INTRODUCTION

Ischaemic stroke is an important cause of morbidity in all age groups. Incidence of stroke ranges from 182 to 342 per 100,000 population in Asia.1 An estimated 3.5 million of the 5.5 million deaths from stroke occur in developing countries each year.2 Stroke in people under 45 years of age is less frequent than in older populations but has a major impact on the individual and society.3

More than two-third of the global burden of stroke is borne by the developing countries, where the average age of patients with stroke is 15 years younger than in the developed countries.4 According to the available data, fewer than 5% of all strokes occur in subjects under 35 years of age in Western countries,5 whereas higher proportions between 19 – 30% were reported in that age group in developing countries.6 Many studies done in Asia have shown an increased prevalence of stroke in the young.7,8 In a systematic review of 15 population-based stroke incidence studies, the rate of total stroke for those aged less than 45 years ranged from 0.1 – 0.3 per thousand person years, while those aged 75 – 85 years, the rate was 10 – 12 per 1000 person years.9

However, a recent study revealed that the risk of stroke has increased by 100% in low and middle income countries over the last decade and the developing world suffers 85% of all stroke-related deaths worldwide.10 Similarly, the first urban population based estimate of lifetime prevalence of cerebrovascular disease in Pakistan shows an alarmingly high burden of disease. In comparison to existing worldwide literature on stroke prevalence, this study shows a prevalence of stroke which is almost twice the highest reported prevalence in the world today.11 This study suggests that patients who have suffered from stroke have an average age of about 50 years which is almost a decade younger than their Western counterparts.

The objective of this study was to determine the etiologic patterns of stroke in relatively younger population, 15 – 45 years of age, particularly with reference to known risk factors.

METHODOLOGY

This was a descriptive study, conducted at the Neurology Department of Jinnah Postgraduate Medical Centre, Karachi, Pakistan.

Consecutive patients with first ever ischaemic stroke admitted in the study centre during calendar year period 2010 were recruited. Patients with intracerebral haemorrhage, head trauma, subarachnoid haemorrhage and transient ischaemic attack were excluded.

Stroke was defined as an episode of focal neurologic deficit with acute onset and lasting more than 24 hours.

ABSTRACT

Objective: To determine the etiologic patterns of ischaemic stroke in young adults.

Study Design: A descriptive study.

Place and Duration of Study: Department of Neurology, Jinnah Postgraduate Medical Centre, Karachi, from January to December 2010.

Methodology: All ischaemic stroke patients aged 15 – 45 years were included. The etiologic patterns were classified using TOAST (Trial of ORG 10172 in acute ischaemic stroke) classification and comparisons were made between different stroke subtypes with reference to traditional risk factors like age, smoking, hypertension, diabetes mellitus and dyslipidemia. Results were described in percentages.

Results: There were 75 cases and higher proportion of patients had ischaemic stroke due to cardiac etiology below the age of 35 years. Nineteen patients had cardioembolic stroke [8 (42.1%) males and 11 (57.9%) females]; 15 patients had large artery atherosclerosis [males 9 (60%), females 6 (40%)]; 17 patients had stroke of determined etiology (SDE), [6 (35.2%) males and 11 (64.8%) females] among whom 47% were due to venous sinus thrombosis. Twelve patients had stroke of undetermined etiology (SUE), [5 (41.6%) males and 7 (58.4%) females] and 12 patients had stroke due to small vessel disease (SVD) [8 males (66.7%) and 4 (33.3%) females.

Conclusion: Cardioembolism, venous sinus thrombosis and premature atherosclerosis are common etiologies in young patients with acute ischaemic stroke.


Etiologic Patterns of Ischaemic Stroke in Young Adults

Khalid Sher, Shahnaz Shah and Suneel Kumar

INTRODUCTION

Ischaemic stroke is an important cause of morbidity in all age groups. Incidence of stroke ranges from 182 to 342 per 100,000 population in Asia.1 An estimated 3.5 million of the 5.5 million deaths from stroke occur in developing countries each year.2 Stroke in people under 45 years of age is less frequent than in older populations but has a major impact on the individual and society.3

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Stroke was defined as an episode of focal neurologic deficit with acute onset and lasting more than 24 hours.
(or lasting < 24 hours with imaging evidence of ischaemic infarct corresponding with current symptoms).

TOAST classification was used to define the etiology of stroke as follows: large artery atherosclerosis, cardioembolism, small vessel disease, stroke of determined etiology and stroke of undetermined etiology. A probable diagnosis was made if the clinical findings, neuroimaging and the results of diagnostic studies were consistent with one subtype and other etiologies had been excluded. A possible diagnosis was made when clinical findings and neuroimaging data were suggestive of specific subtype but other studies could not be carried out.

