ETIOLOGY OF STROKE IN YOUNG PAKISTANI ADULTS; RESULTS OF A SINGLE CENTER STUDY

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ABSTRACT

Objectives: The aim of this study was to determine the demographic profile and incidence of young stroke at a tertiary care setup in Islamabad, Pakistan. **Materials and Methods:** This single centre, cross sectional study was conducted by recruiting 119 patients of either gender, ≥ 12and ≤ 45 years of age with stroke and receiving care at Pakistan Institute of Medical Sciences, Islamabad. **Results:** Total number of young strokes was 119 out of a total of 322 strokes i-e-, 36.9 %; 1/3rd strokes were in ≤ 45 years of age. Ischemic arterial strokes were 47% (56 out of 119) while venous ischemic strokes were 11.7 % (14 out of 119) and almost all in females (13 out of 14; 92.8 %).Infective causes of central nervous system were identified in24.3 % (29 out of 119). 49 patients (41.1 %) had hemorrhagic strokes. Major individual risk factors for stroke included hypertension identified in 35 (29.4 %)followed by diabetes mellitus in 8 (6.7 %) patients. Amongst infectious causes, CNS tuberculosis was the major infection associated with young stroke i-e-, 89.6 % (26 out of 29). **Conclusion:** Nearly 1/3rd of strokes in our population are in young.While risk factors in general for stroke stand true for young stroke as well namely hypertension and diabetes, CNS infections are a major cause of young stroke in Pakistan; particularly CNS TB. While majority of strokes in elderly are ischemic, strokes in young comparatively are almost equally divided between ischemia and hemorrhage i-e-, 1.4:1. 1/5th of these ischemic strokes are due to cerebral venous thrombosis. National level guidelines should therefore adopt different strategies for primary and secondary prevention, laboratory work up and imaging, and treatment of stroke in young.

Key Words: Young stroke; ischemic; hemorrhagic; arterial; venous; infectious; risk factors, family history.

INTRODUCTION

There is significant socioeconomic impact in terms of morbidity and mortality especially when stroke affects young patients. Exact age range for defining young stroke, remains debatable; it is generally believed that the risk factors and underlying etiologies tend to become similar to the older patients at around 45 years of age. Therefore, many research studies define "stroke in young" as occurring in patients at age 45 years or less.[1] Compared to the older adults, the incidence, risk factors, and etiology are distinctly different in younger ischemic stroke. Accordingly, cardioembolism (20%–35%), dissection of extracranial arteries (6%–25%), drugs (10%), and hypercoagable states (5%–10%) are relatively more commonly detected in younger stroke patients. Additional factors such as migraine, pregnancy and oral contraceptive use are also observed more commonly in young people.[2] For all stroke (ischemic and hemorrhagic), overall incidence rates under the age of 45 years range from 7 to 15 in 100,000 people/year.[3] Under the age of 45, there may be a greater incidence of stroke among developing countries, such as Libya with a reported rate of 47 in 100,000 people/year for all strokes.[4] The aim of this study was to determine the demographic profile and incidence of young stroke at a tertiary care setup in Islamabad, Pakistan and to discuss trends along with relative frequencies of its various etiologies. This would help formulate strategic management protocols for stroke in young at tertiary care level and expand our knowledge of this entity in developing countries like Pakistan. Moreover, there is scarce local data from Pakistan regarding young stroke and this study would help define its basic demographics for future studies.

MATERIALS AND METHODS

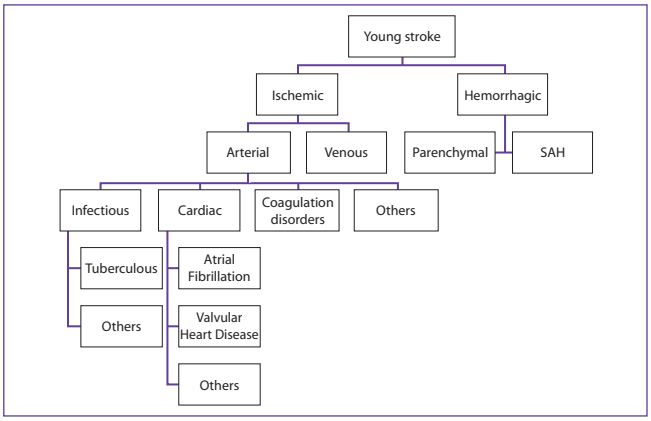
This single center, prospective, descriptive, cross-sectional study was carried out on indoor and outdoor patients of department of Neurology, Pakistan Institute of Medical Sciences (PIMS), Islamabad from January 2014 to January 2015. All the patients of both genders ≥ 12 and ≤ 45 years of age and found to have stroke (ischemic and hemorrhagic) were included in the study. The

