

Young Ischemic Stroke in South Asia: A review

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ABSTRACT

Stroke in young adults may have early impact on quality of life in survivors. Uncontrolled stroke risk factors, lack of treatment facilities and a dense population has made its special significance in South Asia. The main aim of this study is to evaluate incidence, risk factors, etiology and clinical characteristics of young ischemic stroke in South Asia. Incidence of young stroke is more common in South Asian countries than developed western countries and has higher prevalence in rural areas. Traditional risk factors, such as hypertension, smoking, hyperlipidemia and diabetes are associated with majority of cases. Cardioembolism and undetermined etiology contribute to a large proportion of stroke etiology. Appropriate stepwise investigations are suggested to diagnose stroke of other determined etiology. Regular intake of drugs to control risk factors, cessation of smoking, and promote physical activity is suggested to reduce the burden of young stroke.

INTRODUCTION

Stroke is a leading cause of death and long-term disability among young adults.^{1,2} It comprises about 85% of global death in developing countries.³ Most studies on young ischemic stroke were found to be conducted in developed countries. Young ischemic stroke is not a rare event in South Asia. But only a few studies have been reported and stroke is regarded as an under recognized burden here.⁴ According to United Nations statistics division, nine countries are included in South Asia: Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka.⁵ South Asia comprises of more than one fifth of the world population and its people scattered all around the world.⁴ Due to dense population and being in one of the poorest regions, most people in these countries are still abandoned from proper education system, unaware of controllable risk factors like hypertension, diabetes, habit of smoking and alcohol abuse, and lack of healthcare centers and experts. Studies have reported the higher frequency of young stroke patients in these regions than in western countries.^{6,7} South Asian stroke patients were also comparatively found to be younger than the stroke patients in western countries.^{8,9}

In this review, we will describe the incidence, risk factors, etiology and clinical characteristics of young ischemic stroke from various countries in South-Asia. We will further discuss the characteristics of stroke in South Asian countries and other Asian or Western countries.

METHODS

We used "Pubmed" and "Google Scholar" for selection of relevant articles published between 1988 and 2012. The keywords used were: "stroke", "Ischemic stroke", "cerebral infarction", "incidence", "young stroke", "young adults", "etiology", "epidemiology", "female stroke" and "risk factors". These keywords were combined with name of each country in South Asia or their capital or famous place or ethnic group: for example, "Nepalese young stroke", "etiology of stroke in Dhaka", etc. References from these articles were further checked for any related articles. Those articles which were written in English, or at least had English abstract were included. Inclusion criteria for the study were: (a) study should be conducted in South Asia or in South Asian people living in countries

outside South Asia; (b) acute ischemic stroke; (c) age equal to 50 or below during onset; (d) the study should have data related to incidence, risk factors, etiology or clinical characteristics. Exclusion criteria were: (a) cerebral or subarachnoid hemorrhages; (b) Transient ischemic attack. SPSS 14.0 was used to design the clustered bar diagram to graphically display the stroke subtypes in various studies.

Seventeen relevant articles were found to have major discussion topic on incidence, risk factors, etiology and clinical features of young stroke in South Asia. Some of other articles which didn't discuss about young stroke, but have included the stroke patients < 50 years in their studies were also reviewed. Some studies were difficult to analyze and interpret due to the reason that their subjects weren't categorized according to age-group. Most of the studies commonly focused on risk factors and etiology. Clinical characteristics and outcome were found to be reported only in few studies. In most studies, no extensive work-up was found to perform on the stroke cases of undetermined etiology. Maximum number of research papers on young stroke were found to be published from Indian studies. No published journal articles were found from Afghanistan, Bhutan and Maldives.

