

BURDEN OF CAROTID ARTERY DISEASE IN ISCHEMIC STROKE PATIENTS WITH AND WITHOUT DIABETES MELLITUS

Saeed Arif, Khurram Haq Nawaz, Asif Hashmat, Wasim Alamgir, Wasim Wali Muhammad

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the burden of carotid artery disease among the patients of ischemic stroke and to analyze the relationship of associated socio demographic factors including the diabetes mellitus (DM).

Study Design: Cross sectional analytical study.

Place and Duration of Study: Pak Emirates Military Hospital Rawalpindi, from 10th May 2017 to 10th Nov 2017.

Material and Methods: The sample population comprised of 190 patients of ischemic stroke presenting at a tertiary care hospital in Rawalpindi, Pakistan. CT-scan brain was performed to confirm the presence of acute ischemic stroke. Ultrasound Doppler was done by a consultant radiologist to assess the presence of clinically significant carotid artery stenosis. Relationship of age, gender, diabetes mellitus and duration of disease, education status, dyslipidemias and tobacco smoking was assessed with the presence of carotid artery stenosis among the patients of ischemic stroke.

Results: Out of 190 patients of stroke assessed through ultrasound doppler, 53.7% showed the presence of significant carotid artery stenosis while 46.3% had no clinically significant stenosis. Hundred patients were suffering from DM. After applying the logistic regression we found that presence of DM and long duration of DM had significant association with the presence of carotid artery stenosis among the patients of ischemic stroke.

Conclusion: This study showed a high frequency of carotid artery stenosis among the patients of ischemic stroke in Pakistan. Special attention should be paid to the patients who have been suffering from a metabolic disorder like DM. Long duration of DM also emerged as independent risk factor for carotid artery stenosis in our study population.

Keywords: Carotid artery stenosis, Diabetes mellitus, Ischemic stroke.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Cerebrovascular diseases are a common cause of hospital admissions in a developing country like ours¹. Stroke is one of the major cerebrovascular disease which is highly prevalent in all parts of the world^{2,3}. Stroke has been associated with diseases including diabetes mellitus (DM), hypertension, IHD and vasculopathies^{4,5}.

Carotid artery stenosis has been a common finding with increasing age and metabolic diseases^{6,7}. Senile degenerative changes and many metabolic, endocrine and autoimmune disorders can cause narrowing of these major arteries⁵⁻⁸. Carotid artery stenosis has been linked

with various adverse cardiovascular events in the studies done in the past^{7,9}.

Previous research highlights the presence of carotid artery disease among the patients suffering from ischemic stroke. Fleherly *et al.* concluded that atherosclerosis of large vessels like carotid artery is a common cause of ischemic stroke¹⁰. Majority of the patients with carotid artery stenosis had ischemic stroke and post stroke complications in a study done in the China¹¹. Another large study done in Korea showed the high prevalence of ischemic stroke among the patients with type II DM and carotid artery disease¹². Metabolic abnormalities leading to vasculopathies causing the adverse cerebrovascular events is a widely discussed phenomenon nowadays. The emphasis in the modern world is on primary prevention of disorders which will further prevent disability and reduce

Correspondence: Dr Saeed Arif, Resident Neurologist, Pak Emirates Military Hospital Rawalpindi Pakistan
Email: drsaeedarif@gmail.com
Received: 08 Aug 2018; revised received: 28 Sep 2018; accepted: 28 Sep 2018

the burden not only on patients his family and also on the health care system^{12,13}.

The mechanism by which metabolic disease like DM causes the carotid artery stenosis leading to cerebrovascular adverse events is complex and multidimensional. Hypothesis of reactive oxygen species have been widely accepted as cause of atherosclerosis in all the major vessels including the carotid arteries. Plaque formed as a result of this atherosclerotic process causes hemodynamic effects leading to to area reduction and a complicated structure and surface eventually creating emboli or occlusion leading to the phenomenon of ischemia and ultimately stroke¹⁴.

Multiple risk factors have been found associated with the carotid artery stenosis among the patients of DM suffering from stroke. Some of these include increasing age, gender, BMI, dyslipidemias, vessel size and other co-morbid diseases like hypertension and ischemic heart disease^{12,13}.