diagnosis of stroke was made by consultant neurologist on the basis of history, clinical examination and neuroimaging i-e-, Computed Tomography (CT) scan and/ or Magnetic Resonance Imaging (MRI) brain. Exclusion criteria included: patients with head injury, brain malignancy and otherwise unclear diagnosis of stroke. The study was approved by hospital ethical committee and carried out according to international ethical standards of the responsible committee on human experimentation and with the latest version of Helsinki Declaration of 1975. All patients underwent a detailed history taking and physical examination and all relevant investigations were performed including Complete blood count and erythrocyte sedimentation rate, Liver function tests, Renal function tests, serum electrolytes, Random blood sugars, Electrocardiogram, Chest X-ray, Hepatitis serology, urine routine examination, echocardiography, coagulation profile, thrombotic screen, serum lactate, HbA1c, lipid profile, ultrasound abdomen/ pelvis, Cerebrospinal fluid (CSF) routine examination, CSF Acid fast bacillus (AFB) polymerase chain reaction (PCR), CSF AFB Culture and sensitivity, CSF Adenosine deaminase, Human immunodeficiency virus and autoimmune workup where indicated and only those cases were included having definitive findings of stroke and identified cause.Those without any identifiable etiology or risk factor were classified as cryptogenic stroke. Family history was taken from immediate family members and recorded for risk factors. Patients fulfilling the inclusion criteria were enrolled after taking informed written consent from the patients or relatives.The data collected was entered on specifically designed performa prospectively using non-probability, consecutive sampling technique. The data was analyzed using SPSS version 17.0. Descriptive analysis was done and reported as mean ± SD for continuous variables like age whereas frequencies and percentages were calculated for categorical variables such as gender,stroke types and subtypes, individual risk factors, family history of risk factors and laboratory workup results.Data was presented in tabulated forms.

RESULTS

Mean age was 32.3 ± 12.6 years. The age range was 12-45 years. Out of these 57 (47.8%) were males and 62 (52.1%) were females. We received a total of 322 strokes out of which 119 were young strokes i-e-, 36.9 %; 1/3rd. Ischemic arterial strokes were 47 % (56 out of 119) while venous ischemic strokes were 11.7 % (14 out of 119) and almost all in females (13 out of 14; 92.8 %). Infective causes of central nervous system were identified in 24.3 % (29 out of 119). The remaining 49 patients (41.1 %) had hemorrhagic strokes. Major individual risk factors for stroke included hypertension identified in 35 (29.4 %) followed by diabetes mellitus in 8 (6.7 %) patients. Amongst infectious causes, CNS tuberculosis was the major infection associated with young stroke i-e-, 89.6 % (26 out of 29) (Figure 1).

Figure 1: Demographic theme profile for classifying young stroke patients



Out of arterial ischemic non-infectious strokes, 96.2 % (26 out of 27) were cortical infarcts while 3.7 % (1 out of 27) were brainstem related. Out of hemorrhagic strokes, 32.6 % (16 out of 49) were subarachnoid hemorrhages, 63.2 % (31 out of 49) were intracerebral bleeds and 4 % (2 out of 49) were brainstem bleeds. Fig 1

Major individual risk factors were hypertension in 29.4 % (35 out of 119) followed by diabetes mellitus in 6.7 % (8 out of 119) patients. Family history of risk factors was majorly negative but amongst the risk factors identified, hypertension was the commonest (Table 1).