INCIDENCE

Incidence of stroke increases with the advanced age and usually high in male. Few studies have shown the predominance of female in age group below 35, but no such study was reported in South Asian study.^{10, 11} Age limit of young stroke was found to vary with different studies, and usually below 45 or 50 years were specified in most literatures. Prevalence of stroke was found to be more in rural than urban area.^{12, 13} The incidence of

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young ischemic stroke patients was found to be 5% in Pakistan (age \leq 45)¹⁴, 6% in Bangladesh¹⁵, 9.2% in Nepal (age \leq 40)¹⁶ and 3.8% in India (age \leq 40).¹⁷ Although no recent data relating incidence rate is reported from Sri Lanka, previous studies showed the higher stroke rate of about 10-30%.⁹ Similarly, a community study in Pakistan has reported about 30% of stroke patients are \leq 45 years suggesting a high burden of young strokes.¹⁸ In another large population based Iranian study, incidence of young stroke patients was 7.9 per 100000 per year.¹⁹ In contrast to South Asian countries, young stroke was comparatively less in frequency in most of the developed countries⁹: 4.9% in United States (age $<$ 45)²⁰ and 6% in Germany (age \leq 45).²¹

RISK FACTORS

Traditional risk factors of stroke are hypertension, diabetes, atrial fibrillation, smoking and dyslipidemia. Smoking, trauma, oral contraceptives, migraine, drug abuse, obesity, sedentary lifestyle and pregnancy are modifiable risk factors more frequent in young.²² Race, ethnicity, family history of stroke or Transient ischemic attack, and low birth weight were identified as other important non-modifiable risk factors of young stroke which are more prevalent in South Asian people.²³ Multiple risk factors carries the higher risk of stroke, but no risk factors can also be identified in many cases.²⁴

1. Hypertension

Hypertension was found to be the most common risk factor of young stroke in many South Asian studies (Table1).^{9, 14, 15} Some studies showed that hypertension was more associated with intracerebral hemorrhage than cerebral infarction.^{25, 26} High blood pressure is also related with increased risk of stroke death.²⁷ The prevalence of hypertension is higher in South Asia and is predominant in urban areas: 23% in Pakistan, 17% in Sri Lanka and 20-40% in India.²⁸ In a hospital based prospective study in Nepal, hypertension was reported 78% in patients \geq 60years and 74% in patients of age-group 40-59 years²⁹ which is higher than other previous studies.^{16, 26} A study in Pakistan reported the increase in frequency of young stroke is due to higher prevalence of early onset of hypertension in their community.¹⁸ Similarly, higher prevalence of hypertension was found among ethnic South Asian young strokes in United Kingdom and Singapore.^{30, 31}

2. Hyperlipidemia

High level of total cholesterol or low density lipoprotein and low level of high density lipoprotein are associated with ischemic stroke.^{32, 33} Table 1 shows the higher prevalence (83%) of hyperlipidemia among young stroke patients of age-group 15-45 years in Bangladesh.³⁴ Hossain et al and Lipska et al also reported significant number of hyperlipidemic young strokes, 38% and 29% respectively.^{15, 17} Study in Iran, Pakistan and Srilanka showed a relative less prevalence of hyperlipidemia among young stroke.^{9, 14, 35, 36} A comparative study of ethnic South Asians and Whites in United Kingdom reported that the percentage of hyperlipidemic people was significantly higher among young South Asians.⁸ Various studies in Nepal have reported less prevalence of dyslipidemia in their studies.^{26, 37} An Indian study reported 9 young stroke patients of Familial hyperlipidemia, a rarely diagnosed condition in other studies.³⁸

3. Diabetes Mellitus

Diabetes is a known risk factor of stroke and its prevalence in younger age has been increasing worldwide.^{39, 40} Worse prognosis and severe disability was found in stroke patients with diabetes.^{41, 42} Diabetic patients in India were reported to be high, already exceeded 32.7 million in 2000.²⁸ Similar higher trend of diabetes was seen in young stroke patients in India.¹⁷ Prevalence of diabetes in urban areas was found to be higher in Nepal and

Bangladesh, 15% and 8% respectively.^{43, 44} Among ischemic young strokes in South Asia, prevalence of diabetes mellitus was found comparatively lesser than other traditional risk factors, as shown in Table 1.