This study was planned with the purpose to determine the burden of carotid artery disease among the patients of ischemic stroke and to analyze the relationship of associated socio demographic factors including the DM.

PATIENTS AND METHODS

This cross sectional analytical study was conducted at the neurology department of a tertiary care hospital of Rawalpindi between May-November 2017. Screening was performed on all the patients of acute ischemic stroke confirmed on CT-scan or MRI brain as advised by the treating neurologist. Sample size was calculated by using the WHO calculator. Consecutive sampling was done. Ultrasound doppler was performed by a consultant radiologist to look for the presence of significant carotid artery stenosis. Exclusion criteria were the patients less than 40 years or more than 80 years of age or those who did not consent to or those with a past or current history of myocardial infarction or valvular heart disease or with a past or current history of irradiation. Patients who had cancer or had past

history of brain damage due to any other medical, neurological or autoimmune illness or had a hemorrhagic stroke or were not ready to undergo doppler ultrasound were also excluded.

Carotid Artery Stenosis: Clinically significant stenosis varies from study to study but a consensus exists on the range of 50-70% occlusion or above. Less than 50% occlusion is not usually considered significant. Ultrasound doppler technique has been used by a consultant radiologist to measure this parameter precisely^{15,17}.

Ethical approval for the study was obtained from the ethical review board committee of the Military Hospital Rawalpindi. Patients were provided with a detailed description of the study and were inducted into the study after written informed consent. Doppler ultrasound was performed by a consultant radiologist to look for the clinically significant stenosis among these patients of ischemic stroke. Variables in the study included age, gender, presence of DM, duration of DM, education, presence of dyslipidemias and tobacco smoking. Dyslipidemia was defined as the presence of any one of the following high density lipoprotein <40 mg/dl, low-density lipoprotein >130 mg/dl. A history of tobacco smoking was obtained.

The diagnosis of diabetes was based on the plasma glucose criteria, defined as either (i) a fasting plasma glucose level of ≥ 126 mg/dL, (ii) a 2 hour plasma glucose level of ≥ 200 mg/dL after a 75g oral glucose tolerance test, or (iii) a glycosylated hemoglobin level of $\geq 6.5\%$. Duration of DM was classified as <5 years or >5 years. The socio demographic data of the study was entered in a structured performa specially designed for the study.

Characteristics of participants and the distribution of the carotid artery stenosis were described by using the descriptive statistics. Chi-square was used to determine the association. Binary logistic regression analysis was done to evaluate the relationship of age, gender, presence of DM, duration of DM, education, presence of

dyslipidemias and tobacco smoking with the presence of clinically significant carotid artery stenosis. All statistical analysis was performed using SPSS-23. Differences between groups were considered significant if p -values were ≤ 0.05 .

RESULTS

A total of 209 patients of ischemic stroke were enrolled to participate in the study¹⁰. Some patients refused participation or were unable to

the presence of clinically significant stenosis. Mean age of the patients was 66.8 ± 5.963 yrs. Out of 190, 99 (52%) were females and 91 (48%) were male patients. 53.7% showed the presence of clinically significant carotid artery stenosis, while 46.3% had no significant stenosis of the carotid arteries. Hundred patients were suffering from DM. Table-I shows the distribution of the patients with respect to the presence of the clinically significant stenosis. Presence and long duration

Table-I: Characteristics of the study group and their BCC-CI scores.

Socio demographic factors	No Significant carotid artery stenosis (<50% narrowing) n (%)	Clinically significant carotid artery stenosis (50-70% narrowing) n (%)	p -value
Total	88 (46.3)	102 (53.7)	
Age			
55 year or less	71 (80.7)	81 (79.4)	0.827
>55	17 (19.3)	21 (20.6)	
Gender			
Male	41 (46.6)	50 (49.1)	0.738
Female	47 (53.4)	52 (50.9)	
Diabetes Mellitus			
Absent	58 (65.9)	32 (31.3)	<0.001
Present	30 (34.1)	70 (68.7)	
Duration of DM			
<05 years	63 (71.6)	54 (52.9)	0.008
5 years or more	25 (28.4)	48 (47.1)	
Education			
< 10 years	31 (35.2)	43 (42.1)	0.329
10 years or more	57 (64.8)	59 (57.9)	
Dyslipidemias			
No	54 (61.4)	65 (63.7)	0.737
Yes	34 (38.6)	37 (36.3)	
Smoking			
Non Smoker	66 (75)	83 (81.4)	0.287
Smoker	22 (25)	19 (18.6)	

