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Risk factors and subtypes of ischemic strokes in young adults: A tertiary care hospital study from southern part of India

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Abstract

Background: In the last few decades ischemic stroke in young adults (15-45 years) has been increasingly reported. This study was aimed to evaluate the epidemiological features, risk factors and mechanisms of ischemic stroke in young adults.

Methods: From June 2018 to February 2020**,** patients diagnosed with ischemic stroke in the age group of 15-45 years from a tertiary care referral hospital in Hyderabad, India, were consecutively enrolled to study their risk factors, mechanisms and outcome.

Results: Out of 971 patients of ischemic strokes 164 (16.8%) were young adults, among whom 113 (69%) were in the age group 36-45 years. Males constituted 71.3% of cohort. Risk factors were alcohol abuse (39.63%), dyslipidemia (39.02%), hypertension (32.32%), smoking (27.44%), diabetes (25.61%), family history of stroke (23.78%) and past history of stroke (12.20%). As regards subtypes, large artery atherosclerosis constituted 26.22%, lacunar stroke 15.24%, cardio- embolic strokes 15.85%, stroke of other etiology 18.9% and stroke of unknown etiology 23.78%. At the time of discharge, death and dependency in younger adults was 8.53% and 45.12% respectively.

Conclusion: About 90% of young adults with ischemic stroke had at least 1 established modifiable vascular risk factor. Large artery atherosclerosis both intra and extra-cranial was the most frequent mechanism. Stroke due to other etiologies unique to young adults constituted about one fifth of all ischemic strokes.

Keywords: acute ischemic stroke; stroke in young; cerebrovascular accident; etiologies

Introduction

Stroke is one of the commonest causes of mortality and disability across the world affecting around 11million people each year [1]. Although traditionally believed to be common in elderly, about 10% to 20% of strokes occur in young adults aged 18 to 50 years [2].

Compared with stroke in older adults, stroke in the young adults has significantly large social and economic impact by leaving victims disabled during their most productive years and create a long term burden on them, their families and the community. In contrast to older adults, the incidence of ischemic stroke among young adults has been rising globally since the 1980s [3-6]. The incidence is even higher in developing countries sharing almost more than half of the overall stroke burden [1]. As of 2019, World Bank low-income group countries had a stroke associated age- standardized mortality rate 3.6 times, and the disability adjusted life years (DALY) rate 3.7 times higher than the high- income group countries [7]. Earlier Indian studies considered stroke in young

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as a distinct entity and emphasized the need to rule out diverse etiologies including intracranial infections and coagulopathies [8-9]. In view of rapid urbanization of dietary habits and sedentary lifestyle, the risk factor profile of young adults in India has undergone a rapid change in the last few years. This study was planned to reappraise the risk factor profile of ischemic stroke in young adults in a metropolitan city of India.

This study aimed to investigate the risk factors and subtypes of ischemic strokes in young adults between 15 and 45 years of age in the South Indian city of Hyderabad.

Methods

Study design

This is an observational cohort study conducted on consecutively and prospectively enrolled ischemic stroke patients admitted in Krishna Institute of Medical Sciences (KIMS), a tertiary care referral hospital in Hyderabad in South India. The study period was from June 2018 to February 2020**.** Stroke is characterized by focal neurological deficit attributed to an acute focal injury of the central nervous system (CNS) due to cerebral infarction, intracerebral hemorrhage (ICH), and sub arachnoid hemorrhage (SAH), with no apparent cause other than that of vascular origin [10]. Patients between the 15-45 years of age group formed the study population. Their clinical details and risk factors were compared to those >45 years.

