

## A STUDY ON THE ROLE OF DYSLIPIDEMIA AND OTHER UNIDENTIFIED RISK FACTORS IN ISCHAEMIC STROKE IN OUR POPULATION

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### Abstract

**Background:** To find the age incidence and sex ratio of ischaemic stroke at our place. To find out the risk factors of ischaemic stroke with special reference to dyslipidemia and other unidentified risk factors in our population like lipoprotein(a), homocysteine and fibrinogen. **Materials and Methods:** Forty patients of Cerebral Infarction confirmed by CT scan of Brain have been taken for the study from the departments of General Medicine and Neurology, Darbhanga Medical College and Hospital, in a span of one year. Patients with Hemorrhagic stroke or TIA or having potential sources of embolism from heart are excluded from the study. Detail particulars of the patient were taken including name, age, sex, address, occupation, date of admission and date of examination. General survey was done concentrating on waist-hip ratio, carotid pulse, blood pressure, and peripheral signs of atherosclerosis like xanthoma, xanthelesma and locomotor brachialis. Detail examination of nervous system was done- whether the patients were conscious, alert and cooperative, drowsy or unconscious. **Result:** The study on 40 patients of ischaemic stroke carried out at Darbhanga Medical College and Hospital shows that persons in the 6th and 7th decades of life are the most vulnerable to suffer ischaemic stroke; 55% of the study group belonged to the age group between 50-69 years. The mean serum total cholesterol (TCh) level was 196.6mg/dl with only 45% cases having TCh above 200 mg/dl. The mean HDL-C level was 43.2 mg/dl which was normal while only 30% cases had HDL level below 40mg/dl. The mean LDL-C level was raised i.e., 118.85 mg/dl with 47.5% cases had LDL-C level above 100 mg/dl. The mean TG level was raised i.e. 196.43 mg/dl with 55% cases had TG above 150mg/dl. 29 patients i.e., 72.5% of the study group had abnormal comprehensive lipid tetrad index. **Conclusion:** Considering above observation in respect of positive relationship with ischaemic stroke and lipid levels, it appears that comprehensive lipid tetrad index has a direct relationship with stroke incidence.

## INTRODUCTION

Stroke is rapidly developing clinical symptoms and/or signs of focal, and at times global loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.<sup>[1]</sup> By and large, impaired cerebral perfusion, (e.g.: thromboembolism) is responsible for 'ischaemic stroke' whereas in 'hemorrhagic stroke' leakage of blood from damaged cerebral vessels is the main cause. Stroke is the third most common cause of death in developed nations after heart disease and cancer. Among all the neurological diseases of adult life, cerebrovascular accidents are commonest.

In our country, crude prevalence rate (CPR) of stroke is estimated to be around 220 per 100,000 people. In the elderly (55- 65 yrs), CPR is 700 per 100,000 excluding sudden death and TIA. With increasing survival rate in most countries (including India), we are to face an increase of around 30% in number of acute stroke in next 20 years.<sup>[2]</sup>

Older age, family history of thrombotic stroke, diabetes mellitus, hypertension, tobacco smoking, elevated blood cholesterol and other factors are risk factors for atherosclerosis and hence either proven or probable risk factors for ischaemic stroke too.

While the association between serum cholesterol concentration and coronary artery disease is well established, the same between cholesterol and stroke remains elusive. But serum lipids have been directly related to extracranial carotid atherosclerosis

including increased extracranial carotid artery wall thickness. A Meta analysis of four randomised trials comparing HMGCoA educates inhibitors to control includes 30, 187 participants and was found that HMGCoA reductase treatment was associated with decrease in risk of stroke by 19- 32%.<sup>[3]</sup>

Lipoprotein (a) consists of apoprotein(a) molecule bound by a SH link to the apolipoprotein B moiety of LDL particle. Apoprotein (a) has homology with plasminogen and may inhibit fibrinolysis by competing with plasminogen. Patients with high serum Lp(a) appear to have a higher risk of ischaemic stroke.<sup>[4]</sup>

Thrombosis ultimately causes the gravest complications of atherosclerosis. Elevated fibrinogen levels might promote a thrombotic diathesis and is an independent risk factor for the development of cerebral infarction.

Also elevated levels of plasma homocysteine have been associated with an increased risk of ischaemic stroke.<sup>[5]</sup>

Modifiable risk factors can be a helpful in prevention of stroke. Therefore identification of modifiable risk factor is of paramount importance in stroke prophylaxis.

#### **Aims and Objective**

- To find the age incidence and sex ratio of ischaemic stroke at our place.
- To find out the risk factors of ischaemic stroke with special reference to dyslipidemia and other unidentified risk factors in our population like lipoprotein(a), homocysteine and fibrinogen.

