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To study the role of Lipoprotein (a) as a risk factor of ischemic stroke

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ABSTRACT

Aim: To study the role of Lipoprotein (a) as a risk factor of ischemic stroke.

Methods: The study group includes 100 stroke patients consecutive admitted in medicine departments and 100 patients as control group admitted for nonvascular diseases. The severity of ischemic strokes was classified on the basis of National institutes of Health stroke scale at the admission and discharge. 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.

Results: On comparing cases and controls for Lp (a), it was found that the mean value in cases (41.68 mg/dl) which was significantly higher (p= 0.011) than the mean value (30.45 mg/dl) in control subjects. There is significantly high proportion of patients having raised Lp (a) levels in cases compared to that controls. (Z value at 95% confidence levels =3.24). In anterior circulation group the mean Lp (a) level was more as compared to that of posterior circulation group (42.97 mg/dl versus 31.31 mg/dl), but it was not found to be statistically significant (p value = 0.178, >0.05). The mean Lp (a) value in the major stroke group was more as compared to that of minor strokes (46.66 mg/dl versus 36.35 mg/dl) but it was not found to be statistically significant (p = 0.157, > 0.05). Comparing both these groups the mean Lp (a) level in normal renal function patients was more (44.77 mg/dl) than the impaired renal function group (30.15 mg/dl) but it was not statistically significant (p= 0.059, >0.05).

Conclusion: We concluded that there is no predisposition for any stroke subtype (anterior versus posterior circulation) with high Lp (a) values. 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).

Keywords: Lipoprotein (a), ischemic stroke, diabetes, smoking and hypertension.

INTRODUCTION

Stroke is reported as the most common cause of long term disability and the second most leading cause of death worldwide.[1] Almost 80% of strokes are ischemic stroke (IS) and 15–20% are haemorrhagic stroke (HS) in origin[2,3] According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification; IS has been categorised according to the presumed etiological mechanism into five groups: large artery atherosclerosis (LAA), small vessel disease (SVD), cardioembolic disease (CE), other determined etiology (ODE), and undetermined etiology (UDE).[4] Lipoprotein (a) or Lp (a) is a lipoprotein moiety that consists of core

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lipoprotein molecule, containing apoli- poprotein B (apo-B100), to which a glycoprotein of variable molecular weight, apolipoprotein (a) [apo(a)], is covalently attached via a cysteine-cysteine disulfide bond.[5,6] By binding LDL, calcium, and other components into an atherosclerotic plaque on the walls of blood arteries, Lp (a) is hypothesised to speed up the development of atherosclerosis.[7] The LPA gene regulates the variation in Lp (a) plasma concentrations genetically, ranging from 36% in the PROCARDIS[8] consortium to 70–90% in genome-wide association studies, with larger apo(a) isoforms related with lower values of Lp (a).[9,10] The concentrations of Lp (a) range from 0.1 mg/dl to more than 200 mg/dl.[11]

On a cellular level, apo (a) undergoes post-translational changes in the endoplasmic reticulum as a secre- tory protein (ER). The length of time it takes to modify larger apo(a) isoforms is determined by the size of the apo(a) isoform. As a result, larger apo(a) molecules are produced at a slower rate per unit of time, resulting in lower Lp (a) plasma concentrations[6] Plasma Lp (a) concentrations appear to be regulated by synthesis rather than catabolism, according to kinetic studies. Concentration and pathological responses may be influenced by apo(a) sequence polymorphisms. Lp (a)/apo(a) functions may also be affected by changes in circulating Lp (a). Importantly, the relevance of apo(a) in cardiovascular diseases (CVD s) and peripheral vascular disorders, as well as its physiological function, remain unknown, and there is no effective therapeutic option for decreasing increased Lp levels (a).[11]

MATERIAL AND METHODS

This is a prospective case controlled study. The study group includes 100 stroke patients consecutive admitted in medicine departments and 100 patients as control group admitted for nonvascular diseases. 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).[12]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 were included in this study. Patients with hemorrhagic stroke, Patients with cardiovascular cause for emboli (i.e. in case of atrial fibrillation) and Those that are on medication known to influence lipid metabolism were excluded fromth is study. Hypertension, Diabetes mellitus, Smoking and Coronary artery disease parameters were studied

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.[13-14]

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 100 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.

