



Published in final edited form as:

J Stroke Cerebrovasc Dis. 2009 ; 18(4): 304–308. doi:10.1016/j.jstrokecerebrovasdis.2008.11.004.

Young strokes in Sri Lanka: An unsolved problem

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Abstract

Stroke in young adults is more common in India and Sri Lanka and the reasons for this are not well understood. The current study was conducted to elucidate the risk factors and radiologic features in young people (age < 45 years) with ischemic stroke. Sociodemographic data, stroke risk factor information, and laboratory investigations were recorded in 41 cases with first-ever ischemic stroke. Most common risk factors for stroke in the 15- to 45-year-old age group were: hypertension, 8 (21%); family history of stroke, 7 (18%); transient ischemic attack, 6 (16%); hyperlipidemia, 3 (8.0%); and diabetes, two (5%). Age group younger than 15 years included 3 girls and one had a mass attached to the posterior mitral valve leaflet. Our observations underscore the importance of the presence of hypertension, family history of stroke, and transient ischemic attack in young adults and thus to adopt preventative strategies.

Keywords

Stroke in young; Sri Lanka; family history

Stroke is responsible for 5.7 million deaths per year worldwide.¹ The majority of them occur in low- and middle-income countries.² Sri Lanka is a developing country that is multiethnic, multireligious, and multilingual with cultural diversity and widely varying food habits and educational levels among its population, comprising ethnic Sinhalese (74%), Tamil (18.5%), Sri Lankan Moor (7%), and others (0.5%).

Stroke is considered a disease of older age, yet stroke in young adults is more common than generally appreciated.³ Stroke in the young is particularly tragic because of the potential to create a long-term burden for the victims, their families, and the community, contributing to lifelong medical treatment and loss of productivity. However, effective stroke prevention in the young cannot be attempted until the risk factors are clearly documented.

A hospital-based prospective study conducted at the National Hospital of Sri Lanka in 1974 and in 1989 accounted for stroke in young adults (aged 15-45 years): 10.4%⁴ and 33.6%,⁵ respectively. A longitudinal population-based descriptive study⁶ on stroke in the city of Kolkata, India, in 2007 revealed that 8.8% of patients constituted “young stroke,” which is similar to that reported from the Western countries.⁷ However, hospital-based studies⁸ from India in 2001 stated that young stroke (aged 15-45 years) accounts for 15% and 30% of strokes; this figure is possibly biased because of a preferential admission policy. The average age of patients in the developing countries with stroke is 15 years younger than in developed countries.⁹ The reasons for these differences are not well understood. The origin of the majority of strokes in young adults in Sri Lanka is unexplained.^{4,5,10,11} In a postmortem study in the below 40-year age group, 92% of cerebral infarction was a result of occlusive arterial disease of large vessel, nonatherosclerotic vasculopathy.¹²

Several studies reported an association between family history and stroke subtypes.¹³⁻¹⁷ Family history of stroke has been reported as an independent risk factor for ischemic stroke with onset before age 70 years.¹⁸ However, not many studies have investigated family history in patients with ischemic stroke at younger ages.¹⁹⁻²³ To our knowledge, the current study is the first to investigate the association between family history and ischemic stroke at younger ages in Sri Lanka.

We attempted to elucidate the risk factors (including family history of stroke), causes, and radiologic features of those aged younger than 45 years with ischemic stroke in the Neurological Institute of the National Hospital of Sri Lanka and compare our results with previous studies performed in Sri Lanka.

Materials and Methods

We studied 41 (21 male and 20 female) young patients with first-ever ischemic stroke occurring at 45 years of age or younger, attending the clinic and the patients admitted in the ward of the Institute of Neurology, a tertiary referral center at the National Hospital of Sri Lanka, from January 2006 to March 2007. Previous medical records were reviewed. Sociodemographic characteristics including age, sex, and race/ethnicity; stroke risk factor information; and family history of stroke and myocardial infarction (MI) was collected using a structured questionnaire and laboratory investigations. Computerized tomography (CT) scan and/or magnetic resonance imaging (MRI), neurovascular Doppler ultrasonographs, echocardiography, transesophageal echocardiogram (TEE), and blood test findings were recorded. Cerebral infarction was diagnosed on the basis of clinical findings and/or results of neuroimaging, brain CT scan, and/or MRI. Patients with transient ischemic attack (TIA) (i.e., neurologic deficits lasting <24 hours and no acute stroke evident by neuroimaging) were excluded.

Patients were asked whether parents or siblings were affected by stroke and/or MI, at what age, and whether they were alive or dead. When patients were unable to provide adequate family history, it was obtained from a relative. A positive family history was defined as history of stroke or MI in a first-degree relative. We did not attempt to distinguish hemorrhagic and ischemic stroke among the first-degree relatives.

Ethical clearance was obtained from the Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka. Informed written consent was obtained from the participants, with the purpose of the study having been previously explained.