Table 1: Risk Factors in Young Ischemic Stroke patients in South Asia

Country Author/Year	Age group	Total Patients	Risk Factors (%)			
			Smoking	Hypertension	Hyperlipidemia	Diabetes
India - Lipska ¹⁷ / 2007	15-45	214	37	36	29	14
Iran - Harirchian ³⁶ / 2006	15-40	42	24	12	12	5
Pakistan - Razaq ¹⁴ / 2002	15-45	118	21	30	13	30
Bangladesh - Hossain ¹⁵ / 2009	14-45	52	33	58	38	35
- Miah ³⁴ / 2008	15-45	30	30	33	83	7
Srilanka - De Silva ⁹ / 2009	15-45	41	0	21	8	5

4. Smoking and Tobacco chewing

Cigarette smoking is a major independent risk factor for ischemic stroke, particularly in young.⁴⁵ Relative risk of ischemic stroke may increase with the rate of smoking per day and also with the total duration of smoking.⁴⁶ In a Nepalese stroke study, 60% young subjects were found to have habit of smoking.²⁶ Tobacco chewing was found to be more common than smoking in a stroke study in Eastern Nepal.¹⁶ Strong association of smoking and young ischemic stroke has also been reported from India, Iran and Pakistan.^{14, 17, 36, 47} A population based case study in Bangladesh also found betel consumption as an important risk factor for stroke death.¹²

5. Obesity

Obesity and lack of physical activity in young population are the reasons for high prevalence of risk factors for cerebrovascular diseases.⁴⁸ Various studies in India and Pakistan reported significant incidence of obesity among stroke patients.^{35, 49} Unique anthropometry and Thin-fat phenotype among South Asians, where there is low Basal metabolic index and higher amount of central obesity, are the cardiometabolic risk factors.⁵⁰ Abdominal obesity in young, which is more associated with atherosclerosis, hypertension and diabetes, is found to be more common in South Asians than westerners.^{48, 51} Obesity was found to be neglected in most studies of South Asian young stroke. So, a further epidemiological study on obesity in young stroke is needed.

ETIOLOGY

For etiological classification, Trial of Org 10172 in Acute Stroke Treatment (TOAST) is commonly used: 1. Large artery atherosclerosis (LAA), 2. Cardioembolism, 3. Small vessel atherosclerosis (SAA), 4. Other determined etiology, and 5. Undetermined etiology. LAA, SAA and Cardioembolism comprise more than 90% of causes of overall ischemic stroke, but only 50% in case of young ischemic stroke.³⁶ As shown in Figure 1, stroke of undetermined etiology was a major finding among young

patients in studies of Razzaq (46%), Miah (48%) and Lipska (43.5%).

