

Study of Lipoprotein a in Ischemic Stroke Patients

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Abstract- Background: Cerebrovascular disease (CVD) and coronary heart disease (CHD) cause 40%–50% of deaths in developed countries with CVD causing 10%–12% of deaths. Though increased Lipoprotein (a) is a risk factor in developing CHD, its role is poorly defined in etiopathogenesis of CVD.

Aims: To find the association of lipoprotein (a) and lipid profile in ischemic stroke patients after acute phase.

Settings and Design: The study was conducted at Osmania Medical College and Hospital, Hyderabad. 50 cases of ischemic stroke and 50 cases of age and sex matched controls were taken for the study. Informed consent was taken from both case and control.

Materials and Methods: Overnight fasting sample was collected from both case and control. Serum was separated and parameters such as total cholesterol, triglycerides, high density lipoproteins-C, low density lipoprotein-C, lipoprotein (a) were estimated.

Conclusion: A statistically positive correlation was found between serum Total cholesterol, Triglycerides, LDL levels and the risk of stroke. Elevated serum Lp(a) is an independent risk factor of ischemic stroke.

Index Terms- Cerebrovascular disease (CVD) and coronary heart disease (CHD), lipoprotein(a) [Lp(a)]

I. INTRODUCTION

The World Health Organization (WHO) definition of stroke is: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”^{1,2}

Studies in subjects with average lipid profiles indicate that raised lipoprotein(a)[Lp(a)] concentrations are associated with myocardial infarction, coronary artery disease, peripheral atherosclerosis and cerebral ischemia. Lipoprotein(a) is considered as an independent risk factor for atherosclerosis. Due to unique structural homology with plasminogen, it interferes with the function of plasminogen thus increasing thrombotic risk. Several studies have evaluated the association between Lp(a) and ischemic stroke. Several cross sectional studies and a few prospective studies provide contradictory findings regarding Lp(a) as a predictor of ischemic stroke. The meager reports available in Indian patients who have different social, living and dietary habits compared to western population, prompted us to undertake this study.

Structure of lipoprotein (a)

Lipoprotein(a) was described in human plasma by Berg as a genetic variant of β -lipoprotein.³

Lp(a) is an LDL like molecule consisting of an apoprotein (apo) B-100 particle attached by a disulphide bridge to apo(a). Apo(a) is a member of a family of “kringle” containing proteins, such as plasminogen, tissue platelet activator (tPA), prothrombin, factor XII, and macrophage stimulating factor (MSF).^{4,5} Lp(a) shares a high degree of sequence identity with plasminogen.^{4,6}

Modulation of plasma Lp(a) concentrations:

Lp(a) values can be increased as part of the acute phase response, and in diabetes mellitus,²⁸ chronic renal failure,²⁹ nephrotic syndrome,³² cancer, menopause, and hypothyroidism.³⁵

Lp(a) values are decreased in liver failure³⁷ and hyperthyroidism. Furthermore, nicotinic acid, tamoxifen, oestrogens,⁴¹ progesterone, and anabolic steroids might decrease Lp(a) concentrations. Fibrates have been shown, in some studies, to reduce Lp(a) concentrations,⁴³ whereas statins might increase Lp(a) concentrations.

The pathophysiological link between Lp(a) and atherothrombosis:

The accumulation of Lp(a) molecules has been demonstrated in the arterial walls of human coronary and cerebral vessels.¹⁴ This process might be attributed to the tendency of apo(a) to bind to connective tissue elements, such as proteoglycans, glycosaminoglycans, and, specially, fibronectin.¹⁵

Because of the structural homology with plasminogen, Lp(a) has important antithrombotic properties, which could contribute to the pathogenesis of atherothrombotic disease. Lp(a) binding to immobilized fibrinogen and fibrin results in the inhibition of plasminogen binding to these substrates. In addition, Lp(a) competes with plasminogen for its receptors on endothelial cells, leading to diminished plasmin formation, thereby delaying clot lysis and favouring thrombosis.⁵⁵

The presence of oxidized phospholipids in Lp(a), potentially being taken up by the vessel wall, could also accelerate development of atherosclerosis.

