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Original article

A Comparison between Intracranial and Extracranial Arteries Using Neuroimaging in Acute Ischemic Stroke and Its Relation to Risk Factors

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ABSTRACT

Background: Atherosclerotic infarction accounts for a sizable proportion of cerebral infarcts whether occurs from extracranial or intracranial atherosclerotic disease. Despite recent studies on stroke risk factors; it is still unclear whether or not single risk factor specifically affect extracranial or intracranial arteries in stroke patients.

Aim of the work: To determine the difference between intracranial and extracranial steno-occlusive atherosclerosis and its correlation with risk factors of acute ischemic stroke using Magnetic Resonance Angiogram (MRA) and/or Computed Tomography Angiography (CTA) with Duplex.

Patients and methods: All cases diagnosed as acute ischemic stroke were subjected to detailed history, full neurological examination, routine laboratory tests, extracranial vessels assessed by duplex, intracranial vessels assessed by MRA and/or CTA.

Results: 61 patients included in the study (38 males and 23 females), with mean age (64.5 ± 11.4). Extracranial stenosis was (57 patients, 93.4%), while intracranial stenosis was (49 patients, 80.3%). But the intracranial significant stenosis was (45 patients, 73.77%), while the extracranial significant stenosis (26 patients, 42.62%). Hypertension (72.1%), obesity (62.3%), diabetes (57.4%), dyslipidemia (54.1%) and smoking (39.3%), were risk factors equally affecting the extracranial and the intracranial systems in the same descending order. There was a higher prevalence of hypertension among patients with intracranial significant stenosis showing a significant P-value of 0.048.

Conclusion: Extracranial stenosis was more common than the intracranial stenosis, but the intracranial significant stenosis is more prevalent than the extracranial. Hypertension is a significant risk factor for intracranial significant stenosis.

Keywords: Atherosclerotic infarction; Extracranial; Intracranial; Duplex; Magnetic resonance angiography.

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INTRODUCTION

Stroke is one of the leading causes of death in most countries, and first cause of severe neurologic disability in adults[1]. The World Health Organization mentioned that Ischemic stroke is the most common type of stroke, accounting for approximately 70-80% of all strokes[1].There are 15 million people worldwide who have a stroke annually, 5 million die and another 5 million are left permanently disabled, placing a considerable burden on family and community[2]. Despite recent studies on stroke risk factors; it is still unclear whether or not certain risk factors specifically affect different levels of cerebral arteries in stroke patients[3].

Large ischemic strokes in the anterior circulation are caused by occlusion of one of the major intracranial arteries or their branches[4]. The most common causes of arterial occlusion involving major cerebral arteries are emboli, arising from cardiac sources, atherosclerotic arterial narrowing at the bifurcation of the common carotid artery, or from atheroma in the aortic arch. Occlusion of the middle cerebral artery (MCA) or its branches is the most common type of anterior circulation infarct, accounting for approximately 90% of infarcts and two thirds of all first strokes. On the contrary; occlusion of the anterior cerebral artery (ACA) is uncommon, and it occurred through atheromatous deposits in the proximal segment of the ACA[5].

Atherosclerotic infarction accounts for a sizable proportion of cerebral infarcts. Infarction occurs from extracranial or intracranial athero-sclerotic disease due to flow failure or artery-to-artery embolism. Ethnic differences in stroke risk, types of stroke, and distribution of atherosclerosis in vessels supplying the brain have been described in numerous reports. While it is known that intracranial vessel disease is more common than extracranial vessel disease in African Americans and Chinese than in Caucasian stroke patients[6]. Little is known about the distribution of athero-sclerosis; whether affecting mainly the extracranial or the intracranial carotid artery in Egyptian patients who have had a single ischemic stroke[7].

Several therapeutic strategies, including antiplatelet therapy, statin use, carotid endarterectomy (CEA), and carotid artery stenting (CAS), have been proven to reduce the risk of recurrent stroke in patients with symptomatic extracranial carotid stenosis[8]. In contrast, patients with symptomatic intracranial artery stenosis are still at high risk of stroke recurrence despite medical therapy, including antiplatelet therapy, and risk factor modification[9].

