

Original Research Article

Lipoprotein (a) as a risk factor of ischemic stroke: a case-control study

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ABSTRACT

Background: Undoubtedly, stroke is an important public health problem as well as an important precursor of mortality and morbidity. It also leads to loss of disability adjusted life years as it causes long term severe disability. The objective of this study was to study association of lipoprotein (a) in ischemic stroke patients with matched controls.

Methods: This is a prospective case controlled study. The study group includes 100 stroke patients consecutive admitted in medicine/neurology departments of our hospital, and 50 patients as control group admitted for nonvascular diseases. The ethical committee clearance was obtained from the appropriate authority appointed by the institution. Detailed history taking and neurological examination were done in all patients

Results: This case-control study shows that ischemic stroke patients have higher levels of Lp (a) as compared to that of controls. Thus, people with high Lp (a) levels may have higher predilection for developing ischemic stroke. Lp (a) levels do not correspond to stroke severity stroke in our study. Thus, higher Lp (a) levels do not lead to more severe type of stroke. Lp (a) levels do not correlate with the outcome of stroke, hence Lp (a) level may not be a good indicator for assessing prognosis or predicting mortality

Conclusions: This case-control study shows that ischemic stroke patients have higher levels of Lp (a) as compared to that of controls. Thus, people with high Lp (a) levels may have higher predilection for developing ischemic stroke factors for stroke like diabetes, smoking and hypertension do not predisposed to higher Lp (a).

Keywords: Case control study, Lp (a) levels, Renal function, Risk factors

INTRODUCTION

Undoubtedly, stroke is an important public health problem as well as an important precursor of mortality and morbidity. It also leads to loss of disability adjusted life years as it causes long term severe disability.¹ Globally, stroke is third most common cause of mortality only after coronary artery disease and cancer. It caused four million deaths.²

High lipid levels in the blood are the leading risk factor of ischemic heart disease (IHD).³⁻⁵ But recently it was

identified that the lipids can play an important role in the prevention of stroke. A fraction of lipid, identified as lipoprotein (a) was found to be a risk factor for coronary stenosis, myocardial infarction, cerebral ischemia, re-occlusion of aorto-coronary bypass vein grafts, and coronary stenosis.^{6,7} For cases of atherosclerosis, lipoprotein (a) is an independent and important risk factor.⁷ The biological plausibility of lipoprotein (a) as a risk factor has been suggested as its structural similarity with that of plasminogen.⁸ Because of this, it interferes with function of plasminogen thus increasing thrombotic risks.⁹

Various studies have demonstrated that there is a positive relation between increased lipoprotein (a) levels and the risk of thrombotic stroke. But at the same time, cross sectional studies give contradictory results regarding the role of Lp (a) as a risk factor for ischemic stroke.

Hence, this study was undertaken to compare serum lipoprotein (a) in ischemic cerebrovascular disease patients with matched controls.

METHODS

This is a prospective case controlled study. The study group includes 100 stroke patients consecutive admitted in medicine/ neurology departments of our hospital, and 50 patients as control group admitted for nonvascular diseases. The ethical committee clearance was obtained from the appropriate authority appointed by the institution. Detailed history taking and neurological examination were done in all patients.

All subjects were reassessed in intensive care unit, underwent detailed evaluation and neurological examination to localize the lesion. The severity of ischemic strokes was classified on the basis of National institutes of Health stroke scale at the admission and discharge.

Stroke severity was assessed using National Institute of Health Stroke Scale (NIHSS).¹⁰

Inclusion criteria

- All patients satisfying the WHO definition of stroke
- Controls were included based on negative history and clinical features for recent or remote ischemic stroke any other vascular disease like coronary artery disease and peripheral vascular disease.

Exclusion criteria

- Patients with hemorrhagic stroke
- Patients with cardiovascular cause for emboli (i.e. in case of atrial fibrillation)
- Those that are on medication known to influence lipid metabolism (e.g. Statins, sex steroids).

The following parameters were studied

Hypertension: Patients were considered to have hypertension if systolic blood Pressure more than or equal 140 mm of Hg or diastolic blood pressure more that of equal to 90 mm of Hg or both as per the diagnostic guidelines of JNC VII report or if the patient has already been diagnosed to have hypertension earlier.

Diabetes mellitus: Known diabetics on treatment or newly detected patient who satisfied WHO criteria i.e., one of the criteria's mentioned symptoms of diabetes mellitus with random blood glucose > 200 mg/dl, fasting

plasma glucose > 126 mg/dl, 2-hour plasma glucose >200 mg/dl during OGTT.

