ORIGINAL ARTICLE

Ischaemic stroke and peripheral artery disease

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Abstract

Objective: To determine the frequency of atherosclerosis by ankle brachial index in patients with an ischaemic stroke and to assess the association of carotid artery stenosis and ankle brachial index in ischaemic stroke.

Methods: This cross-sectional study was conducted at Abbasi Shaheed Hospital, Karachi, from July 2011 to May 2014, and comprised patients with ischaemic stroke. The patients were classified according to the Asian stroke criteria for classification of brain infarction. Primary outcome measures included carotid artery stenosis and ankle brachial index. The other independent variables were age, gender, body mass index and waist circumference. SPSS 20 was used for data analysis.

Results: A total of 327 patients were enrolled. The overall mean age was 57.6±12.8 years. Besides, 168(51.3%) participants were males. Peripheral artery disease was found in 60(18.3%) patients. Mild carotid artery stenosis was found in 182(55.6%) patients, moderate in 140(42.8%), severe in 3(0.9%) and complete occlusion in 2(0.6%) patients. In patients having mild carotid artery stenosis, 32(17.5%) had peripheral artery disease, whereas in patients with moderate carotid artery stenosis, 25(17.8%) had peripheral artery disease.

Conclusion: Abnormally low ankle brachial index suggesting subclinical peripheral artery disease was 18%.

Keywords: Ischaemic stroke, Peripheral artery disease, Ankle brachial index, Carotid artery stenosis. (JPMA 67: 1138; 2017)

Introduction

Peripheral artery disease (PAD) comprises atherosclerosis of abdominal aorta, iliac and lower extremity artery is an under diagnosed, undertreated and poorly understood entity which is much more common than previously thought.[1] Patients with PAD experience many problems such as claudication, ischaemic rest pain, ischaemic ulcerations, repeated hospitalisations, revascularisations, and limb loss.[1] This leads to poor quality of life and a high rate of depression.[1] They also have a greater likelihood of experiencing a myocardial infarction (MI), stroke and cardiovascular death, and have a higher rate of all-cause mortality compared with the patients without PAD.[1] Approximately 12% of the adult population has PAD, and the prevalence is equal in men and women.[1] Almost 20% of adults older than 70 years of age have PAD.[1] The most common risk factors associated with PAD are increasing age, diabetes, and smoking.[1] The prevalence of PAD was seen to be 4.3% in patients aged more than 40 years compared with 14.5% in those older than 70 years.[1]

Of all the non-invasive methods for the diagnosis of PAD, the ankle brachial index (ABI), segmental analysis and pulse volume waveform analysis are the only techniques that provide physiologic information about perfusion in the limb. The ABI is an assessment of PAD and an indicator of generalised atherosclerosis.[2-4] A low ABI is associated with increased mortality and risk of MI and stroke in the general population, independent of conventional vascular risk factors and prevalent cardiovascular disease.[2-4] Recent evidence suggests that measurement of the ABI may improve the accuracy of cardiovascular risk prediction beyond traditional risk factors in the general population.[2,3] In patients with ischaemic stroke or transient ischaemic attack (TIA), co-existing symptomatic PAD is a powerful predictor of long-term cardiovascular risk and mortality.[2] Yet the prognostic value of low ABI, which is also a highly specific and sensitive test for asymptomatic PAD, has not been established in the population. Two studies reported a high prevalence of low ABI among patients with acute ischaemic stroke or TIA, ranging from 34%[2,5] to 51%.[2,6]

Duplex ultrasonography is a safe (no radiation or contrast agent) and cost-effective method of accurately determining the severity and location of stenosis and differentiating stenosis from occlusion.[1] B-mode or gray-scale imaging is a 2-dimensional image of the artery wall and the lumen, permitting a rough evaluation of the lesion and atheroma characteristics. Colour flow Doppler and pulsed wave Doppler allow an estimation of the stenosis severity on the basis of Doppler-derived velocity criteria.[1] Carotid artery stenosis (CAS) is defined as narrowing of the common and internal carotid arteries. Between 5% and10% of the general population aged over 65 years has an asymptomatic CAS of 50% or greater.[7] The prevalence of asymptomatic CAS 50% or greater was highest in patients with PAD. The degree of asymptomatic CAS is related to various vascular risk factors, including age, smoking,