Annual recurrence rates of ischemic stroke were reported to be as high as 15% in the aspirin arm of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial[10] and as high as 12% in the aggressive medical treatment arm of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial[11]. The SAMMPRIS trial also demonstrated that angioplasty and stenting in addition to aggressive medical therapy were significantly inferior in terms of safety and efficacy when compared with aggressive medical therapy alone[9].

AIM OF THE WORK

The aim of this study is to determine the difference between intracranial and extracranial steno-occlusive atherosclerosis and its correlation with risk factors of acute ischemic stroke using MRA and/or CTA with Duplex.

SUBJECTS AND METHODS

The present study is a cross sectional study, during the period from May 2016 to January 2017. The study includes 61 patients, selected from Al-Azhar University Hospitals and Police institution hospitals stroke units, inpatient neurology departments and outpatient's clinics, after obtaining informed consent. The study protocol was approved by the local ethics committee in Al-Azhar neurology department, Cairo, at 3/5/2016, faculty of medicine for boys, Cairo committee at 26/10/2016, and Al-Azhar University committee at 4/10/2016.

The selected patients fulfilled the following inclusion criteria: Age >18 years; Acute ischemic stroke (duration within 48 hours); and First ever stroke.

Exclusion criteria were: Patients with hemorrhagic stroke; Previous old stroke; Cervico-cephalic artery disease other than atherosclerosis (including dissection and cerebral angiitis); and Refusal of the procedure.

All patients were subjected to: 1) Full medical and neurological history including history of associated comorbidities and risk factors. 2) Full neurological and clinical examination: to confirm the diagnosis. 3) Routine Laboratory Work-up: Complete Blood Count (CBC), Random Blood Sugar (RBS), Renal Function Tests (RFTs), Liver Function Tests (LFTs), uric acid (U.A.), Lipid profile, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), International Normalized Ratio (INR) and other labs when indicates. 4) Electro-cardiogram (ECG). 5) Imaging: There are several types of imaging which are described as follows (Computed tomography, echocardiography, magnetic resonance angiography).

Computed Tomography (CT) brain which was done to exclude intracranial hemorrhage or other diseases that could have caused the neurologic deficit. Magnetic Resonance Imaging (MRI) was done to detect accurate site and number of lesions, whether it is caused by anterior or posterior circulation occlusion. Extracranial vessels are estimated by Carotid duplex for estimating the degree of stenosis of the extracranial carotid system & vertebrobasilar study. Extracranial stenosis will be defined by the presence of plaque narrowing the lumen of arteries and by peak systolic velocity (PSV) criteria, and will be classified according to the North American Symptomatic Carotid Endartrectomy (NASCET) Trial criteria as low degree stenosis (less than 50%), moderate stenosis (50-69%) severe stenosis (70-99%) or total occlusion (100%). Intracranial arteries are estimated by MRA and/or CTA, NASCET criteria were used for stenosis calculations [12]: $[(D_n - D_s)/D_n] \times 100$, where Dn is normal diameter and Ds is stenosed diameter. NASCET stenoses were grouped according to the following grading scale: normal (0–9%), mild (10–29%), moderate (30–69%), severe (70–99%), or occluded (no flow detected).

Statistical Analysis: Data were collected, revised, coded and entered to the Statistical Package for Social Science (SPSS) of International Business Machines (IBM) version 20. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric and qualitative data were presented as number and percentages. Comparison between groups with qualitative data were done by using Chi-square test and/or Fisher exact test only when the expected count found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value < 0.05 was considered significant.

RESULTS

The patient population included in this study comprised of 61 patients, collected between May 2016, to January 2017, confirmed acute ischemic stroke underwent duplex carotid ultrasound and MRA/and or CTA. The distribution of patients per gender are 38 (62.3%) males and 23 (37.7%) females, with an age range from 25 to 87 years, with a mean age of 64.5 years $\pm$ 11.4, and fifty-Four patients (90%) were right-handed.

