 354 cases who had stenosis, 291 (82.20%) cases had mild stenosis (<50%) which was quite large, However, 13.42% female and 17.56% male had severe stenosis (>70%) which was quite low.

In the current study, the risk factors for stroke affecting CIMT were analysed and it showed that the CIMT related to presence of smoking, hypertension, diabetes mellitus and dyslipidemia, but not with hyperuricemia.

Das et al, 2015 [14] with data on 100 subjects indicated that The CIMT was higher among AIS patients who were smokers, hypertensive, diabetic and hypercholesterolemic than non-smokers, normotensive, non-diabetic and normo-cholesterolemic respectively. Sau et al [17] explored that the CIMT is higher among dyslipidemic group (1.71 ± 0.57 mm) compared to non-dyslipidemic group (0.77 ± 0.10 mm) in patients with type 2 diabetes mellitus. They also observed that CIMT has positive correlation with higher blood levels of HbA1C, total cholesterol, triglyceride, LDL-C, VLDL-C and negative correlation with HDL-C.

One of the earlier reports from Van der Meer et al [24], in their The Rotterdam Study (2003) indicated that moderate to severe progression of common CIMT was related to age, male gender, body mass index (BMI), current smoking, and hypertension but not related to lipid levels. Also, Salonen et al [25] showed that among 100 cases with ischemic stroke, the 2 Year progression of CIMT had strong relation with older age, Low density lipoprotein- Cholestrol (LDL-Cholestrol), smoking but not with blood pressure levels and High density lipoprotein-Cholestrol (HDL cholesterol) which is in contrast with our study.

CIMT testing is a non- invasive, not involving radiation, relatively comfort and convenient method with low cost for the patients being examined. CIMT itself may not assume a direct role in ischemic stroke and it tends to be an intermediate factor in the causal pathway between clinical risk factors and stroke.

Regarding the relation between vascular risk factors of ischemic stroke and carotid artery stenosis we found that hypertension showed positive association with carotid artery disease. Among hypertensive patients, we showed that 28 patients had significant carotid artery stenosis (p=0.038). Other risk factors like smoking, diabetes mellitus, dyslipidemia and hyperuricemia also showed positive relation with stenosis of carotid arteries.

Regarding the correlation between vascular risk factors and size of infarction with CIMT and stenosis, we found a highly significant positive correlation between them. This was in accordance with Rashid and Mahmud [26] regarding vascular risk factors and Alagoz et al [27] who stated that larger size of cerebral infarct was positively correlated with the higher degree of stenosis and increased CIMT. This could be attributed to presence of atheromatous plaques and cerebral hypoperfusion that also may lead to more severe strokes [28].

Carotid intima-media thickness (CIMT) is an intermediate predictor for future myocardial infarction and ischemic stroke, and is significantly greater in large artery (atherothrombotic) than small artery ischemic stroke [29].

Like other risk factors, there is emerging evidence that genetics influence on the risk of CIMT. Many candidate genes for carotid IMT had been evaluated in several studies; however, the results have been inconsistent [30,31,32,33]

One systematic review [34] identified more than 140 genetic variants studied as candidates for association with CIMT. The most commonly widely studied genes includes apolipoprotein E (APOE) (ε2/ε3/ε4) [35,36], angiotensin I- converting enzyme (ACE) [37], and 5, 10-methylenetetrahydrofolate reductase (MTHFR) [34].

Other studied selected genes include endothelial nitric oxide synthase (eNOS or NOS 3) gene variants (Glu298-->Asp) [38], Matrix metalloproteinase 3 (MMP3) [31], and interleukin 6. These studied genes are key genes in known candidate pathways for vascular disease. Apolipoprotein E genotype (APOE) is essential for lipoprotein structural integrity and influences cholesterol levels and ischemic heart disease [39]. The ε4 allele is associated with higher cholesterol level and greater CIMT while ε2 allele with lower cholesterol level and CIMT [31-39]. Meta-analysis of 22 published studies showed a significant association between APOE and CIMT [40].

ACE is responsible for conversion of angiotensin I to the vasoconstrictor angiotensin II and also inactivates the vasodilator bradykinin leading to increased vascular tone, vascular smooth muscle growth, neointimal proliferation, and extracellular matrix deposition. Variants associated with higher ACE activity might thus be expected to be related to increased CIMT and plaque formation [31].

Genetic variation in the MTHFR leads to increase in the homocysteine levels and coronary artery disease [41]. Homocysteine increase atherosclerosis risk and thrombosis by enhancing vascular cell proliferation and promoting prothrombotic activity in the vessel wall. MTHFR associations with carotid atherosclerosis have been inconsistent, with several studies [42,43,44,45]

showing no association and others [46,47,48] showing higher IMT.

Controversies in these genetic associations may be attributed to genetic heterogeneity; stratification or confounding of the population; and environment influences modulating expression of an associated genotype.

8. Conclusion

Carotid artery stenosis and CIMT was significantly correlated with the vascular risk factors of ischemic stroke.

List of Abbreviations

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; AIS, Acute ischemic stroke; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CIMT, carotid intima-media thickness; CT, computed tomography; DBP, diastolic blood pressure; DM, diabetes mellitus; EDV, End Diastolic Velocity; GCS, glasgow coma scale; HPN, hypertension; HDL, High density lipoprotein; IMT, intema media thickness; LDL, Low density lipoprotein; PSV, MRI, magnetic resonance imaging; Peak Systolic Velocity; SBP, systolic blood pressure.

Conflict of Interest

The authors declare that they have no competing interests.

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