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systolic blood pressure, and cholesterol.[7] A higher degree of asymptomatic CAS was predictive for future stroke in patients with large or small vessel atherosclerotic disease.[7,8]

This study was conducted to determine the ABI in patients with acute ischaemic stroke and its association with CAS. ABI and CAS are strong predictors of PAD, which predicts the vascular risk, morbidity and mortality. This will help us in strengthening primary and secondary prevention in patients of acute ischaemic stroke with PAD.

Patients and Methods

This cross-sectional study was conducted in the neurology section, department of medicine, Abbasi Shaheed Hospital, Karachi Medical and Dental College, Karachi, from July 2011 to May 2014. All patients with ischaemic stroke aged 15 years or above of either gender were included. Patients with an intracranial bleed or a sub-arachnoid haemorrhage and with end-stage renal disease (ESRD) were excluded.

After a detailed history and a complete systemic examination, all patients included underwent the following investigations: urea creatinine electrolytes (to exclude patients with ESRD), electrocardiogram, and computed tomography (CT) of brain without contrast (to exclude patients with intracranial or sub-arachnoid haemorrhage), carotid Doppler ultrasound, and ankle brachial index. The following investigations were completed according to the patient's requirement: echocardiogram, CT, angiography, etc.

Ankle and brachial systolic blood pressures were measured at baseline with a mercury sphygmomanometer and a high-frequency linear 7 MHz probe (Toshiba Xario) with the subject in the supine position after a five-minute rest. According to the American Heart Association's (AHA) recommendations,[2] the ABI was calculated as the ratio of the higher of the systolic pressures in the posterior tibial or dorsalis pedis artery and average of the right and left brachial artery pressures (in the case of discrepancy of >10 mm Hg between the arms, the higher reading was used). This method has been shown to result in the most accurate estimation of peripheral artery disease. ABI was calculated separately for each leg, and the lower of the two ABI values was used for analysis. In accordance with the transatlantic intersociety consensus for the management of peripheral artery disease[2] and previous studies in patients with stroke, ABI values of <0.9 were defined as low. Patients were diagnosed and labelled as having PAD if the ABI was <0.9.

Ultrasound examinations were performed by well-trained and certified ultrasonologists at the department of radiology. The degree of the CAS at both sides was assessed with colour Doppler-assisted duplex scanning. The severity of CAS was evaluated on the basis of the blood flow velocity patterns. The greatest stenosis observed on the right or the left side of the common or the internal carotid artery was taken to determine the severity of carotid artery disease. Accordingly, all patients were classified into one of the following categories: absence of stenosis; mild stenosis (<50% diameter stenosis), moderate stenosis (>50% to 69% diameter stenosis), severe stenosis (>70% to 99% diameter stenosis) and occlusion (100% diameter stenosis, no flow).[7] North American Symptomatic Carotid Endarterectomy Trial(NASCET) and European Carotid Surgery Trial(ECST) are the international criteria used for symptomatic CAS.[8] However, the above criteria are for asymptomatic carotid artery stenosis. Stroke patients were classified as stated by the Asian Stroke Criteria (ASC) for classification of brain infarction (Table-1).[9]

The primary outcome measures were carotid artery stenosis and ankle-brachial index. The other independent variables were age (which was estimated by national identity card; if the national identity card was not available then it was estimated through major events of the world like the Second World War or freedom of Pakistan), gender, body mass index ([BMI] is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2). Normal range in adult Asian population is 18-22.9, overweight is 23-26.9 and obesity is >27), waist circumference, as stated by International Diabetes Federation, was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Specific values for females >80cm and for males >90cm were defined as central obesity.[10]

The patients were followed up on phone after six months of presenting to the hospital. The outcome variables were death or mortality, morbidity, or complete recovery.