There are 57 patients (93.4%) showed extracranial findings by duplex carotid, 30 patients (49.1%) showed mild stenosis, 10 patients (16.3%) showed moderate stenosis, 8 patients (13.1%) showed severe stenosis while 9 patients (14.7%) showed totally occluded vessels. Extracranial carotid system affection (45 patients 78.9%) was more common than vertebral system affection (2 patients 3.5%), while both systems affection were (10 patients 17.5%). The most common extracranial site of affection was the Internal Carotid Artery (ICA) followed by the Cervical Carotid Artery (CCA) bifurcation.

There are 49 patients (80.3%) showed intracranial findings by MRA and/or CTA, 4 patients (6.5%) showed mild stenosis, 7 patients (11.4%) showed moderate stenosis, 10 patients (16.3%) showed severe stenosis while 28 patients (45.9%) showed totally occluded vessels. The most common intracranial site of affection was the MCA (36.7%) followed by ICA (30.6%) then the basilar and PCA equally affected (20.4%).

Atherosclerosis affects the anterior circulation (18 patients) more than the posterior circulation (4 patients), but both circulations is most commonly seen type (37 patients).

Stroke is more commonly occur in the anterior circulation (41 patients 67.2%) than the posterior circulation (13 patients 21.3%), while, the left

hemisphere (29 patients 47.5%) is more commonly affected by stroke than the right hemisphere (18 patients 29.5%).

Facial nerve is the commonest cranial nerve affected in stroke (75.4%) followed by the trigeminal nerve (9.8%) then the hypoglossal nerve (6.6%). Hemiparesis is the commonest presentation of stroke followed by altered sensorium and slurring of speech. Hypertension (72.1%), obesity (62.3%) and diabetes (57.4%) were the most common modifiable risk factors among patients in our study, followed by dyslipidemia (54.1%), smoking (39.3%) and heart diseases (32.8%). These risk factors equally affecting the extracranial and the intracranial systems in the same descending order, reaching that there are multiplicity of risk factors contributing to the atherosclerotic stenotic process.

Extracranial stenosis (57 patients, 93.4%) was more common than the intracranial stenosis (49 patients, 80.3%). But if we compare the extracranial significant stenosis (>50% stenosis), with the intracranial significant stenosis (moderate stenosis or more), we found that intracranial significant stenosis (45 patients, 73.77%) was more common than extracranial significant stenosis (26 patients, 42.62%), also we found a higher prevalence of hypertension among patients with intracranial stenosis (32 patients), than extracranial stenosis (18 patient), showing a significant P-value of 0.048.

Table [1.a]: A comparison between the extracranial group of significant stenosis ≥50%, and the intracranial group of moderate stenosis or more

Factors of Comparison		Extracranial = 26	Intracranial = 45	X^2	P-value
Gender	Female	12	18	0.256	0.613
	Male	14	27		
Age	<45	1	2	0.009	0.973
	45-46	11	20		
	<65	14	23		
HTN		18	32	3.92	0.048
DM		14	23	0.61	0.435
Pre-Diabetic		1	4		
Smoking		12	22	2.941	0.086

Table [1.b]: A comparison between the extracranial group of significant stenosis ≥50%, and the intracranial group of moderate stenosis or more

Factors of Comparison		Extracranial = 26	Intracranial = 45	X^2	P-value
DLP	Chol	**8**	**14**		**0.969**
	TG	**2**	**3**	**0**	
Obesity	Underweight	**3**	**3**		
	Normal	**11**	**16**		
	Overweight	**11**	**23**	**1.16**	**0.763**
	Obese	**1**	**3**		
Uric Acid		**8**	**12**	**0.8**	**0.371**
IHD		**4**	**8**	**1.333**	**0.248**
AF		**2**	**6**	**2**	**0.157**
TIAs	Ant	**0**	**1**	**1.143**	**0.285**
	Post	**4**	**3**		
Others		**7**	**13**	**1.8**	**0.18**

* HTN = Hypertension, DM = Diabetes Mellitus, DLP = Dyslipidemia, TG = Triglycerides, IHD = Ischemic Heart Disease, AF = Atrial Fibrillation, TIA = Transient Ischemic Attack (in table 1.a, 1.b).