go for the doppler ultrasound and 9 were ineligible due to exclusion criteria (5 gave history of recent myocardial infarction, 2 had autoimmune disease with positive autoimmune profile, 1 was pregnant and 1 had papillary carcinoma of thyroid gland). After excluding all these patients 190 participants were left behind who underwent the doppler ultrasound to assess

of DM had significant association with carotid artery stenosis when chi-square was applied (table-I). Table-II shows that presence of DM and longer duration of this metabolic disease were strongly associated with the presence of carotid artery stenosis when regression analysis was done.

DISCUSSION

Our study showed the understanding of physical and biochemical factors among the patients of stroke in order to relate the pathway which lead to this devastating illness. Biochemical disturbances faced by the diabetics may have lead to accelerated process of atherosclerosis which might have narrowed the carotid arteries and lead to the ischemic stroke. Using the doppler ultrasound we found that more than 53% of our sample population showed the presence of clinically significant carotid artery stenosis. This is similar to the other studies done on stroke patients locally and abroad^{10,12,16}. Diabetics are at a risk of various metabolic,

stroke^{10,18}. Therefore timely screening and treatment of this aspect may prevent the stroke and all the disability and mortality related to it.

Various studies in the past showed the association of DM with carotid artery stenosis among the patients of ischemic stroke^{7,13}. Results in our study also showed strong association of this metabolic disorder with the carotid artery stenosis. This poses a big challenge on our primary care system to reduce the burden of neurologist and other tertiary care departments by controlling diabetes effectively.

Smoking and hyperlipidemias were not related to carotid artery stenosis in our study

Table-II: The correlated factors relating to carotid artery stenosis: the binary logistic regression.

	B	p-value	OR (95% CI)
Age (ref. is 60 years or less)	-0.216	0.567	0.806 (0.384-1.689)
Gender (ref. is male)	-0.401	0.153	0.670 (0.386-1.160)
DM (ref. is no DM)	1.067	0.000	0.603 (0.294-1.238)
Duration of DM (ref. is <05 years)	-0.665	0.074	0.514 (0.248-1.067)
Smoking (ref. is non smoker)	0.461	0.141	1.586 (0.858-2.930)
Education (ref. is 10 years or above)	0.303	0.341	1.354 (0.726-2.525)
Dyslipidemias (ref. is no dyslipidemia)	-0.421	0.188	0.657 (0.351-1.228)

physical and psychological complications which make many variables confounding so that their exact association with the understudied phenomenon cannot be well established.

Some of the factors that might accelerate the process of carotids artery stenosis have been reported as long duration of diabetes, poorly controlled diabetes, increasing age and female gender⁵. Other co-morbidities like hypertension or dyslipidemias may also contribute to this phenomenon directly or indirectly^{12,13}.

Occurrence of stroke in an individual is a multi dimensional phenomenon with genetic, physical, neurological and physiological dimensions. Abnormalities in any one or more of these dimensions in one way or the other may lead to stroke. Alteration in biochemical profile of the body that may occur in DM, dyslipidemias, CRF, CLD etc may lead to enhancement of the atherosclerotic phenomenon causing the blockade of major vessels leading to various kinds of cerebrovascular accidents including

population. These findings were contrary to the findings reported in the literature worldwide¹². Studies involving more patients and sensitive tests may change this association but current findings of our study do not hold this association.

Longer duration of DM was strongly associated with presence of clinically significant carotid artery stenosis in our study. Noh *et al.* produced similar results in a recent study done in korea¹². Even if controlled; DM poses the individuals towards certain damages involving various organs. Vasculopathy remains one of those. More good control and life style modifications may improve this phenomenon but special attention is required by the patients with long standing DM.