Statistical analysis was performed using SPSS 20. Data was expressed as mean, standard deviation (SD), odds ratio (OR) and 95% confidence interval (CI) or as proportions. The association between the independent factors and outcome i.e. ABI for a categorical response variable with two outcomes was assessed initially employing binary logistic regression (one independent variable being analysed for a single-dependent variable with categorical response of two outcomes). Following this, a parsimonious model was developed using multivariable regression (more than one independent variable being analysed for a single-dependent variable) to select, from the identified candidate variables, a subset of variables that were independently associated with ABI. The odds

ratios and associated 95 per cent confidence intervals for variables in the final model were reported. The significance level for the binary logistic regression analysis was p<0.25 and for multivariable regression model was set at p<0.05.

Results

A total of 327 patients were enrolled. Of the total stroke

Table-1: Asian Stroke Criteria for Classification of Brain Infarction (Topographical Classification).

Large Vessel Territory (LVT)	
Probable either A or B	A. New cortical signs (aphasia, agnosia, apraxia, sensory neglect, visual neglect, seizure, hemianopsia) B. MRI/CT show a new cortical lesion compatible with stroke manifestations* and /or a new lesion ≥2cm (If negative repeated MRI/CT ≥48 hours post event recommended)
Definite both A and B	A. New cortical signs (aphasia, agnosia, apraxia, sensory neglect, visual neglect, seizure, hemianopsia) B. MRI/CT show a new cortical lesion compatible with stroke manifestations* and /or a new lesion ≥2cm (If negative repeated MRI/CT ≥48 hours post event recommended)
Small Vessel Territory (SVT)	
Probable either A or B	A. Lacunar syndrome (pure motor hemiparesis, pure sensory stroke, mixed sensorimotor, ataxic hemiparesis, dysarthria clumsy hand) without new cortical signs B. MRI/CT performed ≥ 48 h post event show new subcortical lesion < 2 cm*, no new cortical lesion* and no new lesion ≥ 2 cm*
Definite both A and B	A. Lacunar syndrome (pure motor hemiparesis, pure sensory stroke, mixed sensorimotor, ataxic hemiparesis, dysarthria clumsy hand) without new cortical signs B. MRI/CT performed ≥ 48 h post event show new subcortical lesion < 2 cm*, no new cortical lesion* and no new lesion ≥ 2 cm*

Note: If there is new clinical or imaging evidence* of LVT, patient should be classified as LVT, regardless of new SVT evidence. In brain stem imaging, new lesion* < 1.5 cm is considered SVT.
MRI: Magnetic resonance imaging. CT: Computed tomography.

Table-2: Association of Independent Factors to Atherosclerosis (ABI).

	Total n=327(%)	ABI ≤ 0.9 n=60(%)	ABI > 0.9 n=267(%)	Unadjusted OR (95% CI)	p-value
Age (years)					
≤55	148 (45.3)	24 (40)	124 (46)	0.77 (0.43-1.3)	0.37
>55	179 (54.7)	36 (60)	143 (54)		
Gender					
Male	168 (51.4)	36 (60)	132 (49)	1.53 (0.87-2.71)	0.14*
Female	159 (48.6)	24 (40)	135 (51)		
BMI					
Normal	168 (51.4)	33 (55)	135 (51)		
Overweight	131 (40.1)	19 (32)	112 (42)	0.97(0.63-1.49)	0.88
Obese	28 (8.6)	8 (13)	20 (7)		
WC					
Normal	200 (61.2)	41 (68)	159 (60)	0.68(0.38-1.24)	0.21*
Obese	127 (38.8)	19 (32)	108 (40)		
DM	189 (57.8)	35 (58)	154 (58)	1.03(0.58-1.81)	0.93
HTN	300 (91.7)	49 (82)	251 (94)	0.28 (0.12-0.65)	0.003*
IHD	80 (24.5)	9 (15)	71 (27)	0.49 (0.23-1.04)	0.06*
Hyperlipidaemia	61 (18.7)	9 (15)	52 (19)	0.73(0.34-1.58)	0.42
Smoking	56 (17.1)	12(20)	44 (16)	1.27(0.62-2.58)	0.51
CHF	6 (1.8)	0 (0)	6 (2)	0.7 (0.25-1.03)	0.9
h/o Stroke	50 (15.3)	8 (13)	42 (16)	0.82(0.36-1.86)	0.64
Carotid Bruit	27 (8.3)	7 (12)	20 (7)	1.63(0.65-4.05)	0.29
Cardiac Murmurs	29 (8.9)	6 (10)	23 (9)	1.18(0.46-3.03)	0.73
CAS					
Mild (<50%)	182 (55.7)	32 (53)	150 (56)		
Moderate (50-69%)	140 (42.8)	25 (42)	115 (43)	0.82(0.49-1.34)	0.42
Severe (70-89%)	3 (0.9)	3 (5)	0 (0)		
Occlusion (100%)	2 (0.6)	0 (0)	2 (1)		

