Original Research Article

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Study of Association of Lipoprotein (A) Levels with Carotid Atherosclerosis in Young Patients with Ischemic Stroke

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Abstract

Context: Lipoprotein (a) is an established risk factor for coronary artery disease but its role as a risk factor for stroke is not established. *Aims:* To estimate the prevalence of elevated levels of lipoprotein (a) in young patients (18-55 years) with ischemic stroke and to study the association between lipoprotein (a) plasma concentration and carotid atherosclerosis *Settings and Design:* This observational, cross-sectional, single center study was conductedon 90 young (18-55 years) patients with imaging confirmed ischemic stroke for a duration of 1 year. Lipoprotein (a) samples were taken within 24 hours of presentation to the hospital and values >30mg/dL were considered abnormal. Carotid Doppler was done by a cardiologist unaware of history of patientsl. Patients were divided into two groups: Group A (normal) and Group B (abnormal). Average values of lipoprotein (a) levels in both the groups were taken and compared using appropriate statistical analysis. *Results:* There were 65 males and 25 females in the study. Prevalence of elevated lipoprotein (a) in the study population was found to be 44.4%. It was more than the other traditional risk factors for stroke. Prevalence of carotid atherosclerosis and carotid stenosis in the study was 41.1% and 31.1% respectively. Elevation of lipoprotein (a) was strongly associated with carotid atherosclerosis (p=0.001). Mean values of lipoprotein (a) were statistically higher in the atherosclerosis group than in no atherosclerosis group (p=0.002). Lipoprotein (a) was positively associated with carotid stenosis in a graded manner but its association with CIMT was not significant. The association of lipoprotein (a) and carotid atherosclerosis was independent of other risk factors. *Conclusion:* Lipoprotein (a) is strongly associated with carotid atherosclerosis (especially carotid stenosis) in young patients with ischemic stroke and the association is independent of the traditional risk factors.

Keywords: Ischemic Stroke; Young Population; Lipoprotein (a); Carotid Atherosclerosis.

Introduction

Lipoprotein (a) [Lp (a)] is a plasma lipoprotein consisting of cholesterol rich low density lipoprotein(LDL) particle with one molecule of apolipoprotein B-100 and an additional protein, apolipoprotein (a) attached via a disulfide bond [1]. It plays an important role in accelerating atherosclerosis in coronary, cerebral and peripheral arteries. Elevated Lp (a) levels (>25-30 mg/dL) have been linked to an increased risk of atherothrombotic diseases. Stroke is one of the most common causes of mortality and long term severe disability and place a tremendous burden on health resources. Improved detection and modification of risk factors could reduce the burden of disease. There are well established risk factors for stroke, such as increased blood pressure, increased blood cholesterol, cigarette smoking, carotid stenosis, diabetes mellitus, atrial fibrillation and valvular heart disease. There is a reasonably reliable evidence to suggest that 60-80% of all ischemic strokes can be attributed to these risk factors [2]. There is accumulating evidence that emerging biological markers, including Lp (a) add to the prognostic value of conventional risk factors and may well serve as useful prognostic tools in identifying subjects at risk [2]. There exists a robust and specific relation between increased

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levels of Lp (a) and risk of ischemic heart disease and atherosclerosis**.** However there is no reliable or consistent data regarding association of Lp (a) levels in ischemic stroke. Case-control studies done in past have reported raised Lp (a) concentrations in stroke patients but prospective studies have failed to confirm the association [3]. Extra cranial vascular disease is a still major cause of ischemic stroke in young individuals. The risk rises as the degree of stenosis increases [4]. Carotid Doppler ultrasonography is a popular tool for evaluating atherosclerosis of the carotid artery. It detects not only local, but also generalized atherosclerosis, even in asymptomatic individuals [5].

Elevated Lp (a) concentration is associated with carotid atherosclerosis in older patients with Ischemic stroke but this association has not been explored in young patients of Ischemic stroke. Studies in young have been conducted but in persons who were free of any Cerebro-vascular symptoms and not symptomatic. Very few studies have been conducted in Indian population, despite the fact that Lp (a) levels are genetically determined and vary in different populations and stroke in young consist nearly 20 to 30% of all strokes in India [4]. The present study was undertaken to estimate prevalence of elevated lipoprotein (a) and its association with carotid atherosclerosis in patients of ischemic stroke younger than 55 years of age.