All the patients were uniformly enrolled to determine the site and mechanism of stroke by doing magnetic resonance imaging including angiogram (MRI/MRA) of the brain, carotid doppler, electrocardiogram (ECG), two-dimensional (2D)-transthoracic echocardiography (TTE) and basic blood work-up like complete blood counts, fasting and post lunch blood sugar, Glycosylated hemoglobin (HbA1C), fasting lipid profile, kidney function tests, liver function tests, and thyroid function tests. Among patients with non-identifiable mechanism, one or more of additional investigations including 24-hour Holter ECG monitoring to rule out cardiac arrhythmias, trans-esophageal echocardiography (TEE), digital subtraction angiography (DSA) of brain in selected patients, and prothrombotic profile including serum homocysteine, APLA antibodies, anti-cardiolipin antibodies, MTHFR mutations, antithrombin-3, protein-C, Protein-S, factor-V Leiden mutation and lupus anticoagulant were done.

Defining stroke subtypes

All patients of ischemic stroke were grouped into 5 subtypes, according to the Trial of ORG 10172 in acute stroke treatment (TOAST) system into large artery atherosclerosis (LAA) (intracranial or extracranial), lacunar stroke, cardioembolic stroke, stroke of other determined etiology, and stroke of undetermined etiology [11]. Patients were classified into stroke subtypes based on the review of investigations and clinical assessment by neurologists trained in stroke diagnosis of subtypes. Minimum two neurologists reviewed the data of every patient to determine the mechanism of stroke subtypes. The study was approved by the Institutional Ethics Committee of Krishna Institute of Medical Sciences.

Statistical analysis

IBM SPSS version 22 was used for statistical analysis [10]. Descriptive analysis was carried out by frequency and proportion for categorical variables, mean and standard deviation for quantitative variables. All the quantitative variables were distributed to normal distribution by using thorough visual inspection of histograms and normality Q-Q plots, whereas quantitative variables which are in non-normal distribution were summarized by median and interquartile range (IQR). Categorical outcomes were correlated between study groups by using Chi square test. If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used, and p value < 0.05 was considered as statistically significant.

Results

During the study period, 971 consecutive patients of ischemic stroke were enrolled in the stroke registry of which 164 (16.8%) were young adults between the age of 15-45 years with male to female ratio of 7:3. Nearly two thirds (n=113, 68.9%) belonged to the 36-45 years age group (Table 1). When compared for the traditional risk factors, hypertension, diabetes, coronary artery disease and past cerebrovascular accidents were significantly high in the older (>45years) age group (Table 2). Prothrombotic profile including homocysteine estimation, protein C, S, AT III and factor V Leiden was done in 146 young adults with ischemic strokes, out of whom 38 (26%) had elevated homocysteine levels but none had rest of prothrombotic disorders.

Table 1: Frequency of ischemic strokes in age group 15-45 years (n=164).

Age Group (years)	*Frequency(n)*	*Percentage (%)*
15-25	15	9.15%
26-35	36	21.95%
36-45	113	68.90%

Table 2: Comparison of risk factors of ischemic stroke between the young and older adults.

Risk factor	*Age Group*		*P value*
	15-45 (N=164)	>45 (N=803)	
Male	117(71.34%)	559(69.61%)	0.660
Hypertension	53(32.32%)	597(74.35%)	<0.001
Diabetes	42(25.61%)	434(54.05%)	<0.001
Dyslipidaemia	64(39.02%)	337(41.9%)	0.742
Smoking	45(27.44%)	229(28.52%)	0.780
Alcohol abuse	65(39.63%)	351(43.71%)	0.337
Past history of stroke/Transient Ischemic attack	20(12.20%)	190(23.66%)	0.004
Family history of stroke	39 (23.78%)	162 (20.17%)	0.300
Coronary artery disease	7(4.27%)	199(24.78%)	<0.001

Although stroke due to other determined etiology and stroke of unknown etiology were significantly higher in the young adults, large artery atherosclerosis (LAA) remained the commonest cause (Table 3 and 4). It was seen in 43 (26.22%) patients, of which 25 patients had extracranial LAA and 18 had intracranial atherosclerotic disease (ICAD). About 26 patients (15.85%) had a cardioembolic source of which Chronic Rheumatic Heart Disease was found to be the most prevalent cause with or without atrial fibrillation. One patient with mitral stenosis without atrial fibrillation was detected to have large left atrial appendage clot while 1 patient was having clot over the mitral prosthetic valves.