The optimal level should be no greater than 20 mg/dl, especially in Indian population⁶¹

Aims and objective of study:

The aim of this study is to determine the role of lipoprotein (a) as a marker for ischemic stroke

Material and methods:

The present study, serum lipoprotein (a) levels as a risk factor for ischemic stroke, was conducted in the Department of General Medicine, Osmania General Hospital, Hyderabad for a period of two years from October 2011-October 2013

Study design: Case Control Study

In this study, 50 patients who are survivors of ischemic non cardioembolic stroke with history of sudden onset focal neurological deficit persisting beyond 24 hours were included.

II. SELECTION OF CASES

Diagnosis of ischemic stroke was based on the following criteria:

- Clinical evidence of ischemic stroke
- Cranial computed tomography (CT) scan or magnetic resonance imaging (MRI) consistent with ischemic stroke
- Absence of major predisposing factors to cardiogenic stroke including atrial fibrillation, valvular heart disease, prosthetic heart valves, endocarditis, acute myocardial infarction, dilated cardiomyopathy or ventricular aneurysm.

III. EXCLUSION CRITERIA

- Patients with CT / MRI scan showing intracerebral hemorrhage, tumor, or other mass lesion
- History of head injury
- Patients with coronary artery disease (including asymptomatic patients with electrocardiographic evidence of previous myocardial infarction)
- patients with vasculitis
- Patients with liver, renal, or thyroid disease
- Patients taking drugs which may alter lipid and lipoprotein profiles
- Women on contraceptive pills
- Sepsis
- Malignancy
- Active collagen vascular disease

50 age and sex matched healthy subjects were used as controls. Exclusion criteria were applicable even to the control subjects. All patients were subjected to a detailed history, general physical examination, a detailed neurological examination. History regarding risk factors such as age, sex, hypertension, diabetes mellitus, cardiovascular history, drug history, smoking habits, alcohol intake, family history etc was elicited.

A patient was considered as hypertensive when the patient is already on treatment with antihypertensive drugs or, in accordance with the definition by the Joint National Committee (JNC), when systolic and diastolic blood pressures were ≥ 140 mm Hg and ≥ 90 mm Hg respectively.

A subject was defined as affected by diabetes mellitus if the patient is already on treatment or, according to American Diabetes Association definitions, if fasting glucose in serum was ≥ 126 mg/dl or random blood glucose was ≥ 200 mg/dl with symptoms, or HbA1 C $\geq 6.5\%$

A subject was considered as having dyslipidemia if the patient is already on specific medication or, according to ATP III definition if total cholesterol levels were ≥ 200 mg/dl or triglyceride levels were ≥ 150 mg/dl or LDL levels were > 100 mg/dl or HDL levels were < 40 mg/dl.

Written approval of ethical committee, following the national guidelines was taken before the initiation of study. Blood samples were collected after 21 days of occurrence of stroke. Overnight fasting blood samples were collected without adding anticoagulant to the tube not less than three weeks after the occurrence of stroke, because Lp(a) levels are known to get altered due to acute phase response.

The following investigations were performed in each case:

Complete hemogram - Hemoglobin, Total leucocyte count, differential leucocyte count, ESR, Platelet count ; **Complete urine examination** - **Blood sugar**, Fasting(mg/dl), Postprandial(mg/dl), Random(mg/dl) ; **Renal function tests** - Serum urea(mg/dl), Serum creatinine(mg/dl), serum electrolytes(sodium, potassium in mmol/l) ; ECG; Echocardiography ; X Ray Chest ; CT brain ; MRI brain(whenever required), Plasma lipoprotein (a) levels; **Lipid profile** - Total cholesterol, Serum triglycerides, LDL cholesterol, HDL cholesterol.

Lp(a) estimation is done through nephelometric assay. Nephelometry is a technique for estimation of number and size of particles in a suspension by measurement of light scattered from a beam of light passed through the solution by a nephelometer. Lp(a) can also be estimated by Radio Immune Assay, Rosache strips using micro ELISA, Monoclonal antibodies. Expected normal range : < 30 mg/dl

IV. RESULTS

The present study "Serum lipoprotein(a) levels as a risk factor of ischemic stroke" was conducted on fifty patients of cerebrovascular accidents of ischemic type admitted in the emergency department and wards of the General Medicine department, Osmania General hospital, Hyderabad. Fifty healthy age and sex matched subjects were recruited as controls.