Smoking: Persons who have smoked regularly for at least 1 year in the recent past.

Coronary artery disease: Persons who are known case and history suggestive coronary artery disease.

Methods of collection of data

The study consists of both clinical and biochemical assay.

Detailed history taken and clinical examination was done. All the patients were investigated as per requirement like lipid profile, lipoprotein estimation. blood routine investigations like haemoglobin, total leukocytes count, ESR, platelets, and serum creatinine, blood urea were done in stroke patients. Assessment of stroke outcome was done by using modified ranking scale (MRS) and it is widely used in almost all randomized clinical trials.¹¹⁻¹²

The data was analyzed using mean, standard deviation, standard error and t test. P value less than 0.05 was taken as statistically significant.

RESULTS

The present study is a case control study consisting of consecutive 100 ischemic stroke patients (defined as cases) and 50 controls was undertaken to investigate the association and effect of Lp (a) on stroke and also the effect Lp (a) on severity and outcome of stroke.

Table 1: Prevalence of diabetes among cases and controls.

| Diabetes | Cases | Controls | Total |
|----------|----------|----------|----------|
| Yes | 41 (41%) | 16 (32%) | 57 (38%) |
| No | 59 (59%) | 34 (68%) | 93 (62%) |
| Total | 100 | 50 | 150 |

Among the cases 41 (41%) had diabetes mellitus but among the controls only 16 (32%) had diabetes mellitus. The percentage of diabetes mellitus was higher in cases as compared to controls in the present study.

Table 2: Prevalence of hypertension among cases and controls.

| Hypertension | Cases | Controls | Total |
|--------------|----------|----------|------------|
| Yes | 64 (64%) | 09 (18%) | 73 (48.7%) |
| No | 36 (36%) | 41 (82%) | 77 (51.3%) |
| Total | 100 | 50 | 150 |

Among the cases 64 (64%) had hypertension but among the controls only 9 (18%) had hypertension. The percentage of hypertension was higher in cases as compared to controls in the present study. Among the

cases 23 (23%) were smokers and 77 (77 %) were nonsmokers. In the control group 2 (4%) were smokers and 48 (96%) were nonsmokers are 48% (96%).

Table 3: Prevalence of smoking among cases and controls.

| Smoking | Cases | Controls | Total |
|---------|----------|----------|-------------|
| Yes | 23 (23%) | 02 (04%) | 25 (16.7%) |
| No | 77 (77%) | 48 (96%) | 125 (83.3%) |
| Total | 100 | 50 | 150 |

Table 4: Lipoprotein (a) levels in cases and control.

| Study groups | N | Mean Lp (a) mg/dl | S.D. | Standard error of mean |
|--------------|-----|-------------------|-------|------------------------|
| Cases | 100 | 42.68 | 28.25 | 2.83 |
| Controls | 50 | 31.45 | 21.06 | 2.98 |

On comparing cases and controls for Lp (a), it was found that the mean value in cases (42.68 mg/dl) which was significantly higher ($p = 0.014$) than the mean value (31.45 mg/dl) in control subjects. The association between raised Lp (a) levels defined as >30 mg/dl was also studied among cases and controls by using the z test between two proportions. As depicted in table below it is obvious that there is significantly high proportion of patients having raised Lp (a) levels in cases compared to that controls. (Z value at 95% confidence levels = 3.183).

Table 5: Association between types of stroke and mean lipoprotein levels.

| Type of stroke | N | Mean Lp (a) mg/dl | S.D. | Standard error of mean |
|-----------------------|----|-------------------|---------|------------------------|
| Anterior circulation | 89 | 43.965 | 29.2023 | 3.0954 |
| Posterior circulation | 11 | 32.309 | 16.1745 | 4.8768 |

In anterior circulation group the mean Lp (a) level was more as compared to that of posterior circulation group (43.96 mg/dl versus 32.30 mg/dl), but it was not found to be statistically significant (p value = 0.198, >0.05).

Table 6: Association of LP (a) levels and severity of stroke.

| Severity of stroke | N | Mean Lp (a) mg/dl | S.D. | Standard error of mean |
|--------------------|----|-------------------|-------|------------------------|
| Minor strokes | 35 | 37.326 | 23.82 | 4.0261 |
| Major strokes | 65 | 45.57 | 30.15 | 3.7389 |

Another analysis along the line of raised Lp (a) defined > 30 mg/dl was done in these two groups to see weather raised Lp (a) has predilection for either anterior or

posterior circulation strokes. Even though the levels in the table given below shows that anterior circulation strokes have more numbers of patients with raised values, this was not found statistically significant.

