

## Original Research Article

# Risk factors including prothrombotic work up in young ischemic stroke Indian patients

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## ABSTRACT

**Background:** Stroke in young poses a major health problem. Various Indian studies have shown the incidence of stroke to be 10-15%. Cerebral venous thrombosis and rheumatic heart disease are the leading causes of stroke in the young in India. Thrombophilic factors have been implicated in 4-8% of the young strokes worldwide. Protein C deficiency is the most common thrombophilia marker followed by a deficiency of protein S, Factor V Leiden mutation, and antithrombin (AT) deficiency. Aims and objectives was the study of stroke in young is important for various reasons. The etiology and risk factors are more diverse and different as compared to the elderly. Therefore, these may indicate separate therapeutic approaches. The aim is to study the profile of ischemic stroke cases among the young.

**Methods:** The study was carried out at a tertiary care defence hospital between December 2018 to December 2019. All cases of fresh ischemic stroke who were more than 15 and less than 45 years of age were included. Following clinical evaluation, patients underwent complete haemogram, blood sugar levels, lipid profile and other metabolic parameters. All patients were subjected to chest radiography, 12 lead ECG, and 2D echocardiography, Non-contrast CT head and MRI brain. Prothrombotic work up was also done.

**Results:** A total of 41 patients (12.69%) presented with ischemic stroke before 45 years of age. Out of these 10 (24%) were females and 31 (76%) were male. None of the women smoked or consumed alcohol. Among the males, 19 (47%) smoked more than 10 cigarettes or bidis per day and 9 (22%) were moderate-to-heavy drinkers of alcohol. Hypertension was present in 7 (18%) and diabetes mellitus in 3 (7%) patients. Serum cholesterol was elevated in 7 (18%) patients and triglycerides in 17 (42%). Protein S deficiency was found in 28.8% patients, while protein C deficiency was detected in 21% patients and antithrombin III deficiency in 12% patients.

**Conclusions:** Although traditional risk factors, such as hypertension, diabetes, and smoking, are associated with stroke in both elderly and young, this study shows that other modifiable risk factors such as alcohol consumption were also prevalent. The most common etiological cause was found to be venous infarction followed by cardio embolic cause. Deficiency of Protein S was the most common prothrombotic defect followed by deficiency of Protein C.

**Keywords:** Brain Ischemia, Protein C, Risk Factors, Stroke

## INTRODUCTION

While the peak age of stroke occurrence is 55 to 65 years, events occurring at a younger age assume importance as

they may have causative factors which are different from the conventional ones. Moreover, the overall disease burden on the society increases with the economically productive group affected. While a specific definition of “young stroke” is lacking, the vast majority of authors consider “young stroke” to pertain to individuals under 45 years of age.<sup>1</sup>

Cerebral venous thrombosis and rheumatic heart disease are the leading causes of stroke in the young in India. Other conditions such as tubercular meningitis and autoimmune angitis, coagulopathy, elevated lipoprotein (a), homocysteine, and elevated anti cardiolipin antibodies have also been reported.<sup>2</sup>

Diabetes, hypertension, heart disease, current smoking, and long-term heavy alcohol consumption are major risk factors for stroke in young adults as in older population. An ever-increasing number of pro-thrombotic states have been associated with stroke. Specific tests to exclude many of these uncommon disorders are expensive, not widely available. Protein C deficiency is the most common thrombophilia marker followed by a deficiency of protein S, Factor V Leiden mutation, and antithrombin (AT) deficiency.

## METHODS

The study was carried out in Army Hospital (Research and Referral), which is a tertiary care hospital for the armed forces between December 2018 to December 2019. All cases of fresh ischemic stroke reporting, referred, or transferred to this hospital (within two weeks of ictus) who were more than 15 and less than 45 years of age were included; while follow up cases of stroke (stroke onset beyond 2 weeks) and patients in whom stroke could not be confirmed by neuroimaging were excluded in this study.

This Observational study was carried out between December 2018 and December 2019 after approval from the ethical committee.

### Data collection technique and tools

Patients were included in the study after an informed consent from them or their immediate relatives. Detailed history was obtained from the patient or relatives with emphasis on time of onset of symptoms, mode of onset of symptoms, and risk factor details. Following clinical evaluation, patients underwent the following investigations: complete haemogram, blood sugar levels (fasting and post prandial), lipid profile (12- hour fasting state), and other metabolic parameters.

All patients were subjected to chest radiography (for any evidence of cardiomegaly), 12 lead ECG, and 2D echocardiography to detect cardiac abnormalities. Neuroimaging was performed in all in the form of non-contrast CT head and MRI brain (T1, T2, flair, diffusion

studies) while Magnetic Resonance Angiography (MRA) brain was carried out in selected cases. Prothrombotic work up including Protein C, protein S, antithrombin III, Factor V Leiden was done

Data was analysed in a descriptive manner and p-values were calculated using the chi-square test.

## RESULTS

A total of 41 patients (12.69%) had ischemic stroke before 45 years of age. Out of these 10 (24%) were females and 31 (76%) were male. None of the women smoked or consumed alcohol. Among the males, 19 (47%) smoked more than 10 cigarettes or bidis per day and 9 (22%) were moderate-to-heavy drinkers of alcohol.