Table 1: Risk factor stratification of young stroke patients with arterial strokes

Risk Factor Category	Risk Factor	Total n (%)
Self/ patient		
Vascular	Hypertension	35 (29.4 %)
Cardiac	Left apical thrombus/ mass	1 (0.8 %)
	Atrial fibrillation	2 (1.6%)
	Mitral stenosis (VHD)	2 (1.6 %)
	Anticoagulation (for cardiac cause)	1 (0.8 %)
Metabolic	Diabetic	8 (6.7 %)
	CKD/ ESRD	2 (1.6 %)
	HBV (DCLD)	1 (0.8 %)
	HCV (DCLD)	4 (3.3 %)
Hematological	Hemophilia	1 (0.8 %)
	Post-partum	3 (2.5 %)
Personal	Smoking	5 (4.2 %)
Cryptogenic stroke	None	24 (20.1%)
Family history		
Vascular	Hypertension	16 (13.4 %)
Metabolic	Diabetic	7 (5.8 %)
CNS	CVA (old)	60 (50.4 %)
None	None	42 (35.2 %)

Table 1: Risk factor stratification of young stroke patients with arterial strokes: LV = left ventricular, VHD = valvular heart disease, CKD = chronic kidney disease, ESRD = end stage renal disease, HBV = hepatitis B virus, HCV = hepatitis C virus, DCLD = decompensated chronic liver disease, CVA = cerebrovascular accident. None of the patients had positive thrombophilia screen done on two occasions. Only one was positive for SLE and had ischemic cortical stroke while workup for causes like HIV and other vasculitides were negative in all.Cardiac risk factors responsible for strokes included mitral stenosis and atrial fibrillation in 1.6 % each (2 out of 119) while left ventricular thrombus and anticoagulation in 0.8 % each (1 out 0f 119). (Table 1)

DISCUSSION

Asian countries exhibit a great diversity in disease patterns. They comprise almost two-third of the world's total mortality due to stroke. [3] The purpose of this study was to explore existing epidemiological data on stroke, highlight the temporal trends in stroke epidemiology in various regions and predict future patterns based on these observations. Our search revealed that there is a lack of good epidemiological data from most Asian countries. Important observations include a rise in stroke incidence in Pakistan, an earlier age at onset compared with the West, and an overall relative increase in the proportion of strokes in young people. [3, 4, 5] As incidence of young stroke is on the rise, there is need for sound epidemiological data from all over the world to understand the disease better and plan policy-level interventions to decrease its burden. Incidence of young stroke is greater among men than women, particularly in 35 to 45 year old age group. Some population-based studies, however, have showed an increased incidence among women under 30 years. 3Our results show that 119 out of a total of 322 strokes i-e-, 37 % were in ≤ 45 years of age. This makes an annual incidence at a single center to our observation of 37 % i-e-, 1/3rd of all strokes. In 5–10% of cases, antiphospholipid antibody syndrome results in stroke.[5] Before the age of 20,7 to 10% of Sickle cell affectees experience stroke. [3] In Iran,as many as 32% of cases of young ischemic stroke are attributed to rheumatic heart disease.[6] Compared to arterial strokes, cerebral venous thrombosis (CVT) is an uncommon cause of young stroke i-e-,<1% of cases.[7] Rare causes of non-atherosclerotic arteriopathies contribute to 15–35% of cases of young stroke as a collective group including Sneddon's syndrome; Moyamoya disease (22–27% of all young ischemic stroke) in Asian populations; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); vasculitis; prior chemoradio therapy and HIV infection (up to 7% of cases of young stroke in Nigeria).[3] Oral contraceptive use is associated with a 2- to 5-fold increased risk of stroke of all subtypes, depending on the estrogen content.[8] According to our study, both males and females were almost equally affected (57 versus 62 respectively). According to one study, the ratio of male to female patients does not significantly differ in the younger cohort which is similar to our data results, 1:1.08.[9] Major individual risk factors for stroke included hypertension identified in 35 (29 %) followed by diabetes mellitus in 8 (7 %) patients. Family history of risk factors was majorly negative but amongst the risk factors identified, hypertension was the commonest. (Table 1) According to one study, in India, China, Philippines, Thailand, Sri Lanka, Iran, Pakistan and Nepal, there has been a rapid increase in stroke mortality and prevalence of hypertension. Hypertension and stroke occur at a relatively younger age in Asians.[10] This concurs withour findings that most important cause of stroke is hypertension; up to 29 % diagnosed cases to our observation. CVT is an uncommon and frequently unrecognized type of stroke that accounts for 0.5% to 1% of all strokes as suggested by Bousser et al.In this study, venous ischemic stroke accounted 11.7 % (14 out of 119) and almost all in females (13 out of 14; 92.8 %), which incomparison to the findings of Bousser et al. is quite high. CVT is more commonly seen in young individuals.[11] In a series of intracerebral hemorrhage cases in young people presented by Janghorbaniet al., CVT explained 5% of all cases which is comparable to our data but the incidence of CVT as a cause of stroke in our population is alarmingly high and should be pondered upon.[12] Data for stroke is scarce from locations where infections are prevalent, making it difficult to reach conclusions on how populations differ in terms of risk of infectious stroke. Few prospective studies of stroke in the setting of infections have been done.Most infectious pathogens have anecdotal evidence to support a link with stroke;so is evident in this study. Infectious etiologies were found in 24% of all young strokes (29 out of 119) with slight male predominance (16 malesvs 13 females). Among all infection related stroke cases,CNS tuberculosis was found in 89% of patients (26 out of 29).According to Misraet al., stroke in CNS tuberculosis occurs in 15-57% of patients especially in advance stage. Majority of strokes are asymptomatic because of being in a silent area, difficult to identify as patient might be indeep coma or are associated with other pathologies such as spinal arachnoiditis or tuberculomas.[13] Stroke in the young requires a different approach to investigate and manage than stroke in the elderly, given the differences in the relative frequencies of possible underlying causes.