The mean Lp (a) value in the major stroke group was more as compared to that of minor strokes (45.57 mg/dl versus 37.32 mg/dl) but it was not found to be statistically significant ($p = 0.165$, > 0.05).

High Lp (a) (defined as >30 mg/dl) was more prevalent in major stroke than minor strokes but this was not found to be statistically significant.

Table 7: Association of the Lp (a) level and outcome of stroke.

| MRS at discharge N | | | Mean Lp (a) mg/dl | S. D. | Standard error of mean |
|----------------------|----------------|----|-------------------------|---------|------------------------------|
| Favorable outcome | Up to 2 | 31 | 46.539 | 33.0302 | 5.9324 |
| Poor outcome | 3 and above | 69 | 40.951 | 25.8936 | 5.9324 |

In this study patients with poor outcome who had raised Lp (a) defined as >30 mg/dl were 44 out of 69 and patients with good outcome who had raised Lp (a) were 19 out of 31. The z test between two proportions was applied but showed no statistical significance in the difference noted.

Table 8: Renal impairment and Lp (a).

| Renal function | Serum creatinine | N | Mean Lp (a) mg/dl | S.D. | Standard error of mean |
|----------------|------------------|----|-------------------|-------|------------------------|
| Normal | up to 1.2 mg/dl | 81 | 45.23 | 29.98 | 3.33 |
| Impaired | above 1.2 mg/dl | 19 | 31.82 | 15.51 | 3.56 |

Comparing both these groups the mean Lp (a) level in normal renal function patients was more (45.23 mg/dl) than the impaired renal function group (31.82 mg/dl) but it was not statistically significant ($p = 0.062$, >0.05).

Table 9: Association of LDL cholesterol to Lp (a).

| LDL groups | N | Mean Lp (a) mg/dl | S.D. | Standard error of mean |
|-----------------|----|-------------------|-------|------------------------|
| Up to 130 mg/dl | 33 | 38.633 | 27.23 | 4.74 |
| Above 130 mg/dl | 67 | 44.678 | 28.72 | 3.51 |

In the present study, it was seen that raised LDL levels and raised Lp (a) levels did not statistically correlate.

Comparing the mean Lp (a) levels in males and females (43.17 versus 41.65 mg/dl) in stroke patients, there was no statistically significant difference (p value = 0.803, >0.05). The number of patients having raised Lp (a) levels defined as >30 mg/dl constitute 45 out of 68 males stroke subjects and 18 out of 32 female strokes subjects (66.20% versus 56.30%).

Table 10: Comparison of Lp (a) levels between males and females in the stroke patients group.

| Gender | Lp (a) | Mean Lp (a) mg/dl | S.D. | Standard error of mean |
|--------|--------|-------------------|-------|------------------------|
| Male | 68 | 43.17 | 26.85 | 3.26 |
| Female | 32 | 41.65 | 31.44 | 5.56 |

DISCUSSION

Lp (a) and stroke

On comparing ischemic strokes and controls for lipoprotein (a), the serum lipoprotein (a) levels in cases were found to be 42.68 ± 28.25 mg/dl (mean \pm SD) which was significantly ($p = 0.014$) higher than those in control subjects (31.45 ± 21.06 mg/dl). This is one of the cardinal finding of this study. This study demonstrates that the people with high Lp (a) levels are at greater risk for developing ischemic strokes.

In the study conducted by Jurgens G and Koltringer P the lipoprotein (a) plasma levels of the ischemic cerebrovascular disease group (mean, 20.5 ± 23 mg/dl; median, 9.5) were significantly elevated compared with those of controls (mean, 14.2 ± 23.1 mg/dl; median, 5) and highly significant between ischemic cerebrovascular disease group patients and the controls in the range of 30 to 60 years ($p < 0.001$).¹³ Interestingly the mean and median value in the present study and control groups was much higher than in this study. This may represent a population bias.