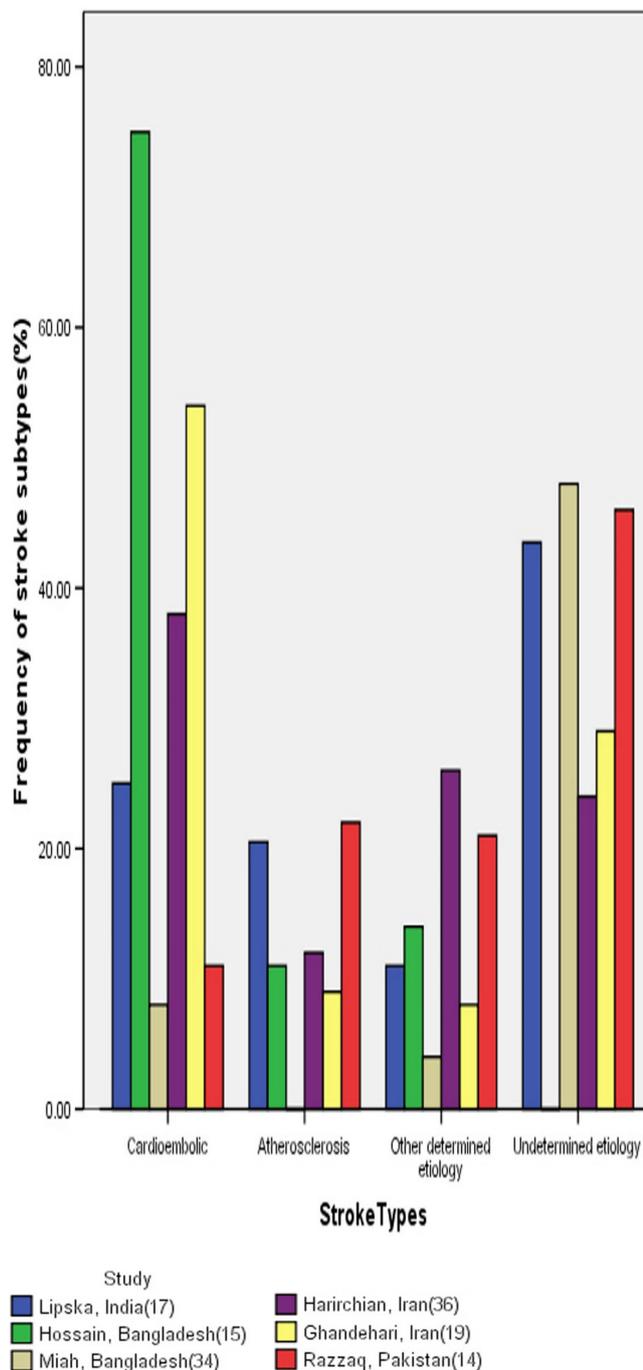


Figure 1: Stroke subtypes in different South Asian studies of young ischemic stroke

1. Large and small artery atherosclerosis

Doppler ultrasonogram and angiography are the important tools to diagnose the atherosclerosis of large cerebral arteries. Small arterial atherosclerosis is a common finding in young adults with history of hypertension and diabetes.^{52, 53} But atherosclerosis was found to be less common in most of the studies. This may be due to lack of use of vascular imaging applications in hospitals of South Asia. In a previous angiographic study, atherosclerosis of large vessels, especially internal carotid artery, was the major findings in young stroke in India.⁵⁴

2. Cardioembolism

Cardioembolism is a common cause for about 20% of ischemic stroke in young adults.⁴⁵ South Asian studies have shown that Transesophageal echocardiography (TEE) has an important role to diagnose varieties of causes of cardioembolism among young stroke.^{19, 45} In an Indian study, TEE was also found to be superior to Transthoracic echocardiography (TTE) in detecting mitral valve prolapsed and other cardiac abnormalities.⁵⁵ Figure 1 shows higher frequency of cardioembolism was present among young ischemic stroke patients of Hossain and Ghandehari.^{15, 19} Valvular heart diseases, including congenital and acquired, were the major findings in their studies. Other common sources of cardioembolism in young stroke were infective endocarditis, cardiomyopathy, myxoma, acute myocardial infarction, akinetic ventricular segment, etc (Table 2).

Table 2: Frequency of cardioembolic causes of young ischemic stroke in South Asia

Cardioembolic Sources	Hossain ¹⁵ Bangladesh N=52	Samiullah ²⁵ Pakistan N=43	Harirchian ³⁶ Iran N=42	Ghandehari ¹⁹ Iran N=124	De Silva ⁹ Srilanka N=41
Valvular Heart Disease	34(67%)	7 (14%)	12(28.5%)	58(47%)	7(17%)
Infective endocarditis	4(8%)	0	1(2.5%)	2(1.5%)	0
Cardiomyopathy	0	2 (4%)	0	0	2(5%)
Cardiac myxoma	0	1 (2%)	0	1	0
Complete Heart Block	0	0	1(2.5%)	0	0
Coarctation of Aorta	0	0	1(2.5%)	0	0
Cardiac Surgery	0	0	1(2.5%)	0	0
Acute Myocardial Infarction	0	0	0	3(2.5%)	0
Akinetic left ventricular segment	0	0	0	2(1.5%)	0
Left ventricular thrombus	0	0	0	1	0
Atrial fibrillation	0	0	0	0	1(2.5%)