Results

Demographic Features of the Patients

The cohort consisted of 41 (21 male and 20 female) patients, covering all the provinces except the Northern Province, with first-ever ischemic stroke. Patients younger than 45 years who were admitted to or visited the clinic of the Institute of Neurology, National Hospital of Sri Lanka, were included. A total of 38 patients were between the ages of 15 to 45 years. Of these, there were 21 (55%) men (19 Sinhalese, one Tamil, and one Moor) with a mean age of 33 years and 17 (45%) women (16 Sinhalese and one Tamil) with a mean age of 36 years. The study population aged younger than 15 years comprised 3 female patients (two Sinhalese and one Tamil) with a mean age of 7 years.

Risk factors

Age Group: 15 to 45 Years Old

In all, 27 (71%) patients of the 38-patient cohort in the 15- to 45-year-old age group with ischemic stroke did not have the following conventional risk factors: hypertension (HT), diabetes mellitus (DM), or hyperlipidemia (HL). The 5 most common patient risk factors were: (1) HT in 8 (21%); (2) family history of stroke in 7 (18%; one male and 6 female) who were all Sinhalese (specifically, family history of stroke only in 4 [one male with maternal history and 3 female {two with maternal and one with paternal history}]); family history of stroke and MI in 3 female patients [one with paternal history, one with maternal and paternal history, and one with paternal history and brother with MI]; and family history of MI in two male patients [one with maternal and one with paternal history]; (3) TIA in 6 (16%); (4) HL in 3 (8%); and (5) DM in two (5%). Cigarette smoking and alcoholism were not found in the cohort.

Ten (26%) (7 male and 3 female) patients had potential cardiac causes. Five (13%) patients had valvular heart diseases: 4 (10%; 3 male and one female) with mitral valve prolapse (two with mitral regurgitation [MR] and one with mitral stenosis and MR) and one with tricuspid regurgitation. Two female patients had atrial septal defect, two male patients had cardiomyopathy and one had irregular rhythm, one male patient had MI, and one female patient had a history of rheumatic fever. All patients were Sinhalese except one Tamil male patient with mitral valve prolapse with MR and mitral stenosis.

Three (8%) patients had prolonged prothrombin time. Antiphospholipid antibody tests (lupus anticoagulant [LA] and anticardiolipin antibodies) were performed in 26 (68%) patients from the ages of 15 to 45 years and all 3 patients younger than 15 years. Prevalence of 8% (2/26) of antiphospholipid antibody positivity was seen in the 15- to 45-year-old age group. Anticardiolipin antibodies and LA was positive in a 34-year-old woman with left capsuloganglionic lacunar infarct and a history of systemic lupus erythematosus. LA was positive in one woman who developed left-sided hemiparesis at the age of 22 years, 1 week after childbirth. Right-sided cerebral infarct was shown on CT scan, having a history of hypothyroidism. Two (5%) patients had eclampsia (developed stroke 2 days and 1 month after delivery and both had high blood pressure during pregnancy). Nine (24%) patients had multiple risk factors (Table 1). All 38 patients underwent radiologic investigations (CT or MRI). Brain CT scan was performed in 34 (89%), MRI in 21 (55%), carotid duplex scan in 24 (63%), TEE in 10 (26%), and echocardiography in 38 (100%).

Classification of stroke was based on Oxfordshire Community Stroke Project.²⁴ In all, 31 patients with cerebral infarction confirmed by brain imaging had two total and 10 partial anterior circulation infarcts; 9 had posterior circulation infarct and 10 had lacunar infarcts. Seven patients in whom CT scan did not show an infarct were classified based on simple

clinical findings: 5 patients as having lacunar syndromes and 3 patients as having posterior circulation syndrome.

Age Group: Younger than 15 Years

Three girls aged 1 year and two months, 5 years, and 14 years (two Sinhalese and one Tamil) did not show causative factors except the 14-year-old patient, whose 2-dimensional echocardiogram and TEE showed a mass attached to the posterior mitral valve leaflet. The radiologic findings for the 3 patients were right-sided infarct, left-sided posterior parietal infarcts, and bilateral middle cerebral artery (MCA) infarct, respectively.

Discussion

To our knowledge, this is the first comprehensive study to evaluate risk factors for ischemic stroke in young adults in Sri Lanka. Stroke in the young poses a diagnostic challenge. A prospective study of stroke in young adults in 1972 at Badulla Hospital, Sri Lanka, servicing a largely rural population, found 44 cases of cerebral infarction caused by occlusive vascular disease confirmed angiographically; none had HT, DM, or hypercholesterolemia.¹⁰ Of the 152 patients admitted to General Hospital, Colombo, Sri Lanka, during a 10-year period, 108 (71%)⁴ and 27 (71%) in the 15- to 45-year age group in the current study did not have conventional risk factors of HT, DM and HL. Later, two studies were done in a urban hospital indicating the adverse effect of urbanization.