*Is used for significant variables at p<0.25
ABI: Ankle brachial index. BMI: Body mass index. OR: Odds ratio. CI: Confidence interval. WC: Waist circumference. DM: Diabetes mellitus. HTN: Hypertension. IHD: Ischaemic heart disease.
CHF: Congestive heart failure. CAS: Carotid artery stenosis.

Table-3: Follow-up Status of Patients - n (%).

	Total n=327(%)	ABI ≤ 0.9 n=60 (%)	ABI > 0.9 n=267 (%)	X^2	P-value
Patients Follow-up					0.47
Death	72(22)	17(30)	55(21)		
Disabled	38(11.6)	6(10)	32(12)		
Functional Independence	163(49.8)	30(50)	133(50)		
Lost to FU	54(16.5)	7(10)	47(17)		

ABI: Ankle brachial index
FU: Follow-up.

cases, 245(75%) were definite large vessel territory, 55(17%) were probable large vessel territory stroke, 17(5%) cases were of definite small vessel territory stroke, while 10(3%) strokes were probable small vessel territory (Table-1).

The overall mean age was 57.64±12.8 years (range: 30-100 years). Besides, 168(51.4%) were males and 159(48.6%) were females. ABI < 0.9 was found in 60(18%) subjects and only 11(3%) patients had symptomatic PAD.

Of the patients having PAD (ABI< 0.9), 24(40%) were less than or equal to 55 years of age and 36(60%) were more than 55 years of age. Moreover, 36(60%) were males and 24(40%) were females, whereas 33(55%) had normal BMI, 19(32%) were overweight and 8(13%) were obese.

Also, 41(68%) of them had normal waist circumference, 19(32%) were obese, 35(58%) were diabetics, 49(82%) were hypertensive and 9(15%) had experienced ischaemic heart disease (IHD). CAS was divided into mild, moderate, severe and complete occlusion. In patients with PAD, 32(53%) suffered from mild, 25(42%) with moderate and 3(5%) patients having severe carotid artery stenosis (Table-2).

Four variables were found to be associated significantly with ABI: gender, waist circumference (WC), hypertension (HTN) and IHD (p<0.25 each). More than one independent variable was analysed in the same model for a single outcome, i. e. ABI. In addition to gender, WC, HTN and IHD variables, a further five statistically non-significant variables, including age, gender, dyslipidaemia, diabetes, PAD and smoking, were added due to their possible clinical association with the ABI. One variable was identified which was independently associated with ABI using multivariable analysis. Hypertensive was three times more likely to have PAD/ABI compared to non-hypertensive (OR 3.13; 95% CI for OR: 1.36-7.2; p= 0.007).

Total mortality was observed among 72(22%) patients, morbidity among 38(12%), 163(50%) patients completely recovered and 54(16.5%) had lost to follow-up. In patients with an ABI<0.9, mortality was seen in 17(30%) patients, morbidity in 6(10%), complete recovery in 30(50%) and 7(10%) were lost to follow-up (Table-3).