Table 3: Comparison of stroke mechanisms between young and older adults.

Parameters	*Age Group*		*Chi square*	*P value*
	15-45 (N=164)	*>45 (N=803)*		
Large artery Atherosclerosis	43 (26.22%)	233 (29.14%)	0.569	0.451
Small vessel disease	25 (15.24%)	368 (45.83%)	52.805	<0.001
Cardio embolic stroke	26 (15.85%)	129 (16.06%)	0.005	0.946
Stroke of other etiology	31 (18.9%)	21 (2.62%)	71.000	<0.001
Stroke of unknown mechanism	39 (23.78%)	52 (6.48%)	47.838	<0.001

Table 4: Stroke of other determined etiology (n=31).

CADASIL	6
Moya-Moya	4
RCVS	4
CNS vasculitis	4
Tuberculous vasculitis	2
Fungal vasculitis	1
HIV Vasculitis	1
Arterial dissections	3
APLA syndrome	1
CNS Behcet's	1
OCP related stroke	1
AML-M3	1
Cocaine abuse	1
Hemiplegic migraine	1

Abbreviations: CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, RCVS: Reversible Cerebral Vasoconstriction Syndrome, APLA: Anti-phospholipid antibody syndrome, OCP: oral contraceptive pills, AML-M3: Acute myeloid leukemia- M3type.

Other cardiac sources of embolism included left atrial myxoma in 1, severe LV dysfunction in 2, congenital heart diseases including PFO and ASD- Ostium secundum variant in 1 each, suggesting cardiac diseases as an important risk factor for stroke in young adults. Only 16 (9.76%) young patients and 73 (9.09%) patients >45years underwent thrombolysis. Among the young adult patients,14 (8.53%) while among the older adult patients 39 (4.85%) died of stroke or related complications during the course of hospitalization (Table 5).

Table 5: Outcome at the time of discharge.

mRS score	*Age group*	
	15-45 (N=164)	*>45 (N=803)*
0-2	76(46.34%)	421(52.42%)
3-5	74 (45.12%)	343 (42.71%)
6	14 (8.53%)	39 (4.85%)

Abbreviations: mRS: modified Rankin scale

Discussion

Incidence of young stroke per 100 000 person-years has been varyingly reported from 5 to 15 in many European studies to 20 in most Northern-American, Australian and Asian studies and up to 40 in some African countries and Iran [11]. Earlier population based studies in India have shown an overall incidence of stroke up to 23-145 per 100,000 persons per year [8, 12, 13]. However, the prevalence of stroke in young adults has been reported from 10-36% [14]. The reason for varying prevalence of stroke in young adults from different studies in India is due to differences in the cut off age criteria, differences in the inclusion criteria regarding hemorrhagic or ischemic strokes and differences in data from population based versus hospital based registries reflecting the referral bias. In our study, stroke in young adults constituted 16.8% of all ischemic strokes admissions, which is in conformity with most of the hospital based registries of stroke in young adults in India [14]. Among these, incidence was more among those over the age of 35years, when the effects of premature atherosclerosis are more likely to manifest, as has been found in a prior Indian study as well [15]. The male predominance in our study, also noted in previous north Indian study from Delhi may be partly due to higher exposure of males to alcohol and smoking or because of a socio-cultural practice in India, which manifests as males being more prompt to seek treatment at referral centres [16].