DISCUSSION

In our study, we found that the mean age of occurrence of stroke was (64.5 ± 11.4) years, and stroke was more common in males, 38 (62.3%) of them were males, while 23 (37.7%) were females. These results were in agreement with previous studies[13,14].

Age is indeed the most important risk factor for all stroke types. This is in agreement with most studies of stroke, which concluded that age has been identified as a marker of risk for stroke[15]. We found that the mean age of the patients who had extracranial carotid stenosis was slightly higher than the mean age of those with isolated intracranial disease, corresponding to Dawber[16]. This might

suggest that extracranial stenosis represents a more advanced atherosclerotic process[14].

The majority of patients included in our study presented with hemiparesis, altered sensorium and slurring of speech as the most common associated neurological deficits. These findings are partially consistent to previous studies done in Egypt [13,14].

Also is in agreement with Siddique et al.[17] and Omkar Prasad et al.[18], hypertension (72.1%), obesity (62.3%) and diabetes (57.4%) were the most common modifiable risk factors among patients in our study, followed by dyslipidemia (54.1%), smoking (39.3%) and heart diseases (32.8%), which is partially agree with previous studies that found hypertension to be the commonest risk factor for stroke[19].

Similarly, **Al-Rajeh** et al.[15] reported that the significant risk factors for stroke among Saudi population are hypertension followed by diabetes mellitus, heart disease, and smoking.

Alemayehu and Birhanesilasie [21] has shown smoking (61%) and hypertension (60%) to be the most common risk factors for stroke among patients admitted to Nepal Medical College.

Control of hypertension has been shown to reduce the stroke incidence with achievement of 42% relative risk reduction [22, 23]. It has been shown that cigarette smoking causes 10% of occlusive stroke[24].

Niyar et al. in general population observational study[23], have shown a dose-response relationship between cigarette smoking and stroke. Ex-smokers were found to have stroke rates similar to patients who had never smoked. Sedentary lifestyle is a risk factor for atherosclerosis[26].

Diabetic patients are at increased risk for all forms of ischemic stroke and are more likely to have hypertension and hyperlipidemia [23]. Whether or not tight control of blood sugar on patients with diabetes reduces stroke risk is, however, uncertain[24]. Patients with diabetes are two to three times more likely to have ischemic stroke when compared with nondiabetic individuals [28]. Diabetes mellitus was associated with 26.25% of ischemic stroke [29].

Observational studies suggest that higher total and low-density lipoprotein cholesterol levels are associated with a greater risk of ischemic stroke [24]. Our study showed presence of hypercholesterolemia in 32.8%, high triglycerides in 4.9%, and having both of high cholesterol and triglycerides in 16.4% of our patients.

Heart diseases are considered a risk factor for stroke. Twelve of our patients had ischemic heart disease with eight patients having atrial fibrillation. Atrial fibrillation is arguably the most important cardiac risk factor for stroke [29].

The risk of stroke in the average patient with non-rheumatic atrial fibrillation is approximately 5% a year, and patients with valvular atrial fibrillation have 17-fold higher risk of acquiring stroke [24]. Family history of stroke and previous history of TIA were present in few patients. Robert and Zamzami[30] found positive family history of stroke in 14% of stroke patients in Saudi Arabia. In the current study, a lower rate (1.63%) was recorded, which can be attributed to lower level of consanguinity among Egyptians compared to Saudi Arabian population.