Discussion

To our knowledge, this was the first study showing frequency of peripheral artery disease in ischaemic stroke in Pakistan. In this cross-sectional, hospital-based study, ankle brachial index was used to determine the presence and absence of PAD. A total of 327 patients were enrolled with a mean age of 57.6±12.8 years. PAD was found in 18% of the individuals with ischaemic stroke. These results were comparable to the findings of three recent studies that reported PAD prevalence in patients with stroke. In a German epidemiological trial on ABI[11,12] the prevalence of ABI <0.9 was 18% in a total sample of 6,880 unselected primary care patients and 30% in 607 patients with a history of stroke. The Italian post-operative analgesic therapy observational survey (PATHOS) study[5] examined 1,758 patients admitted in one of 49 hospital departments for acute coronary syndromes (57%), acute ischaemic stroke (29%) or TIA (14%), the prevalence of ABI <0.9 was 34% among 755 patients with stroke or TIA. In the Scala study[13] the prevalence of ABI <0.9 was higher at 51% among 852 patients with stroke or TIA admitted to 85 stroke units across Germany. This higher prevalence may partly be explained by a higher mean age and a higher proportion of patients with atherosclerotic stroke in Scala.[13] Busch et al. reported an ABI <0.9 in 31% participants, of whom 29% had a history of PAD.[2] A Japanese study reported a prevalence of PAD of 17%, had analysed 58 retrospectively selected patients with ischaemic stroke,[14] which was similar to our study. Topakian et al.[15] stated a prevalence of PAD of 45%.

We found that PAD was more in patients above 55 years of age but there was no significant difference between the two age groups. Similarly, Busch et al.[2] and Topakian et al.[15] reported that the prevalence of PAD was seen in older age groups with a mean age of 69.5±12.1 years.[15] A study conducted in Korea showed a prevalence of PAD in stroke

of 35% and were seen in older age groups (mean age 69.9±8.7 years).[16]

In this study, among 60 cases having PAD more than half had a normal BMI. Tiosan et al.[17] demonstrated that increased baseline obesity is associated with the development of new-onset high ABI measurements over a mean four year follow-up. In a total of 327 cases of stroke, the majority had mild carotid stenosis, followed by moderate stenosis. In patients with PAD a similar proportion had mild and moderate carotid stenosis. Topakian et al.[15] stated that ABI of <0.9 was significantly associated with a presence of carotid stenosis of >50%.

In our study an ABI <0.9 was associated with hypertension and diabetes, though hypertension and diabetes both were found to be the commonest risk factors respectively. On the contrary, ABI of <0.9 was associated with hypertension diabetes mellitus and congestive heart failure (CHF) as stated by Topakian et al.[15]

The total mortality after a period of 6 months was 22%, morbidity was 12%. In the SCALA study an increased risk of recurrent stroke or cardiovascular death during a mean follow-up of 17.5 months was seen in patients with a low ABI.[6] Tanaka et al. reported that not only a low ABI but a borderline ABI was independently associated with a higher incidence of all-cause death, cardiovascular death, and cardiovascular events, cardiovascular risk factors including smoking, diabetes, hypertension and total cholesterol even after adjustment for various cofactors.[18,19]

Pathological effects of abnormal ABI have been derived from the endothelial dysfunction, which is the initial step of atherosclerosis,[19] and is a predictor of not only cardiovascular events but also the development of heart failure (HF).[20] Kajikawa et al.[21] reported that even in subjects with borderline ABI significant endothelial dysfunction can be observed. A meta-analysis identified 11 studies (5,374 patients) that were not significantly heterogeneous. Pooling-adjusted hazard ratios showed that low ABI was associated with both an increased hazard of recurrent stroke (hazard ratio, 1.70; 95% confidence interval, 1.10-2.64) and an increased risk of vascular events or vascular death (hazard ratio, 2.22; 95% confidence interval, 1.67-2.97).[22] Clinical practitioners should be familiar with the ABI measurement and utilise the ABI to detect and treat PAD patients early.

Our study had several limitations. It lacked follow-up, hence predictive value of low ABI in terms of future risk of atherothrombotic events such as recurrent stroke, angina, myocardial infarction, death or disability is not known. No data was systematically collected on the incidence of recurrent stroke during or after a hospital stay. The patients underwent a one-time measurement of ABI to diagnose PAD during the hospital stay. However, ABI is a reliable tool but there is some evidence suggesting repeated measurements over time may be preferable.[18]

Conclusion

Abnormally low ABI suggesting subclinical PAD was 18%. Large longitudinal studies are required to confirm whether information on ABI needs to optimise its role in secondary prevention of certain subgroups.

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