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Table 1: Prevalence of diabetes among cases and controls

Diabetes	Cases=100	Controls=100	Total
Yes	45(45%)	35 (35%)	80 (40%)
No	55(55%)	65 (65%)	120 (60%)
Total	100	100	200

Among the cases 45 (45%) had diabetes mellitus but among the controls only 35 (35%) 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=100	Controls=100	Total
Yes	65 (65%)	31 (31%)	96 (48%)
No	35 (35%)	69(69%)	104 (52%)

Among the cases 35(35%) had hypertension but among the controls only 31 (31%) had hypertension. The percentage of hypertension was higher in cases as compared to controls in the present study. Among the cases 29 (29%) were smokers and 71 (71 %) were nonsmokers. In the control group 5 (5%) were smokers and 95 (95%) were nonsmokers.

Table 3: Prevalence of smoking among cases and controls

Smoking	Cases=100	Controls=100	Total
Yes	29 (29%)	5 (5%)	32(16%)
No	71 (71%)	95 (95%)	168 (84%)

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	41.68	25.25	2.63
Controls	100	30.45	20.06	2.78

On comparing cases and controls for Lp (a), it was found that the mean value in cases (41.68 mg/dl) which was significantly higher (p= 0.011) than the mean value (30.45 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 =3.24).

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	86	42.97	25.26	3.25
Posterior circulation	14	31.31	14.29	4.44

In anterior circulation group the mean Lp (a) level was more as compared to that of posterior circulation group (42.97 mg/dl versus 31.31 mg/dl), but it was not found to be statistically significant (p value = 0.178, >0.05).

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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	37	36.35	20.82	4.12
Major strokes	63	44.66	28.15	3.87

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 (46.66 mg/dl versus 36.35 mg/dl) but it was not found to be statistically significant ($p = 0.157$, > 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	30	44.55	30.66	5.66
Poor outcome	3 and above	70	39.85	21.69	5.89

In this study patients with poor outcome who had raised Lp (a) defined as >30 mg/dl were 45 out of 70 and patients with good outcome who had raised Lp (a) were 20 out of 30. The z test between two proportions was applied but showed no statistical significance in the difference noted.

Comparing both these groups the mean Lp (a) level in normal renal function patients was more (44.77 mg/dl) than the impaired renal function group (30.15 mg/dl) but it was not statistically significant ($p= 0.059$, >0.05). 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 (42.87 versus 40.77mg/dl) in stroke patients, there was no statistically significant difference (p value = 0.74, >0.05). The number of patients having raised Lp (a) levels defined as >30 mg/dl constitute 47 out of 70 males stroke subjects and 20 out of 30 female strokes subjects (65.55% versus 54.45%).

DISCUSSION

On comparing ischemic strokes and controls for lipoprotein (a), the serum lipoprotein (a) levels in cases were found to be 41.68±25.25 mg/dl (mean±SD) which was significantly ($p = 0.011$) higher than those in control subjects (30.45±20.06 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 ($p<0.001$).[15] 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 ± SD), which were significantly ($p<0.01$)

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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).[16]

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.[17]

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.[18] 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.[19]

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.

There was no significant association between types of stroke and Lp (a) levels. In anterior circulation group the mean Lp (a) level was more as compared to that of posterior circulation group (42.97 mg/dl versus 31.31 mg/dl), but it was not found to be statistically significant (p value = 0.178, >0.05). 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.20 [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.[21,22]

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.[20]

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.[21,23] 13 Cross sectional studies conducted by Kooten FV et al, found no association between cardiovascular risk profile, severity of stroke, stroke characteristics, and prognosis.[20]

In the present study only 3 (3%) patients had expired. 2 patient was found to have high (>30 mg/dl) and the 1 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.

Comparing both these groups the mean Lp (a) level in normal renal function patients was more (44.77 mg/dl) than the impaired renal function group (30.15 mg/dl) but it was not statistically significant (p= 0.059, >0.05).

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 (42.87 versus 40.77mg/dl) in stroke patients, there was no statistically significant difference (p value = 0.74, >0.05).

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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.

CONCLUSION

We concluded that there is no predisposition for any stroke subtype (anterior versus posterior circulation) with high Lp (a) values. 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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