Informed consent was taken and purpose of the study was explained to patients or their informants. After detailed history and examination, all patients underwent standard diagnostic investigations. The laboratory investigations included complete blood counts (CBC), ESR, urine examination, liver function tests, glycosylated haemoglobin (Hb A1C), lipid profile and renal function tests. Thrombophilia screening and immunologic studies (anti-nuclear and anti-ds DNA antibodies) were performed in patients when indicated. Electrocardiogram (ECG), echocardiogram, X-ray chest, imaging studies of brain including CT scan, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) of brain and duplex ultrasound study of extra cranial vessels were carried out routinely in all patients.

Smoking was defined as current use of > 1 cigarette per day. Dyslipidemia was defined as receiving lipid lowering agent, total cholesterol > 240 mg/dL and LDL cholesterol > 160 mg/dL. Diabetes mellitus was defined as receiving oral hypoglycemic agents/insulin treatment with glycosylated haemoglobin level ≥ 6.5%. Hypertension was defined as receiving antihypertensive treatment, ECG evidence of left ventricular hypertrophy with no evidence of valvular heart disease, presence of hypertensive retinopathy and persistently elevated blood pressure > 48 hours after the acute ictus (SBP > 140 and /or DBP > 90 mmHg).

Data was entered on a pre-designed proforma. Results of demographic characteristics, etiologic patterns and risk factors were analyzed using SPSS (Statistical Packages for Social Sciences) version 11.0. Chi-square test was used to compare the effect of modifiable risk factors on two variants of young stroke.

**RESULTS**

A total of 75 patients aged 15 – 45 years were admitted with a diagnosis of ischaemic infarct over the period of one year. There was an overall female preponderance (F/M ratio 1.1/1). However, this ratio was not uniform throughout all stroke subtypes. Females outnumbered males in stroke due to cardioembolism and determined as well as undetermined etiologies, whereas males outnumbered females in stroke due to large artery atherosclerosis and small vessel disease.

Patients were subgrouped into three age groups. Majority of patients having evidence of cardioembolic source and stroke due to determined etiology fell between 15 – 29 years of age while more than 60% of those with stroke due to large artery atherosclerosis and small vessel disease were found to be in advanced age groups of 40 years and above (Table I).

Cardioembolism was the most frequent cause of young stroke (25%). It was followed by stroke due to determined etiology (23%) and large artery atherosclerosis (20%). Small vessel disease (16%) and stroke due to undetermined etiology (16%) were least frequent etiologic patterns (Table II).

Among the cardiovascular sources, majority were due to valvular heart disease followed by prosthetic heart valves and infective endocarditis. There were no patients with non-valvular atrial fibrillation or sick sinus syndrome; or medium risk cardioembolic source.

In patients with stroke due to determined etiology, females outnumbered males by 1.8:1. Pregnancy related phenomenon was the major cause of stroke in this category. Venous sinus thrombosis was found to account for 47% of these cases followed by arterial dissection in 23% and connective tissue disorders in 18%.

Stroke due to large artery atherosclerosis was seen in a high percentage of cases. However, this pattern was more frequent after 30 years of age not seen between 15 – 30 years of age.

**Table I: Demographic characteristics (age and gender) of patients (n = 75).**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Cardioembolism (n = 19)</th>
<th>Large artery atherosclerosis (n = 15)</th>
<th>Stroke due to determined etiology (n = 17)</th>
<th>Stroke due to undetermined etiology (n = 12)</th>
<th>Small vessel disease (n = 12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 – 29</td>
<td>10 (52.6%)</td>
<td>0 (0%)</td>
<td>12 (70.6%)</td>
<td>3 (25.0%)</td>
<td>0 (0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>30 – 39</td>
<td>8 (42.1%)</td>
<td>6 (40%)</td>
<td>4 (23.5%)</td>
<td>7 (58.3%)</td>
<td>4 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>40 and above</td>
<td>1 (5.3%)</td>
<td>9 (60%)</td>
<td>1 (5.9%)</td>
<td>2 (16.7%)</td>
<td>8 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (42.1%)</td>
<td>9 (60%)</td>
<td>6 (35.2%)</td>
<td>5 (41.6%)</td>
<td>8 (66.7%)</td>
<td>0.393</td>
</tr>
<tr>
<td>Female</td>
<td>11 (57.9%)</td>
<td>6 (40%)</td>
<td>11 (64.8%)</td>
<td>7 (58.4%)</td>
<td>4 (33.3%)</td>
<td></td>
</tr>
</tbody>
</table>
There were 12 (16%) patients who could not meet probable as well as possible TOAST criteria for etiologic classification.

Smoking, hypertension and dyslipidemia were statistically significantly associated risk factors in this series of younger stroke patients as well (Table III).

However, diabetes mellitus was found to have insignificant association in any of the etiologic patterns of stroke.

Table II: Distribution of causes of young stroke.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolism</td>
<td>19</td>
<td>25.3%</td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>15</td>
<td>20.0%</td>
</tr>
<tr>
<td>Stroke due to determined etiology</td>
<td>17</td>
<td>22.7%</td>
</tr>
<tr>
<td>Stroke due to undetermined etiology</td>
<td>12</td>
<td>16.0%</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>12</td>
<td>16.0%</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table III: Comparative analysis of modifiable risk factors in variants of young stroke: chi-square test used to compute the differences in proportions.