Observations based on history, general examination and systemic examination were made on the same proforma. Serum lipoprotein(a) levels along with other investigations were also assessed as per proforma.

Statistical analysis was done using the Pearson Chi Square test. The data was analyzed systematically and observations are presented are follows:

AGE DISTRIBUTION

The mean age in cases was 54.38 years with a S.D of 12.35. The mean age in controls was 52.9 years with a S.D of 11.34. Thus, the cases and controls were comparable in respect to age.

GENDER DISTRIBUTION ; Male female ratio is 1.17 among the cases and 1.5 in controls.

COMPARISON OF RISK FACTORS IN CASES AND CONTROLS - Table 1

Risk factors		Cases		Controls	
		Yes	No	Yes	No
1	Hypertension	36	14	30	20
2	Diabetes	32	18	28	22
3	smoking	22	28	20	30
4	Alcohol	30	20	26	24
5	Obesity	30	20	19	31
6	Family history	3	47	0	50

Hypertension Distribution

- Hypertensive patients are 36 and 30 in cases and controls respectively.
- On further statistical analysis, this variable was not found to be statistically significant(p=0.205)

Diabetes Mellitus Distribution

- Diabetic patients are 32 and 28 in cases and controls respectively.
- Statistical analysis showed that this variable is statistically insignificant (p=0.413)

Smoking Distribution

- Smokers are 22 ,20 in cases and controls respectively.

- Further analysis shows that this variable is statistically insignificant (p=0.685)

Alcohol Distribution

- Alcoholics are 30 and 26 in cases and controls respectively.
- Further analysis did not reveal significant relation between alcoholism and stroke(p=0.420)

Obesity Distribution

- Obese patients are 30 and 19 in cases and controls respectively.
- On further analysis, the difference was found to be statistically significant(p=0.027)

Total Cholesterol Distribution - Table 2

	No. of cases	Mean cholesterol	Standard deviation	p value
Cases	50	193.52	38.99	0.435
Controls	50	187.3	40.50	

- On further analysis, this was not found to be statistically significant (p=0.435)

Triglyceride (TG) Distribution - Table 3

	No. of cases	Mean level triglyceride	Standard deviation	p value
Cases	50	138.06	35.44	0.0894
controls	50	124.6	42.68	

- Statistical analysis showed that this was insignificant (p=0.0894)

LDL Cholesterol Distribution - Table 4

	No. of cases	Mean LDL levels	Standard deviation	p value
Cases	50	104.74	27.30	0.032
Controls	50	91.96	31.38	

- On further analysis, it was found that LDL cholesterol is statistically significant in relation to ischemic stroke (p= 0.032)

HDL Cholesterol Distribution - Table 5

	No. of cases	Mean HDL levels	Standard deviation	p value
Cases	50	52.02	13.374	0.4705
Controls	50	50.3	10.150	

- Further statistical analysis showed that this variable was statistically insignificant (p=0.470)

Lipoprotein (a) Distribution

Lipoprotein(a) level distribution found in cases and controls in this study is depicted in table 6 and table 7