Male preponderance has been reported in young patients with ischemic stroke older than 15 years in Asian countries: 76.3% in India (age 15-45 years),²⁵ 75.2% in Korea (age 15-44 years),²⁶ 71.4% in Taiwan (age 18-45 years),²⁷ 62.8% in Israel (age 17-49 years),²⁸ and 54% (age 15-45 years) in the current study. An exception to the Asian male predominance of early-onset stroke is India, with 48% male in the age group of 15 to 45 years.²⁹

HT has been identified as the most common risk factor for stroke in the 15- to 45-year-old age group: 21% in the current study and 20% in the study at the General Hospital, Colombo.⁴ However, none had HT in the study done in the rural Badulla Hospital,¹⁰ indicating the adverse effect of urbanization. Up to 75% of people with elevated blood pressure in a community may be unidentified or inadequately treated and physicians can still further reduce the incidence of stroke by identification and improved treatment of HT.³⁰

The second most common risk factor identified in the 15- to 45-year age group in the current study was family history of stroke, present in 7 Sinhalese (18.4%). Twin and family studies have determined that there is a significant familial or genetic component underlying the occurrence of stroke³¹ and that a positive family history is a significant risk factor for future stroke among offspring.³² There is evidence that familial aggregation is strongest in young-onset stroke and that the magnitude of aggregation increases with decreasing proband age.^{33,34} Meta-analysis review of all published twin studies on stroke and studies of family history of stroke suggested a stronger genetic influence in younger age groups.³⁵

Both paternal and maternal histories have been reported to be associated with an increased risk of stroke.³⁶ Family history of stroke was present in 6 female probands (6/17 [35%]) and one male proband (1/21 [5%]), with maternal history present in 4 (3 female probands and one male proband) and paternal history present in 3 female probands in the current study. Systematic review and meta-analysis shows that female patients are more likely to have a maternal than a paternal history of stroke,³⁷ but the finding of the current study shows that female probands have 50% (3/6) maternal history of stroke. Familial aggregation of stroke in the current study (7/38 [18%]), with a female preponderance (6/17 [35%] v 1/21 [5%]), and 50% maternal history of stroke in female probands warrants further studies to ascertain

genetic and/or shared environment or the complex interplay between genetic and environmental factors and/or common familial exposure to environment or lifestyle risks in the current study.

TIA was present in 6 (15.8%) patients in the 15- to 45-year-old age group in the current study. TIA remains a significant independent risk factor for both stroke and MI.^{19,38} In a large US study, 11% of patients with a history of TIA developed stroke during a 90-day period after the event; half of all strokes occurred in the first 2 days.^{20,39} Occurrence of TIA provides an opportunity to prevent stroke in a group at very high risk.

HL and DM was seen in 3 (8%) and two (5%) patients in the 15- to 45-year age group in the current study compared with 8 (5%) each in the study done in the General Hospital, Colombo.⁴

Childhood stroke results in significant mortality and long-term morbidity.⁴⁰ In all, 7.3% (3/41) patients had childhood stroke (<15 years) in the current study as compared with 2.75% (3/109) reported in India.²⁹ Considering its devastating effect so early in life, further multi-center studies are needed with a large sample size of childhood stroke.

In an autopsy study of 10 patients (age < 40 years) with occlusive cerebrovascular disease, a new disease entity of “transient embologenic aortoarteritis” was described. However, in the last two decades no further study has confirmed these findings.⁴¹

The incidence of cerebellar infarction in patients with stroke at all ages is approximately 1.5%.⁴² The higher percentage, 4 (10.5%) in the 15- to 45-year age group, in the current study warrants further study.

Our study does have some potential shortcomings.

Sri Lanka is a developing country with 85% of its population living in rural areas and a growing number of internally displaced persons because of the protracted war. These people possibly have limited access to tertiary care hospitals. Our study is a tertiary care hospital-based study and may be subject to selection bias. The Institute of Neurology is the only national tertiary care hospital in Sri Lanka and patients are referred from other hospitals throughout Sri Lanka. Hence, our study is likely to be biased in favor of disabling and complicated stroke cases. Lady Ridgeway Hospital for Children is a tertiary referral national pediatric hospital in Sri Lanka with an annual admission of 73,554 and 69,399 children and infants in 2004 and 2005, respectively.⁴³ Three cases (<15 years) in our study may not reflect the true prevalence of stroke in the younger than 15-year-old age group.

The small sample of 41 patients (3 patients aged < 15 years and 38 patients aged 15-45 years) and 7 patients with family history of stroke may result in diminished statistical power to detect more moderate associations with risk factors. Family history data were obtained from patients who may not be the most accurate and complete family informant about the occurrence of stroke in their relatives. The high incidence of strokes of indeterminate origin may possibly be a result of incomplete investigation of our patients.

Our observations underscore the importance of the presence of HT, family history of stroke, and TIA in young adults for screening and prevention to reduce the burden of ischemic stroke in young adults.

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Table 1

Risk factors for patients of young stroke, 15- to 45-year-old age group

Risk factors	No.	Percent
Conventional risk factors (HT, DM, HL) not found	27	71
HT	8	21
Family history of stroke	7	18
Transient ischemic attack	6	16
HL	3	8
MVP with MR	3	8
DM	2	5
Autoimmune diseases		
Anticardiolipin antibodies	1	3
Lupus anticoagulant and anticardiolipin antibodies	1	3
Eclampsia	2	5
Multiple risk factors	9	24
Smoking and alcohol	0	0

Abbreviations: DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; MR, mitral regurgitation; MVP, mitral valve prolapse.