Hypertension was present in 7 (18%) and diabetes mellitus in 3 (7%) patients. Serum cholesterol was elevated in 7 (18%) patients and triglycerides in 17 (42%). Two women were on oral contraceptives at the time of occurrence of the stroke. In cardioembolic stroke, the most common cardiac lesion was rheumatic heart disease (3 patients), followed by dilated cardiomyopathy (1 patient) and patent foramen ovale (1 patient).

Venous infarct (CVT) was the most common cause found in this group (n=26; 63.41%). Cardio embolic causes were found in 5 patients (12.19%) (Table 1).

**Table 1: Causes of stroke in young.**

Cause	Number of patients	%
CVT	26	63.41
Cardio embolic	05	12.19
Others	10	24.39

**Table 2: Procoagulant profile in stroke in young (n=41).**

Factor	Number of patients	%
Protein C	9	21.95
Protein S	11	28.82
Antithrombin III	05	12.19
Factor Va Leiden Mutation	01	2.43

Protein S deficiency was found in 11 patients, while protein C deficiency was detected in 9 patients and antithrombin III deficiency in 5 patients (Table 2).

**Table 3: Profile of venous infarcts.**

Venous infarct	Number of patients	%
With parenchymal lesion	20	76.92
No parenchymal lesion	06	23.08

Statistically 76.9% (n=20) patients had venous infarcts with parenchymal lesion while 23.08% (n=6) patients had venous infarcts without parenchymal lesion (Table 3).

## DISCUSSION

Various Indian studies have shown the incidence of stroke to be 10-15%.<sup>3</sup> Trivandrum stroke registry showed the incidence of stroke in young to be only 3.8%.<sup>4</sup> this study showed a prevalence of 12.69% of stroke in young.

An overall male preponderance was seen. This is similar to data from Indian and western studies.<sup>5-8</sup> However, some population-based studies reveal an increased incidence among women under 30 years old, as do some case series, while studies also show risk of haemorrhagic stroke more in men, with no significant sex difference in risk of infarct or SAH.<sup>9,10</sup>

However, all patients with CVT were female. Traditional risk factors such as hypertension, diabetes mellitus, and deranged lipid profile were detected in this study, of which only hypertension was significantly associated with ischemic stroke. Hypertension was reported as a risk factor in most studies. Diabetes mellitus has been reported as a risk factor for ischemic stroke from India and Switzerland, but this was found in only 7% of the cases.<sup>6,11</sup>

Important modifiable risk factors such as smoking, and alcohol consumption were found to be significantly associated with ischemic stroke in this study. High alcohol consumption is associated with ischemic stroke, due to the reversal of beneficial effect of light consumption on lipid metabolism and increases the risk of acute ventricular and supraventricular cardiac arrhythmias, marked blood pressure elevation, platelet activation, and humoral hypercoagulability.<sup>12</sup> The association of alcohol consumption with stroke was higher in this study, then reported by other studies.

The most common etiological cause was found to be venous infarction (63.41%), followed by cardio embolic causes in 12.19%. Cerebral venous thrombosis and rheumatic heart diseases have been reported to be the most common causes of stroke in young in India.<sup>2</sup> However, our patients had no infective endocarditis, which is usually common association of rheumatic heart disease. Tubercular meningitis, coagulopathy, elevated homocysteine levels are also reported as other cause of stroke in young in India.<sup>1</sup>

This study showed protein S deficiency to be the most common cause of venous infarction (26.82%) followed by protein C deficiency (21.95%). Anti-thrombin III deficiency was found in 12.1 % and Factor V Leiden in 2.4% of patients. Camerlingo et al, evaluated non-haemorrhagic stroke in 50 patients and found protein C deficiency in three of them.<sup>13</sup> Similarly, Jha et al, found one patient of protein C deficiency in stroke in young at

high altitude.<sup>14</sup> The incidence of protein S deficiency in patients younger than 45 years of age with unexplained venous thrombosis is 10% or greater. Munts et al, from Netherlands, presented a case series of consecutively studied 120 patients (52 men and 67 women), with median age of 38 years, who presented with acute cerebral infarction or TIA.<sup>15</sup> Decreased protein S was found in 20 patients. Currently it appears that the prevalence of hereditary anti-thrombin deficiency in general patient population with thrombotic or thromboembolic events is about 3% to 8%.<sup>16</sup> These patients have increased risk of venous thrombotic events and pulmonary thromboembolism.

A study in BHU India has shown significant reduction in biological and immunological activity of AT-III in 98 patients of occlusive stroke.<sup>17</sup> Most of the earlier published studies from India did not have information regarding these inherited prothrombotic states due to lack of laboratory facilities and resources to conduct these tests. But in recent times, Pai et al, recruited 612 consecutive patients from various hospitals of Bombay over a period of 9 years and tested them for the common thrombophilia markers protein C, protein S, antithrombin and factor V Leiden mutation.<sup>18</sup> Around 18% of the patients were positive for the thrombophilia markers studied. Protein C deficiency was the most common thrombophilia marker followed by a deficiency of protein S, FVL mutation, and AT deficiency.

## CONCLUSION

Stroke in young requires a different approach to investigate and treat. This is due to the different underlying etiology as compared to elders. Although traditional risk factors, such as hypertension, diabetes, and smoking, are associated with stroke in both elderly and young, this study shows that other modifiable risk factors such as alcohol consumption were also prevalent. The most common etiological cause was found to be venous infarction followed by cardio embolic cause. Deficiency of Protein S was the most common prothrombotic defect followed by Protein C.

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