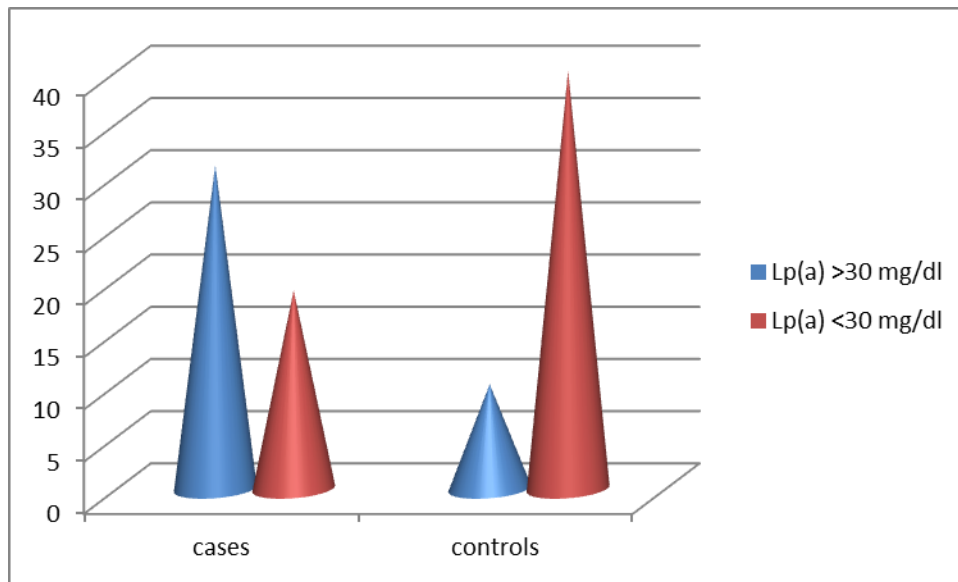
Table 6

Lp(a) levels	Cases	Controls	Total
>30 mg/dl	31(62%)	10(20%)	41(41%)
<30 mg/dl	19(38%)	40(80%)	59 (59%)
Total	50 (100%)	50(100%)	100 (100%)

Table 7

	No. of cases	Mean Lp(a) levels	Standard deviation	p value
Cases	50	34.664	12.76	0.005
Controls	50	28.084	10.118	

- 31 cases and 10 control subjects enrolled in this study had Lp(a) levels >30 mg/dl.
- 19 cases and 40 control subjects had normal values <30 mg/dl



On further analysis, this variable was found to be statistically significant($p=0.005$).

V. DISCUSSION

This study, which was a case control study, was conducted in the Osmania General Hospital, in the Department of General Medicine, for a period of 2 years during which 50 cases of ischemic stroke and 50 controls were studied.

In the present study there are 36(72%) hypertensives and 14(28%) normotensives among cases. Among controls 30(60%) were hypertensives and 20(40%) were normotensives. Analysis revealed p value of 0.205. Therefore, there is no significant relation between systemic hypertension and stroke. These results are consistent with studies of Zenker et al¹⁸ and Van kooten et al¹⁹

In the present study there were 32(64%) diabetic patients among cases whereas 18(36%) were non-diabetics. Among controls 28(56%) were diabetics and 22(44%) were non-diabetics. Analysis showed p value = 0.413(Not significant). Therefore, there is no significant relation between diabetes and stroke.

The mean Lp(a) levels in a study done by Marques et al in 2004²⁰ in 26 type 2 Diabetes Mellitus and 34 non diabetics with ischemic stroke were both statistically significant. The mean Lp(a) levels in diabetics was 29.49 mg/dl +/- 23.09 and in non diabetics was 44.81 mg/dl +/- 44.34 with a p value of 0.115, indicating that Lp(a) levels are a risk factor independent of the diabetes status of the individual. Similar results were seen in our study.

In the present case control study, 50 cases of ischemic stroke had a mean plasma lipoprotein(a) value of 34.664 mg/dl with a S.D of 12.76. This was statistically significantly higher than mean lipoprotein(a) concentration (28.084mg/dl with S.D of 10.118) in healthy controls. This indicates that serum lipoprotein(a) levels are a risk factor for ischemic stroke

Shintani et al²¹ evaluated 54 patients with cerebral infarction to evaluate the role of lipoprotein(a) in ischemic stroke. When patients with atrial fibrillation were excluded to omit cardiac

embolic strokes from analysis, the group consisted of 45 patients. The mean lipoprotein(a) levels in the study were 25 mg/dl with a S.D of 21 and p value of <0.025.

Nagayama et al²² evaluated 101 serum lipoprotein(a) levels in 101 patients with ischemic stroke and 37 normal control subjects, taking the clinical profiles into consideration. The mean lipoprotein (a) levels were 40.2 mg/dl with a S.D of 20.1 and p value of <0.01.

Jurgens et al²³ in 1995 analyzed serum lipoprotein (a) levels and other lipid parameters in 265 patients with ischemic cerebrovascular disease. The mean lipoprotein(a) level was 40.2 mg/dl with a S.D of 31.8. the p value was found to be statistically significant ($p<0.001$)

In all the above studies, the mean lipoprotein(a) levels were greater than 30 mg/dl except in the study done by Shintani et al, but even in this study the relation between high levels of lipoprotein (a) and ischemic stroke was statistically significant.