Hemorrhagic stroke is common, and vascular imaging is recommended given a high frequency of underlying vascular anomalies. To our observation, ischemic arterial strokes were 47 % (56 out of 119), venous ischemic strokes were 11.7 % (14 out of 119) i-e-, total ischemic were 70; while 41 % (49 out of 119) were hemorrhagic. While majority of strokes in elderly are ischemic, strokes in young comparatively are almost equally divided between ischemia and hemorrhage according to previous available data. In our study ischemic stroke was more frequent even in the young population i-e-, 1.4:1 (70 vs 49 respectively) and 1/5th of ischemic ones (14 out of 70) are due to cerebral venous thrombosis.It is also important to explore the possibility of illicit drug use in these cases. With regard to ischemic stroke, the increased frequency of dissection mandates a high index of suspicion for imaging the extracranial and intracranial vessels. Whilst the commonest cause of cardioembolic stroke in the elderly is atrial fibrillation, in a young patient transesophageal echocardiography looking for the presence of a patent foramen ovale ± an atrial septal aneurysm has a higher yield. One must not forget, however, that atherosclerosis still contributes to a large proportion of stroke in young patients and likely explains at least some of the ethnic differences noted in the incidence of stroke, emphasizing the need for aggressive risk factor management. This, as well as differences in the prevalence of other causative etiologies, such as rheumatic fever and infection, combined with a younger background population age distribution, and venous thrombosis per se, may contribute to an increased incidence of young stroke in developing countries. Finally, the incidence of stroke appears greater in women than men under the age of 30, and women are at increased risk of hemorrhage and infarction in puerpurium. Additional history, including use of the oral contraceptive pills and testing for antiphospholipid antibodies, therefore, must be taken as routine in young stroke.[3, 11, 12, 13]

LIMITATIONS

This study has a number of limitations. Firstly, it is a single center trial and hence, the results cannot be readily generalized to the population of the entire country. Secondly, the results are limited both by the duration of the study as well as the sample size. A more extensive study period with a bigger sample size will reflect the population trends in a better manner. Therefore further research in young stroke is needed, particularly population-based studies utilizing standardized methodology. Such an effort will provide clarity by enabling comparison of incidence rates between countries and trends overtime, and insights into underlying etiological mechanisms.

CONCLUSIONS

Nearly 1/3rd of strokes in our population are in young.While risk factors in general for stroke stand true for young stroke as well namely hypertension and diabetes, CNS infections are a major cause of young stroke in Pakistan; particularly CNS TB. While majority of strokes in elderly are ischemic, strokes in young comparatively are almost equally divided between ischemia and hemorrhage i-e-, 1.4:1. 1/5th of these ischemic strokes are due to cerebral venous thrombosis. National level guidelines should therefore adopt different strategies for primary and secondary prevention, laboratory work up and imaging, and treatment of stroke in young.

DISCLAIMER

The authors declare that they do not have any conflict of interest.

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