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Large artery atherosclerosis/small vessel disease (n = 27)</th>
<th>Stroke due to determined etiology/stroke due to undetermined etiology (n = 29)</th>
<th>p-value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>13 (48.1%)</td>
<td>6 (20.6%)</td>
<td>0.030*</td>
<td>3.55</td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td>4 (14.8%)</td>
<td>3 (10.3%)</td>
<td>0.700</td>
<td>1.5</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>16 (59.2%)</td>
<td>9 (31.0%)</td>
<td>0.034*</td>
<td>3.23</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (40.7%)</td>
<td>4 (13.7%)</td>
<td>0.034*</td>
<td>4.29</td>
</tr>
</tbody>
</table>

* Statistically significant (p < 0.05).

**DISCUSSION**

This study was conducted on all consecutive adult patients with first ever ischaemic stroke in young age group (15 – 45 years). Internationally recognized TOAST classification system was applied in all patients with acute ischaemic stroke < 45 years of age and evaluated the role of traditional risk factors with reference to various subtypes of ischaemic stroke.

Acute ischaemic stroke was classified into five subtypes based on TOAST classification. Cardioembolism was found to be the most frequent cause of acute ischaemic stroke (25%) in young adults followed by stroke due to determined etiology (23%).

In comparison with the study by Nedeltchev et al. carried out at Switzerland, this study showed similarly high frequency of stroke due to cardioembolism and stroke due to undetermined etiology but the interesting aspect of the present study was the higher frequency of stroke due to large artery atherosclerosis (20% vs. 4%). When results were compared with study by Lipska et al. in neighbouring country, there was close resemblance in the frequency of etiologic subtypes.

There was higher frequency of traditional stroke subtypes due to large artery atherosclerosis and small vessel disease in this study (20% and 16%) as well as in an Indian study (12% and 4%). Among cardiovascular causes, valvular heart disease was found to be the most frequent cause of acute ischaemic stroke, similar to the results found in South Indian as well as Helsinki study. Prosthetic heart valves were the next frequent cause of cardioembolism in this series.

While comparing with Bergen stroke study, a significant difference was found. Patent foramen ovale was found to be the most frequent cause followed by mechanical heart valves in Bergen stroke study and rheumatic heart disease was conspicuously absent from the list of causes of young stroke. However, rheumatic heart disease was found to be the frequent cause of young ischaemic stroke in a Taiwanese study.

In this series of patients, stroke due to determined etiology made up 23% of total number of cases. But interesting feature was very high proportion of pregnancy related stroke due to venous sinus thrombosis. Lanska et al. reported that frequency of peripartum intracranial venous thrombosis is 8.9 – 11.6 cases per 100000 deliveries, while higher frequency was reported by Khealani et al. where arterial dissection was next frequent determined etiology followed by collagen vascular disorders like Takayasu arteritis and systemic lupus erythematosus (SLE). This was in sharp contrast to the Bergen stroke study and Helsinki young stroke registry data where arterial dissection was found to be the most frequent etiologic pattern among determined causes. It could be due to difference in the study design between their studies.

In the Baltimore-Washington cooperative young stroke study; hypertension, diabetes mellitus and current smoking emerged as important risk factors for stroke. The accumulation of traditional risk factors in males and with aging explains the increased frequency of ischaemic stroke due to large artery atherosclerosis and small vessel disease in those above 35 years of age.

When subgroup were dichotomized into stroke due to large artery atherosclerosis and small vessel disease, similar to the results found in South Indian, as well as Helsinki study. Prosthetic heart valves were the next frequent cause of cardioembolism in this series.

The unexpectedly high frequencies of modifiable risk factors in this study indicate a need for primary and secondary precaution strategies in young adults.

The main limitation seems to be the relatively small number of patients recruited in this study. However, it is to be taken into account that these patients were consecutive cases of young ischaemic stroke admitted.
in our unit through emergency department over a period of one year in the largest tertiary care hospital of a mega city.

Majority of other studies have recruited their patients over a number of years which may reflect overall decreased incidence of young stroke compared to old stroke. Some cases of etiologic diagnosis may have been missed by lack of Holter monitoring.

Traditionally, cardioembolism and other rare prothrombotic and collagen disorder are counted as cause of young stroke, but this study provides valuable information about role of traditional risk factors in young stroke patients. This study also gives insight into the significance of other potentially preventable and treatable etiologies like arterial dissection, venous sinus thrombosis and rheumatic heart disease as a cause of stroke in younger patients.

CONCLUSION

Cardioembolism, venous sinus thrombosis and premature atherosclerosis are common etiologies in young patients with acute ischaemic stroke.

REFERENCES