The most common stenotic part affected extracranially, was the ICA [Left (LT) > Right (RT)], then the CCA bifurcation. While the most common occluded site extracranially was the LT ICA (88.8%). The most common site of extracranial stenosis was ICA, supported by **Suwanwela NC, Chutinetr** [31]. The cervical segment of the internal carotid artery (C1 segment) was the most commonly involved one.

Out of the 49 patients having intracranial findings, 4 (6.55%) patients had mild stenosis, 7 (11.4%) patients had moderate stenosis, 10 (16.3%) had severe stenosis, 28 (45.9%) patients had total occlusion. The most common site of intracranial stenosis, was the MCA (36.7%) supported by Ku et al. [32]. Then, the intracranial part of ICA (30.6%), followed by the basilar and PCA equally affected (20.4%).

The most commonly affected segment in each artery was as follows: In MCA, the M2 segment was the most commonly affected segment followed by M1 = M3. In ICA, its origin (extracranial part) was the most commonly affected part, followed by the supra-clinoid segment (intracranial part). Regarding

the basilar artery, the mid-basilar segment then the distal part, while the proximal part is the least commonly affected segment. While PCA, the P1 segment followed by the P2 segment. Regarding the ACA, the A1 segment was the most commonly affected segment.

In this study the M2 segment of the MCA is the most affected segment in contrast to thesis study referred in Ahmed [14] where the horizontal segment of the middle cerebral artery (M1 segment) was the most commonly involved one. Anterior circulation stroke was in 41 patients (67.2%), 13 patients (21.3%) stroke occurred at posterior circulation. The Left hemispheric stroke 29 patients (47.5%) was more prevalent than right hemispheric stroke 18 (29.5%), while stroke occurring bilaterally in 14 patients (23%).

Hypertension, obesity, diabetes mellitus, dyslipidemia and smoking were risk factors equally affecting the extracranial and the intracranial systems in the same descending order, reaching that there are multiplicity of risk factors contributing to the atherosclerotic stenotic process. In contrast to thesis study referred in Ahmed[14] where there was a higher prevalence of smoking among patients with extracranial internal carotid stenosis.

It has already been indicated that the extracranial atherosclerotic lesions tended to coexist in patients with coronary heart disease and were commonly associated with hypercholesterol-emia [33].

These reports are not consistent with our results. In our study, extracranial stenosis (57 patients, 93.4%) was more common than intracranial stenosis (49 patients, 80.3%). This was in agreement with the studies conducted in the white population Mazighi et al. [34] and Iranian population Wityk et al. [35] where extracranial stenosis (58% and 57% respectively) was more common than intracranial stenosis (42% and 43% respectively).

But if we compare the extracranial significant stenosis (>50% stenosis), with the intracranial significant stenosis (moderate stenosis or more), we found that intracranial significant stenosis (45 patients, 73.77%) was more common than extracranial significant stenosis (26 patients, 42.62%), also we found a higher prevalence of hypertension among patients with intracranial stenosis (32 patients), than extracranial stenosis (18 patient), showing a significant P-value of 0.048. these results supported by previous studies[36,37].

This was in agreement with the studies conducted in the South Korean Population (52% intracranial and 48% extracranial stenosis). Felberg et al.[38] showed (52% intracranial stenosis and 48% extracranial stenosis).

The high prevalence of extracranial stenosis maybe is due to the easily accessible duplex ultrasound as a part of the initial investigations in stroke & due to its limitation in examining the intracranial vasculature. Hence, the Egyptian patients don't reach the advanced level of investigations that is required to assess the intracranial vessels post stroke.

Finally, there are no universally accepted criteria for grading intracranial artery stenosis, and this somewhat limit interpretation of the comparison between prevalence of intracranial stenosis in our study and prior studies on this topic.

Conclusion

No single risk factor could be attributed to atherosclerotic extracranial or intracranial stenosis, so the combination of risk factors is the main contributor in the stenosis. Extracranial stenosis is more common than the intracranial stenosis.

Financial and Conflict of interest disclosure

Authors declare that there was no conflict of interest.

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