## **MATERIALS AND METHODS**

Forty patients of Cerebral Infarction confirmed by CT scan of Brain have been taken for the study from the departments of General Medicine and Neurology, Darbhanga Medical College and Hospital, in a span of one year. Patients with Hemorrhagic stroke or TIA or having potential sources of embolism from heart are excluded from the study. Detail particulars of the patient were taken including name, age, sex, address, occupation, date of admission and date of examination. The patient was enquired about the date of onset of stroke, symptoms like- weakness of extremities, headache, vomiting, impaired consciousness, convulsions, loss of speech, CNS abnormalities like ptosis, diplopia, blurring of vision, facial weakness, nasal intonation and regurgitation; pain paresthesia, bladder and bowel habits, fever, neck pain. Patients was enquired about risk factors like hypertension, diabetes, heart disease, dyslipidemia, addiction like smoking, drug history like oral contraceptive pills, sedentary habits and past history of stroke or TIA. Family history of hypertension, stroke, AMI/IHD, premature death and diabetes is enquired.

#### **Examination of the patient:**

General survey was done concentrating on waist- hip ratio, carotid pulse, blood pressure, and peripheral

signs of atherosclerosis like xanthoma, xanthelesma and locomotor brachialis. Detail examination of nervous system was done- whether the patients were conscious, alert and cooperative, drowsy or unconscious. Speech and articulator and handedness ( Right/ left ) were examined. Spine and cranium were examined and whether there was any meningeal sings was noted. The cranial nerves were examined in details specially 2nd and 7th cranial nerves. Motor functions were examined including nutrition, power, tone and coordination of upper and lower limbs. Frank hemiplegia/hemiparesis, and hemianesthesia, visual field defects were specially noted. Test for superficial sensation (pain, touch, and temperature), deep sensation (vibration sense, muscle, position joint and pressure sense) and cortical sensation (2 point discrimination, stereognosis, graphaesthesia) were done. Reflexes including superficial like plantar and deep tendon reflexes were elicited. Test for cerebellar functions were done Gait was noted. Bladder and bowel functions were examined. Any trophic changes like bed sore, trophic ulcer, charcoat joints were noted. Examinations of other systems like CVS, Respiratory, GI, and Haematopoetic system were also examined.

Routine investigations were done, like Complete Hemogram, Fasting Blood sugar, Urea, Creatinine, Urine for RE. Serum lipid profile (TCh, LDL-C, HDL-C, TG, VLDL-C), Serum lipoprotein(a), Serum Homocysteine, Plasma Fibrinogen, Comprehensive lipid Tetrad index, Cardiovascular, Chest X-ray PA view, ECG, Echo Doppler study, CT scan of Brain, MRI and MRA (where needed).

## **RESULTS**

The study on 40 patients of ischaemic stroke carried out at Darbhanga Medical College and Hospital shows that persons in the 6<sup>th</sup> and 7<sup>th</sup> decades of life are the most vulnerable to suffer ischaemic stroke; 55% of the study group belonged to the age group between 50-69 years.

Males were more affected than females, the sex ratio of male: female in our study group was 3:2. Hypertension was the most prevalent risk factor in our study group (87.5%). Ischaemic heart disease was present in 35% cases of the study group as revealed by ECG and Echocardiography, which gives us an idea, that atherosclerosis is a generalised process affecting both coronary and cerebral circulation.

Right-sided hemiplegia was more frequent (55%). On CT scan of Brain, it was seen that basal ganglion and paraventricular infarction was commonest. 14 cases had right – sided infarct, 12 had left- sided infarcts while 14 patients had bilateral infarct. Single site infarct occurred in 45% cases while multiple site infarcts occurred in 55% cases. Anterior circulation ischaemic stroke was commonest, comprising 70% of the study group, 12.5% comprised posterior circulation and 17.5% comprised both territory infarcts. Small vessel stroke was commonest

comprising 30 cases i.e. 75% while large vessel infarct comprised 6 cases i.e. 15% while combined lesion comprised 4 cases i.e. 10%.