3. Other determined etiology

Stroke of other determined etiology is an important finding in young strokes. Table 3 displays frequency and distribution of various causes of stroke of other determined etiology with preferred investigations. Arterial dissection is an important cause of stroke among young adults in western countries.⁵⁶

Table 3: Distribution of other determined causes of Young Stroke and preferred investigations

Other determined causes	Study	Patients (%)	Investigations
Carotid/Vertebral Arterial dissection	Lipska ¹⁷	15(7%)	Angiography (CTA, DSA, MRA)
Oral contraceptives	Razzaq ¹⁴	1(0.9%)	Clinical history, Protein C and S, Fibrinogen factor, Factor VII, Factor X
	Hossain ¹⁵	2(3.8%)	
	Harirchian ³⁶	3(7%)	
Systemic Lupus Erythromatosus	Hossain ¹⁵	1(1.9%)	ANA, anti-dsDNA, ANCA
	Lipska ¹⁷	1(0.5%)	
Migraine	Samiullah ²⁵	2(4%)	Clinical history, exclude other causes of headache
	Razzaq ¹⁴	3(2.5%)	
Moyamoya Disease	Hossain ¹⁵	1(1.9%)	MRI, Angiography
	Lipska ¹⁷	1(0.5%)	
Pregnancy	Hossain ¹⁵	2(3.8%)	Protein C/S, Antithrombin, Serum titer for hepatitis B/C, HIV, Syphilis
	Samiullah ²⁵	6(12%)	
Vasculitis	Miah ³⁴	2(4%)	ESR, CRP, ANCA, Angiography, Biopsy of involved organ
Central nervous system infections	Samiullah ²⁵	17(34%)	Cerebrospinal fluid examination
Homocysteinemia	Lipska ¹⁷	1(0.5%)	Homocysteine Level
Takayasu Arteritis	Lipska ¹⁷	1(0.5%)	ESR, CRP, Angiography
Fibromuscular dysplasia	Lipska ¹⁷	1(0.5%)	Angiography
Antiphospholipid syndrome	Lipska ¹⁷	1(0.5%)	Lupus anticoagulant and anticardiolipin antibodies
Nephritic syndrome	Samiullah ²⁵	2(4%)	Renal function test, Urine analysis, Protein C/S, Antithrombin

CTA= Computed tomography angiography, DSA= Digital subtraction angiography, MRA= Magnetic Resonance Angiography, ANA= Antinuclear antibody, dsDNA= double stranded deoxyribonucleic acid, ANCA= Antineutrophil cytoplasmic antibodies, MRI= Magnetic resonance imaging, HIV= Human immune deficiency, ESR= Erythrocyte sedimentation rate, CRP= C-reactive protein.

Since angiography is not a routine investigation technique in most South-Asian countries,¹⁴ diagnosis of arterial dissection is not common. However, Lipska et al have reported about 7% of arterial dissection in their study. In an etiological study of young stroke in 1984, meningovascular neurosyphilis in men and puerperal cerebral venous thrombosis in women were the common findings among Indian patients.⁵⁷ Stroke in Antiphospholipid syndrome, diseases associated with increased lipoprotein and homocysteine or protein S deficiency or antithrombin III deficiency, snakebite, etc were also reported from various Indian studies.⁵⁸⁻⁶² South Asian people are at higher risk of deaths and disabilities due to infectious diseases.⁶³ Infectious diseases like meningitis, syphilis, malaria, borreliosis, varicella-zoster vasculopathy and cerebral vasculopathy due to human immunodeficiency virus are the well-known causes of stroke worldwide, but are unusual findings in most studies.^{11,64,65} In a study of

young Pakistani patients, infective meningitis was recognized as a major cause of stroke (34%) as shown in Table 3.²⁵ Tuberculous meningitis (TM) was diagnosed in 53% and bacterial meningitis in remaining patients which showed the higher prevalence of infectious diseases in Pakistan. Since prevalence of TM among Nepalese adult patients was found to be high, central nervous system infections are important findings to be sought for in young strokes.⁶⁶