Our study has few limitations as well. Randomized selection of study subjects from all the stroke patients was not done. Therefore, the results of the present study cannot be generalized. We used the cross-sectional study method. Therefore, the cause and effect

relationships remain unclear and further studies to look into these associations using longitudinal epidemiological data are suggested. Doppler ultrasound is a user dependent tool in which there is always a chance of over or under reporting of the finding. Severity of carotid artery disease was not assessed and made part of the analysis. Therefore longitudinal studies involving more sample size and sophisticated study design are suggested to ascertain the association between carotid artery stenosis, ischemic stroke and DM.

CONCLUSION

This study showed a high frequency of carotid artery stenosis among the patients of ischemic stroke in Pakistan. Special attention should be paid to the patients who have been suffering from a metabolic disorder like DM. Long duration of DM also emerged as independent risk factor for carotid artery stenosis in our study population.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Wasay M, Zaidi S, Jooma R. Non communicable diseases in Pakistan: burden, challenges and way forward for health care authorities. *J Pak Med Assoc* 2014; 64(11): 1218-19.
2. Khan MI, Khan JI, Ahmed SI, Haq U. The epidemiology of stroke in a developing country (Pakistan). *J Neurol Stroke* 2018; 8(1): 00275.
3. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in south, east, and south-east asia: A Review. *J Stroke* 2017; 19(3): 286-94.
4. Saengsuwan J, Suangpho P, Tiamkao S. Knowledge of stroke risk factors and warning signs in patients with recurrent stroke or recurrent transient ischaemic attack in Thailand. *Neurol Res Intl* 2017; 2017: 8215726.
5. Gurol ME, Kim JS. Advances in stroke prevention in 2018. *J Stroke* 2018; 20(2): 143-44.
6. Howard G, Roubin GS, Jansen O. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: A meta-analysis of pooled patient data from four randomised trials. *Lancet* 2016; 387(10025): 1305-11.
7. Noh M, Kwon H, Jung CH, Kwon SU, Kim MS, Lee WJ et al. Impact of diabetes duration and degree of carotid artery stenosis on major adverse cardiovascular events: A single-center, retrospective, observational cohort study. *Cardiovascular Diabet* 2017; 16(1): 74-83.
8. Prasad K. Pathophysiology and medical treatment of carotid artery stenosis. *Intl Coll Angiol* 2015; 24(3): 158-72.
9. Qaja E, Bhimji SS. Carotid artery stenosis. [Updated 2017 Jun 24]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2018 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK442025/>
10. Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D et al. Carotid artery stenosis as a cause of stroke. *Neuro-epidemiology* 2013; 40(1): 36-41.
11. Li X, Ma X, Lin J, He X, Tian F, Kong D. Severe carotid artery stenosis evaluated by ultrasound is associated with post stroke vascular cognitive impairment. *Brain Behav* 2017; 7(1): e00606.
12. Noh M, Kwon H, Jung CH, Kwon SU, Kim MS, Lee WJ, et al. Impact of diabetes duration and degree of carotid artery stenosis on major adverse cardiovascular events: A single-center, retrospective, observational cohort study. *Cardiovasc Diabetol* 2017; 16(1): 74-82.
13. Sun B, Li X, Liu X, Ge X, Lu Q, Zhao X et al. Association between carotid plaque characteristics and acute cerebral infarction determined by MRI in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2017; 16(1): 111-20.
14. Prasad K. Pathophysiology and medical treatment of carotid artery stenosis. *Int J Angiol* 2015; 24(3): 158-72.
15. Wasay M, Azeemuddin M, Masroor I. Frequency and outcome of carotid atheromatous disease in patients with stroke in Pakistan. *Stroke* 2009; 40(3): 708-12.
16. Afridi A, Afridi Z, Afridi F, Afridi A. Frequency of carotid artery stenosis in ischemic stroke patients. *J Med Sci* 2017; 25(3): 340-43.
17. Evans NS. Carotid artery stenosis. Disease mangament, the cleaveland clinic foundation. 2016.
18. Sun B, Zhao H, Liu X, Lu Q, Zhao X, Pu J et al. Elevated hemoglobin A1c is associated with carotid plaque vulnerability: Novel findings from magnetic resonance imaging study in hypertensive stroke patients. *Sci Rep* 2016; 6: 33246-254.