In the study conducted by Nagayama M et al, lipoprotein (a) levels in patient with atherothrombotic stroke were 28.0 ± 19.6 mg/dl (mean \pm SD), which were significantly ($p < 0.01$) higher than those in patients with lacunar stroke and in normal control subjects (16.4 ± 13.5 and 11.7 ± 10.5 mg/dl respectively).¹⁴

In the study conducted by Shintani S et al the serum lipoprotein (a) levels ≥ 42.6 mg/dl, which was the 95th percentile level of the control subjects, was significantly increased in the total cerebral infarction group ($p < 0.025$) and the perforating artery occlusion group ($p < 0.025$) compared with the control group.¹⁵

Lp (a) and stroke risk factors

In the present study, no association was found between hypertension, diabetes mellitus, smoking and lipoprotein

(a) concentration. This was similar to the study conducted by Pedro-Botet et al.¹⁶ Such an association has been recently described by Asplund et al in this study, menopausal status was the strongest independent predictor of Lp (a) level in women ($p = 0.010$), also concluded that hypertensive subjects treated with diuretics had significantly higher Lp (a) than hypertensive on other agents.¹⁷

Study finding supports the hypothesis that lipoprotein (a) is a marker for atherosclerosis. Since genetic factors may influence the concentration of the protein moiety more than environmental factors, genetic factors may have a significant role in determining the predisposition to stroke prevalence. A study of lipoprotein (a) concentrations and stroke in different ethnic groups should be of interest.

Lp (a) and types of stroke

There was no significant association between types of stroke and Lp (a) levels. Here we divided the cases into anterior circulation and posterior circulation strokes. The anterior circulation stroke group had more Lp (a) levels than posterior circulation counterparts but were not statistically significant ($p = 0.198$). Result is same as study by Fop van Kooten et al, found that there is no plausible relationship between Lp (a) and the clinical subtype of stroke.¹⁸ Murai et al and Woo et al found elevated levels of Lp (a) in patients with a cortical infarction but not in patients with lacunar strokes, suggested that Lp (a) level has strong association with large vessel disease that small vessel disease.^{19,20}

Severity of stroke and Lp (a)

The stroke patients were stratified by using NIHSS into major strokes (NIHSS ≥ 7) and minor strokes (NIHSS < 7). Lp (a) was found to be elevated in major strokes but was not statistically significant. Our result is similar to the cross-sectional studies conducted by Kooten FV et al that found no association between severity of stroke and Lp(a) level.¹⁸

Outcome of strokes and Lp (a)

In the present study, no association was found between the MRS outcome and the Lp (a) level similar to several population and hospital based cross sectional studies like Murai et al, Zenker et al, Jurgens G and Koltringer P et al.^{19,21} 13 Cross sectional studies conducted by Kooten FV et al, found no association between cardiovascular risk profile, severity of stroke, stroke characteristics, and prognosis.¹⁸

In the present study only 2 (2%) patients had expired. One patient was found to have high (>30 mg/dl) and the second patient had normal (less than 30 mg/dl) Lp (a) level. Hence, no conclusion can be drawn regarding Lp (a) level and mortality in ischemic strokes.

Lp (a) and renal impairment

An analysis was done to find any association of the renal impairment and Lp (a) levels. Relatively few studies have examined the relationship of renal diseases to Lp (a) concentrations, an important risk factor for vascular diseases. Diabetic subjects have been reported to have both increased Lp (a) concentrations and an increased risk of renal failure, thereby possibly confounding the Lp (a) renal failure association.

Thus, to summarize though there was an increased Lp (a) level in patients having ischemic stroke, there was no positive correlation between Lp (a) with stroke severity, stroke subtype or with in hospital outcome.

The results of the present study have largely a negative connotation for Lp (a) and this has to some extent has thwarted an attempt by previous studies to vilify Lp (a) as a sinister marker for vascular events. Our observation that Lp (a) has no statistical association with stroke risk factors, stroke severity or stroke outcome provides a sigh of relief and reiterates the benign nature of this molecule. However, it is a scientific aphorism that results that are unprecedented or appear unconventional be further ascertained by larger population based studies. We agree that our study is beset with flaws and limitations but at the same time we feel that it may serve as a pilot study and a template upon which larger studies may be embarked.⁷

CONCLUSION

There is no predisposition for any stroke subtype (anterior versus posterior circulation) with high Lp (a) values. There is no statistical association between renal impairment and Lp (a) levels. There is also no positive correlation between Lp (a) and LDL levels. There is no gender predilection for high value of Lp (a). Lastly the risk factors for stroke like diabetes, smoking and hypertension do not predispose to higher Lp (a).

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Ethical approval: The study was approved by the institutional ethics committee

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