CLINICAL CHARACTERISTICS AND LESION PATTERN

Advance neuroimaging techniques such as Diffusion weighted imaging (DWI) and magnetic resonance angiography (MRA) have high degree of reliability in diagnosis of acute ischemic infarction in young patients and are frequently used in the study of lesion pattern and vessels status of cerebral arteries.⁶⁷ Intracranial large artery disease was found to be common among ethnic South Asians in Singapore.³¹ Among major intracranial vessels, middle cerebral artery is the commonest site of stenosis in young patients.⁵⁴ Ethnic South Asians in England reported higher frequency of lacunar infarction in younger age-group.⁸ In a study in Sri Lanka, OSCP (Oxfordshire Community Stroke Project) classification was used to classify the young stroke.⁹ They also reported the majority of cases were lacunar infarcts and partial anterior circulation infarcts, followed by posterior circulation infarcts. Hemiplegia or hemiparesis and dysarthria were the most common clinical presentations.^{14,26} Razzaq et al reported the parietal lobe as the most common site of infarction.¹⁴ They further categorized the infarction into large size(>3cm), medium size(1.5-3.0cm) and small size(<1.5cm) which were found in 46%, 20% and 34% of their young patients respectively.

AFGHANISTAN:

No studies regarding incidence on stroke cases has been reported from Afghanistan.⁶⁸ In account of stroke mortality, WHO estimated 118.6/100,000 deaths in 2002.⁶⁹ In their study, young women (15-49 years) showed the BMI $\geq 25\text{kg/m}^2$ in 11.5% of cases which may be a rising risk factor for young stroke.^{48,69} Another study in Kabul showed the significant hypertensive cases (14.33%) among university students.⁷⁰ Risk factors like hypertension, diabetes and coronary artery diseases were also found to be highly prevalent in Afghani population.⁷¹ According to WHO data 2011, age adjusted stroke death rate in Afghanistan was estimated to be 109.47 per 100,000 of population.⁷²

BHUTAN:

No surveys on incidence or prevalence of stroke have been reported from Bhutan. According to STEP 2007, risk factors like hypertension, diabetes, alcohol, lack of exercises, low intake of fruits and vegetables and high intake of salty butter tea "suja" are common in Bhutanese community.⁷³ Every single person of Bhutan is associated with 1-2 risk factors of non-communicable diseases. Smoking is not acceptable in Bhutanese culture, and banning of Tobacco has made this risk factor less common in Bhutan.⁷⁴ According to WHO data 2011, age adjusted stroke death rate in Bhutan was estimated as 117.68 per 100,000 of population.⁷⁵

MALDIVES:

According to Steps survey, risk factors like hypertension, diabetes, tobacco use, less physical activity, low consumption of fruits and vegetables, and obesity are highly prevalent, and are the major risk factors of stroke in Maldives.⁷⁶ 10-year risk of stroke was also high in poor community with higher predominance in male.⁷⁶ World Health Organization (WHO) data has shown that 6.5% of total deaths in Maldives are due to stroke.⁷⁷ According to WHO data 2011, age adjusted stroke death rate in Maldives was 37.56 per 100,000 of population.⁷⁸

CONCLUSION

Ischemic stroke in young in this region can mainly be attributed to hypertension and smoking. Hyperlipidemias, diabetes mellitus, obesity, less physical activity, stress and drug abuse are the rising risk factors. So, healthy lifestyle changes and pharmacological interventions should be aggressively applied to modify these risk factors. Valvular heart diseases, arterial dissection, cardiomyopathy, infective meningitis, autoimmune and genetic disorders are common findings. The cause of young stroke remained undetermined in majority of studies. A further extensive diagnostic work up is thus recommended to determine the etiology in young ischemic stroke. FAST (Face, Arm, Speech, Time) test, which is a useful way to diagnose stroke by paramedics, needs to be popularized in South Asian countries.⁷⁹ Use of emergency thrombolysis is needed

to be promoted in clinical practice which may lead to early neurological improvement and decrease post-stroke economic burden. Further, the services of stroke rehabilitation center should be considered to improve the stroke care facility and to decrease the death rate of stroke patients.

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