Study	No. of cases	Mean Lp(a)	p value
Jurgens et al	265	41.1 +/- 31.8	<0.001
Nagayama et al	101	40.2 +/- 20.1	<0.01
Shintani et al	45	25 +/- 21	<0.025
Our study	50	34.6 +/- 12.7	0.005

Jurgens et al²³, in their study on lipoprotein (a) and other lipid factors on ischemic vascular disease found significant correlation between LDL cholesterol and ischemic stroke. Similar observation was made in our study (LDL cholesterol $p=0.032$)

Our study showed the role of obesity as an independent risk factor in ischemic stroke. There is some controversy about the effect of obesity on Lp(a). In a study conducted by James Corsetti et al²⁴, lipoprotein(a) concentrations were not influenced by obesity, visceral fat content, or weight loss after a very low energy diet. However, there is also some evidence that obese individuals have higher Lp(a) values and that weight loss (by diet or surgical intervention) is associated with a significant reduction in these values. The mechanism(s) responsible for these changes remains to be defined.

Our study did not reveal significant relation between total cholesterol and ischemic stroke. This is consistent with the studies conducted by Lindgren et al²⁵, Zenker et al²⁶, which showed no correlation between total cholesterol and stroke.

In Atherosclerosis Risk In Communities (ARIC) study conducted by Ohira et al²⁷ in 2006 in 14221 subjects for a period of 13.5 years, it was showed that high lipoprotein (a) concentration is associated with a higher incidence of ischemic stroke in blacks and white women, but not in white men. Further studies are needed in Indian population to establish this difference in racial and ethnic groups.

Hoque MM et al²⁸ conducted a case control study to evaluate the lipoprotein(a) as a risk factor for CVD (cerebrovascular disease). Subjects were grouped as group-I (30, healthy control), Group-II (60, Hemorrhagic CVD) and group-III (60, Ischemic CVD). Fasting (12 hr) blood samples were collected from all subjects and in CVD cases samples were collected after 24 hr of attack. Lipid profile and Lp(a) conc. were measured in all samples. Mean serum Lp(a) concentration in Group-I, Group-II and Group-III were found to be 17.6 +/- 7.4 mg/dl, 31.9 +/- 15.6 mg/dl and 44.8 +/- 24.0 mg/dl respectively. Both the groups of CVD cases showed significantly higher level of serum Lp(a) concentration compared to healthy control. CVD cases did not differ statistically in respect of their lipid profile when compared with control. Moreover the serum Lp(a) concentration of CVD cases found to show no correlation with their lipid profile, suggesting the serum Lp(a) concentration a possible independent risk factor for CVD.

Findings of the present study run in parallel with the above authors. The results of our study indicate that high lipoprotein (a) levels are an independent risk factor for ischemic stroke and thus the need to find methods for its prevention and management.

VI. SUMMARY

The present conventional risk factors are unable to explain this emerging epidemic of cerebrovascular disease, hence the search for new, modifiable, preventable and treatable risk factors is necessary. Among them, the relation between stroke and anti oxidant deficiencies, raised homocysteine, selenium and low plasma ascorbic acid levels has received considerable attention. Four decades of research on lipoprotein(a) have seen it emerge as a clinically important molecule. Evidence has been gained for Lp(a) involvement in the development of CHD to a point where routine measurement of Lp(a) in patients at risk must be recommended. Further, except nicotinic acid which in very large, usually intolerable doses decreases Lp(a) levels, no other drug is found to be effective. Hence, it is imperative to strictly control additional risk factors in individuals with elevated Lp(a).

The present study was conducted with the aim to study lipoprotein(a) with reference to ischemic stroke. This study, which was a case control study, was conducted in department of General Medicine, Osmania General Hospital, Hyderabad. It included 50 ischemic stroke patients who were compared with age and sex matched controls during a period of two years.

After evaluating the findings for statistical significance, it is concluded from our study that the mean +/- S.D concentration of serum Lp(a) was significantly higher than that of controls. The present study proved a significant correlation between elevated serum Lp(a) and ischemic stroke (p=0.005). Obesity and elevated LDL were also found to be significant risk factors of ischemic stroke.

VII. CONCLUSION

1. Elevated serum Lp(a) is an independent risk factor of ischemic stroke.
2. Reducing the circulating values of Lp(a) might prove difficult. It is imperative to control additional risk factors in individuals with elevated lipoprotein(a).
3. Measurement of serum Lp(a) as a screening tool for the risk of vascular events should be considered in patients with various known risk factors.

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