The current study identified a relatively high frequency of hypertension (32.32%) in young stroke patients, although the prevalence was lower compared to the older ischemic stroke patients. In Helsinki Young Stroke Registry, hypertension was prevalent in 51.7% of patients in 45-49 yrs age group [17]. Similarly, while hypertension was an important overall risk factor for ischemic stroke in (OR 3.14) INTERSTROKE study [18], a substantial risk augmentation was observed for those ≤45 years (OR, 8.53), for all strokes including ischemic and hemorrhagic strokes. In the Global Burden Study, the population attributable risk (PAR) for hypertension was highest in Southeast Asia (54.8%) and lowest in Eastern and Central Europe and the Middle East (40.7%) [19].

One-fourth (25.61%) of the young stroke patients in the present study were diabetic. This is the highest prevalence of diabetes in young strokes reported so far internationally (10%) or even from India (13.9%) [17, 20]. The population attributable risk (PAR) for diabetes mellitus in young adults is 4.8% (95% CI 2.9 to 6.7) and it is also associated with a higher risk of stroke (OR=1.9; 95% CI 1.5 to 2.3) [11].

In the present study, 27.44% of young strokes were active smokers. In the previous study from north India only 9.5% of young strokes were smokers, suggesting the increasing trend of smoking among the young [16]. In India, smoking unfiltered tobacco in the form of bidi and tobacco chewing poses the greatest risk, especially in the low-income populations. Cerebral infarction is 1.6 times more common in young smokers (15–45 years old) than non-smokers [21]. Several studies involving multiple ethnicities have shown early-onset ischemic stroke to be associated with smoking, with OR ranging from 1.6 to 7.7 [22]. The cumulative dose effect of smoking without a significant heterogeneity between etiologic subtypes has been shown, thus proving to be one of the most important modifiable risk factors for stroke.

Almost 40 % of the young strokes in the present study were habitual alcoholics consuming at least 200 ml of alcohol on a daily basis. In the young stroke study from North India, the prevalence of alcohol was only 9.5% in young strokes [16]. The risk of long-term or recent heavy drinking with ischemic stroke is established in prior studies [23, 24].

Almost 10% of the young strokes in the present study had a past history of stroke and 2.44% had a prior history of transient ischemic attack (TIA). However, 65% of these patients were not on any treatment emphasizing the importance of spreading awareness regarding secondary prevention in the community. Almost one-fourth (23.78%) of the young strokes in the present study had a family history of stroke highlighting its importance in stroke in young adults.

In our study, 90% of young adults had at least 1 and about 80 % had more than 1 modifiable risk factors of ischemic stroke (Figure 1). Findings from our study support the observation that modifiable risk factors previously established in older populations also account for a large part of stroke in young adults, with 4 risk factors contributing almost 80% of stroke risk [25]. However, about 10% of young adults with stroke in this study had none of the common vascular risk factors.

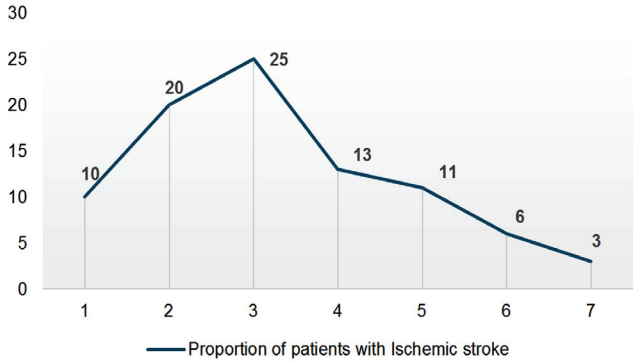

Figure 1: Number of modifiable risk factors present in ischemic strokes in young adults.

In our study, large artery atherosclerosis (LAA) was the most prevalent stroke subtype comprising around 26% of the young patients. Previous study from north India had showed 14.7% of LAA but did not include intracranial large artery disease [16]. The prevalence of Stroke due to lacunes/small vessel disease (SVD) was higher (15.24%) in comparison to 6.8% from earlier study [16]. In our study 15.85% had a cardioembolic source almost comparable to the earlier study (14%) suggesting that young adults with ischemic strokes should undergo cardiac evaluation, for rheumatic and congenital heart diseases [16].