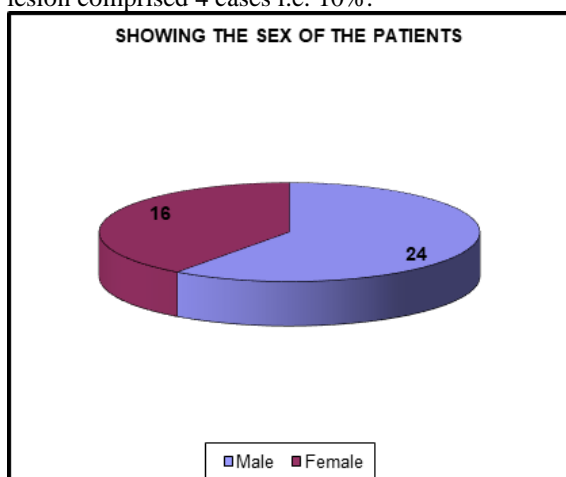


Figure 1: Pie diagram showing sex distribution of patients

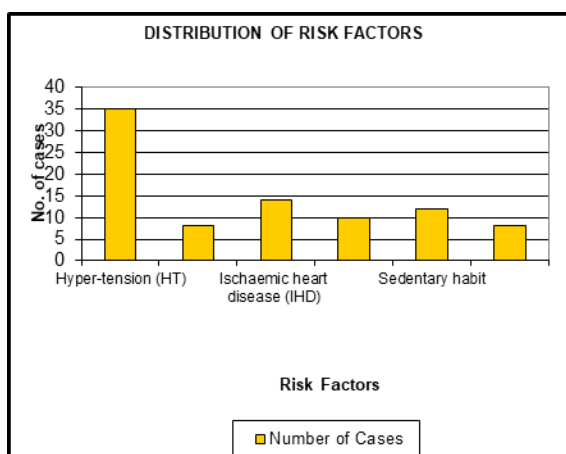


Table 1: showing the age of the patients

Total no. of cases	Age (years)		
	Range	Mean	Standard Deviation (S.D.)
40	35 – 75	53.43	7.84

## DISCUSSION

40 cases were included in our study, among which 24 were male and 16 female. The sex Ratio at our Hospital from the study was Male: female =3:2 or 1.5. There is small excess of males, which is most prominent in middle to old age, disappears in the very elderly and probably absent in young.<sup>[6]</sup> This finding is quite similar to our finding.

Our study is collaborating with the study by Kelkar et al 1996,<sup>[7]</sup> where also male (69%) is more than female (31%), the ratio of male and female being 2.22 (out of 81 patients). The youngest patient in this series was of 35 years age and the oldest was 75 years. Mean age was 53.43 years. In the young age group i.e. below 40 years, there are 8 patients among which 5 are male and 3 female. The age incidence of ischaemic stroke below 40 years at our Hospital is 20%. Between 40-49 years, there are 6 patients among which 4 male and 2 female. The age incidence

Figure 2: ?

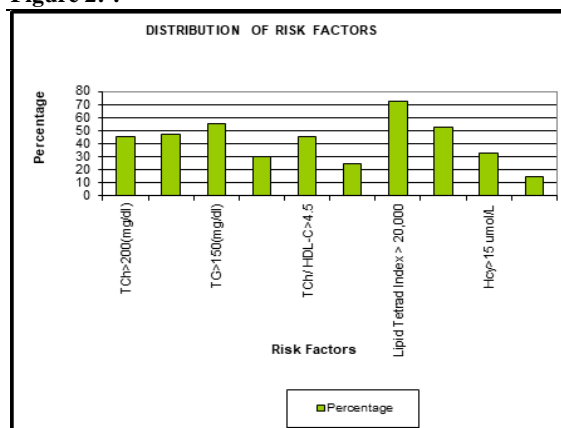


Figure 3: Bar Graph showing of distribution of risk factors

The mean serum total cholesterol (TCh) level was 196.6mg/dl with only 45% cases having TCh above 200 mg/dl. The mean HDL-C level was 43.2 mg/dl which was normal while only 30% cases had HDL level below 40mg/dl. The mean LDL-C level was raised i.e., 118.85 mg/dl with 47.5% cases had LDL-C level above 100 mg/dl. The mean TG level was raised i.e. 196.43 mg/dl with 55% cases had TG above 150mg/dl. 29 patients i.e., 72.5% of the study group had abnormal comprehensive lipid tetrad index. The mean serum Lp(a) of the study group was raised i.e., 38.10 mg/dl. 52.5% of the study group had Lp(a) level above 30 mg/dl. The mean serum homocysteine level was just raised i.e., 15.34 µmol/l with only 32.5% cases had level above 15 µmol/l. The mean plasma fibrinogen level was 312.4 mg/dl with only 15% cases having level above 400 mg/dl.