Interestingly, the strokes of other etiology, unique to stroke in young stroke, formed the third common stroke subtype (18.90%) in this study. The most common etiology in this group was cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) found in 6 patients. The stroke risk in CADASIL, associated with mutation in the NOTCH3 gene begins around age 40 to 50years. It may present as ischemic stroke, TIA or migraine with auras [26]. Moya Moya disease was found in 4 patients of our young strokes. All of them had mild strokes and were referred for revascularization surgery. It can be genetic or acquired, presents in childhood or later in the third and fourth decades of life. A cerebral blood vessel is occluded, typically at the base of the brain and multiple tiny blood vessels develop to try to replace the blood supply which are typically fragile [27]. There were 4 patients, all women, of ischemic strokes due to Reversible Cerebral Vasoconstriction Syndrome (RCVS) spectrum disorder among whom 3 were in postpartum state and 1 on immunomodulation. RCVS typically presents with a thunderclap headache with or without focal neurological deficits and is more common among women. Triggers may include a rapid rise in blood pressure, vasoconstrictive drugs, migraines and postpartum state. It can cause ischemic stroke or intracerebral hemorrhage or sometimes a combination of both [28]. Nine patients of CNS vasculitis included primary CNS vasculitis in 3, secondary to Rheumatoid arthritis in 1, tuberculous vasculitis in 2, fungal vasculitis in 1 and HIV vasculitis in 2.

APLA syndrome was identified in 1 patient. Arterial dissections of internal carotid artery was found in 3 young stroke patients all of which were spontaneous without any prior history of trauma unlike the previous studies [29]. Other causes included oral contraceptives, hemiplegic migraine, Behcet's, AML- M3 (Promyelocytic leukemia) and cocaine abuse in 1 each patient. Despite the good number of prothrombotic workups (N=146) we did not detect a single case of protein C, protein S, anti-thrombin-III or factor V Leiden mutations suggesting the rarity of these disorders as a cause of ischemic strokes in young adults. Despite extensive workup, almost one-fourth (23.78%) of the patients' stroke etiology were of undetermined etiology, which however is less than 42.5% of underermined etiolgy strokes reported from the previous north Indian study in young adults, possibly due to greater availability of investigations at present [16].

All patients received the standard treatment of acute ischemic stroke including intravenous thrombolysis in 16(10%) and mechanical thrombectomy in 1 patient. About half the number of patients were dependent for the activities of daily living at the time of discharge. The death rate from ischemic stroke was nearly twice that in older adults. Our study has shown significant disability and death in young adults with ischemic stroke inspite of the state of art treatment received by them. This could have been due to delay in seeking medical care, early onset multiple vascular risk factors and stroke severity among the young adults. This emphasizes the importance of public awareness and early lifestyle modification for stroke prevention in this important age group.

Limitations and future directions

This is a single centre-based study on patients hospitalised for stroke and therefore may reflect referral bias of a tertiary care centre. Non-fatal or non-disabling strokes treated on primary level or out-patient basis were not included in this study. The same could have resulted the higher proportion of poor outcome in the study population. Community level evaluation of stroke incidence and prevalence of the risk factors is warranted. Also, a long term follow-up of young stroke patients can give an estimate of the impact of stroke on personal and social aspects of an individual.

Conclusion

In this observational study young adults constituted

about 16% of hospital admissions of all ischemic strokes. Almost 90% of these had at least one modifiable stroke risk factors. Large artery atherosclerosis both intra and extracranial was the most frequent mechanism but stroke due to small artery disease and cardio-embolism due to rheumatic heart disease was also seen in significant proportion. Etiologies unique to young adults constituted only about one fifth of all strokes. The study highlights the need for community education about the stroke risk factors towards primary and secondary prevention of stroke from a young age.

Conflicts of interest

Authors declare no conflicts of interest.

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