between 40-49 years is 15%. Between 50-59 years, there are 12 patients, 7 male and 5 female, age incidence is 30%. Between 60-69 years, there are 10 patients, 6 male and 4 female, age incidence is 25%. In the age group 70 or above, there are 4 patients, 2 male and 2 female, age incidence is 10%. This is similar to the findings of Sachdeva et al (1977),<sup>[8]</sup> Gupta et al (1965),<sup>[9]</sup> Jolly et al (1971),<sup>[10]</sup> and Arwing & Merritt (1955).<sup>[11]</sup>

P.M. Dalal (1997),<sup>[12]</sup> made an observation that high blood pressure was major risk factor in both sexes at all ages of stroke. In our study 8 patients suffered from diabetes mellitus i.e., 20% of all ischaemic stroke patients were diabetic. In the young age group, 3 out of 5 patients have diabetes mellitus while in above 40 years group, 5 out of 27 patients have diabetes. Data from Northern Manhattan Study showed that the prevalence of diabetes to be as high as 22% and 20% among elderly blacks and Hispanics

respectively.<sup>[13]</sup> Our findings in our population are similar to their findings.

14 patients of the study group had ischaemic heart disease as was evident from history; examination and ECG or Echocardiography i.e. 35% of all ischaemic stroke patients gives evidence of Ischaemic Heart Disease. In Framingham Study, after 36 years of follow up, 32.7% patients had prior coronary heart disease (Stroke 7th edition). This suggests that atherosclerosis is a generalised disorder affecting both cardiovascular and Cerebrovascular system.

Among 40 patients studied, paraventricular and basal ganglion infarction was the commonest. 14 cases had right-sided infarction, 12 cases had left-sided infarction while 14 cases had bilateral infarction. Single lesion comprises of 18 cases i.e., 45% while multiple lesion was present in 22 cases i.e., 55%. Right-sided hemiplegia was the commonest. 22 patients i.e., 55% of the study group had right-sided hemiplegia while 40% had left-sided hemiplegia. Anterior circulation territory involvement was the commonest comprising 28 cases i.e., 70% while posterior circulation comprised 5 cases i.e., 12.5% while 7 cases i.e., 17.5% belong to combined territories. Approximately 80% of ischaemic stroke occurs in carotid or anterior circulation and 20% occur in vertebrobasilar or posterior circulation (Bradley 2000). So our findings are similar to the above-mentioned findings. Small vessel disease was the commonest comprising 30 cases i.e., 75% while large vessel infarct comprise 6 cases i.e., 15% while combined lesion comprised 4 i.e., 10% cases. Patients with potential sources of embolism from heart were excluded from the study. Among ischaemic strokes, thrombotic strokes consist of 25% cases out of which lacunar strokes consist of 20-25% while large vessel disease consists of 1-5%.<sup>[14]</sup> This is similar to our findings where small vessel disease was the commonest comprising 30 out of 40 cases.

In our study we found that the mean serum cholesterol was 196.6 mg/dl, range was from 130 to 306 mg/dl. Mean HDL-C was 43.2 mg/dl, LDL-C mean was 118.85 and mean TG was 196.43 mg/dl. The number of cases having total cholesterol above 200 mg/dl was 18 i.e., 45% of the study group had hypercholesterolemia. 19 cases had LDL-C above 100 mg/dl i.e. 47.5% of the study group had adverse LDL-C level.<sup>[15]</sup> 22 cases had TG level above 150 mg/dl comprising 55% of the study group. Range of TG was from 85-718 mg/dl. 12 cases had HDL-C level below 40mg/dl i.e., 30%. Range of HDL was from 26-63 mg/dl. TCh/HDL ratio was more than 4.5 in 18 patient's cases i.e., 45% of cases had this adverse lipid ratio. The ratio of total cholesterol to HDL-C was significantly higher and concentration of HDL was lower in stroke cases in Madras, India (16). LDL/HDL ratio was more than 3.5 in 10 cases in 25% of the study group had this adverse lipid ratio. 21 cases had serum lipoprotein (a) level above 30mg/dl i.e. 52.5% of the study group had raised Lp(a) level. The mean Lp(a) of study group was high i.e., 38.10 and range was from 10.5-88 mg/dl.

Enas observed that abnormal i.e., more than 20,000 indexes predict coronary risk due to dyslipidemia. As similar to coronary risk as observed by Enas, 72.5% ischaemic stroke patients have unfavourable index.

In our study we found mean serum total cholesterol was 196.6 mg/dl i.e. in the upper limit of normal, mean LDL-C was 118.85 i.e., slightly raised, mean TG 196.43 mg/dl that is raised and mean HDL-C was 43.2 mg/dl that is normal. Therefore the values of serum total cholesterol, LDL-C and TG tallies with the observation of Manoria et al.<sup>[16]</sup>

Chopra et al 1997 observed that young male with high level of serum cholesterol, LDL-C and TG and young female with high level of serum cholesterol had increased risk towards cerebrovascular diseases. Bansal 1973 revealed that increased TG and VLDL-C were significant risk factor for stroke in young individuals. It is noteworthy that serum cholesterol levels impose low relative risk for ischaemic stroke with advancing age. Hypercholesterolemia as a risk factor for coronary heart disease too loses its importance beyond 70 years of age.<sup>[14-16]</sup>

A meta analysis of four randomised trials (45, CARE, AFCAPS/TEXCAPS, LIPID) comparing HMGCoA reductase inhibitors treatment was associated with 19-32% risk of stroke (Harrison 20th edition). Robinson observed high levels of LDL-C in ischaemic stroke which tallies with our findings. Ana Rova Nubiola and Mendez reported significantly lower fasting HDL-C and higher TC/HDL ratio in stroke patients similar to our study. The importance of knowing the status of lipid profile as a risk factor for stroke is that by manipulating it favourably through life style modifications and pharmacological interventions, one may hope to prevent many a thrombotic stroke.

Sandholzer et al observed that in Asian Indians the Lp(a) level varies between 15 mg/dl to 60 mg/dl which may go up to 100 mg/dl in rare cases. These findings tallies with our findings where mean Lp(a) is 38.1 mg/dl i.e. just above normal and range is 10.5-88 mg/dl. On the contrary about 80% of Caucasians have serum level of Lp(a) ranging from 7-30 mg/dl.<sup>[8-10]</sup> It has been observed that Lp(a) levels in Asian Indians settled in various countries are significantly elevated. Indeed Lp(a) levels in Asian Indians are higher compared to all the ethnic groups (with the exception of blacks). The adverse effect of high levels of Lp(a) are somewhat blunted in blacks by other factors; low LDL-C and TG and high HDL-C, while the adverse effects of Lp(a) among Asian Indians are augmented by high TG and LDL-C, and low HDL-C.<sup>[11-13]</sup>

In this study, the mean serum homocysteine (Hcy) level was 15.34  $\mu$ mol/L, the range was from 6-58.9  $\mu$ mol/L. Total number of cases having serum homocysteine levels above 15  $\mu$ mol/L was 13 i.e. 32.5% of the study group had elevated homocysteine levels. Tambe AB observed eleven clinical studies to search for relationship between Hcy and Cerebrovascular disease. In nine studies, there was significant relationship while 2 prospective studies

lacked evidence for an association between hyperhomocysteinemia and Cerebrovascular disease. Results from NHANES 1988-94 showed that persons in highest Homocysteine quartile were older. This is similar to our study where mean Hcy level in young age group (<40years) was 14.1  $\mu\text{mol/L}$  whereas in group (>40years) mean Hcy was 17.13 among 50-59 years and 16.38 among 60-69 years. (Results from the Third National Health and Nutritional Examination Survey 1988-94, NHANES). Indian data on the role of homocysteine in ischaemic stroke is not conclusive.<sup>[13,14]</sup>

Plasma fibrinogen critically influences platelet aggregation and blood viscosity, interacts with plasminogen binding and in combination with thrombin mediates the final step in clot formation. In addition, fibrinogen associates positively with age, obesity, smoking, diabetes, and LDL -C and universally with HDL-C alcohol use physical activity and exercise level.<sup>[16,17]</sup> In our study, the mean plasma fibrinogen level was 312.4 mg/dl; range was from 120-480 mg/dl. Among these cases, only 6 patients had their fibrinogen level above 400 mg/dl that is 15% had hyperfibrinogenemia. Kristensen et al observed that mean plasma fibrinogen level was 312 mg/dl for ischaemic stroke patients and 234 mg/dl for control patients, which is similar to our observations. It may be argued that increase in plasma fibrinogen in the patients studied was simply due to response to stress, for fibrinogen is known to be an acute phase reactant. But in our study, maximum values were taken when acute phase response had subsided. In a prospective study of stroke survivors, a statistically high plasma fibrinogen level was observed in a group of patients in the period when acute phase response had subsided and many of these individuals developed a second cerebrovascular event within next 2 years.<sup>[16-18]</sup>

## CONCLUSION

Considering above observation in respect of positive relationship with ischaemic stroke and lipid levels, it appears that comprehensive lipid tetrad index has a direct relationship with stroke incidence. A larger population – based study will further establish the exact status of various risk factors in patients with ischaemic stroke in our population. On the basis of our findings a large population based study is needed to further correlate the lipid tetrad index and its role in stroke and its prevention.

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