Material and Methods

This prospective, cross-sectional, single center study was conducted on 90 patients of ischemic stroke presenting to a tertiary hospital over a period of one year. All the patients included in the study were CT/MRI confirmed cases of ischemic stroke in the age group of 18-55 years with onset of complaint within last one month. The study was approved by the hospital ethics committee and all the patients gave written informed consent as an approval for their participation in the study.

Every patient's information was documented including history, presenting complaints, age, sex, systolic blood pressure, history of smoking diabetes mellitus, family history. Body mass index and waist-hip ratio was calculated. Detailed physical and neurological examination was done. Diagnosis of cerebral infarction was confirmed by cerebral computerised axial tomography or magnetic resonance imaging.

For lipoprotein (a) levels, sample were taken within 24 hours of presentation to the hospital and were measured using Latex Agglutination Turbidimetery method in the Department of Biochemistry. Values >30mg/decilitre were considered abnormal. Blood glucose, liver function tests, renal function tests, triglycerides, total and HDL cholesterol were measured by standard enzyme methods.

Carotid Doppler was done by a cardiologist unaware of history or laboratory tests of patients using Philips I 33 sonograph and L11 MHZ linear probe. Subject was in supine position with neck hyperextended and rotation of head for facilitation of procedure. Intima media thickness (IMT) in mm was measured at the end of diastolic phase at the distal common carotid artery, area of bifurcation and first proximal internal carotid artery. Mean of right and left IMT >0.8 mm was considered abnormal.

Patients were divided into two groups. Group A (normal) included patients with no atherosclerosis and Group B (abnormal) included patients with plaque or intimal thickening visible. Lp (a) concentrations were compared with degree of carotid stenosis estimated on duplex.

Descriptive statistics was analyzed with Microsoft Excel and SPSS for Windows. Continuous variables were presented as mean±SD. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed variables between groups was performed using student's t- test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann Whitney U test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Results

In the present study of 90 patients presenting with ischemic stroke patients (18-50) years of age), 65 (72.2%) were male and 25 (27.8%) female with male to female ratio of 2.6:1. Forty (44.4%) patients had elevated lipoprotein (a) level, while 37 (41.1%) patients had carotid atherosclerosis.

Mean age of our study population was 43.6 (±9.16) years and most (48.9%) of patients were in the age group of 45-55 years.Same trend was seen in the subgroups of elevated Lp (a) (52.5%) and carotid atherosclerosis 24 (64.9%). Most patients were having lacunar stroke (33.3%), followed by large vessel stroke (27.8%). Prevalence of cardio-

embolic, other causes and stroke of undetermined etiology was 6.7%, 10% and 22.2% respectively.

Mean values of Lp (a) were highest in large vessel stroke [57.2 (±9.16mg/dL)], followed by the subgroup of other causes (43.1±29.6mg/d:) and lowest in the cardio-embolic stroke. Mean values of Lp (a) in the study population was found to be 35.5 (±28.09) mg/dL. Mean value was higher in females [40.44 (±28.28) mg/dL] than male population [33.3 (±28.1) mg/dl]. Its prevalence (44.4%) was higher than the traditional risk factors like homocysteine (41.1%), cholesterol (31.1%), triglycerides (43.4%) and diabetes mellitus (31.1%), slightly less to smoking (46.75%) and equal to hypertension (44.5%).

CIMT was increased in 17.8% of patients of total patients. Carotid stenosis was seen in 31.1% of the patients, out of which 21.1% had mild stenosis (less than 50%), 3.3% had moderate stenosis (50-70%) and 6.7% of the patients had severe stenosis (> 70%).

Association of Lp (a) with CIMT alone was positive but statistically not significant OR 2.44 (95% CI 0.8 to 7.44; p>0.05). However association with carotid stenosis alone was positive with significance OR 4.122 (95% CI 1.59 to 10.67; p=0.003).

The association of carotid stenosis and lipoprotein (a) appeared to be graded. Mean values were 28.93 (±22.9), 49.9 (±27.33), 34.67 (±25.31) and 60.16 (±28.15) mg/dL in the groups with no stenosis, mild stenosis, moderate stenosis and severe stenosis. However, the number patients with moderate stenosis is less (n=3) to make any definite comment (Tables 1, 2,3).

Elevation of Lp (a) was positively associated with carotid atherosclerosis. This association was strong, OR 4.269 [95% CI 1.74 to 10.44] and statistically significant (p=0.001) (Table 4).

Moreover, mean value of lipoprotein (a) in Group A and Group B was 28 (±28.17) mg/dL and 46.54 (±27.99) mg/dl respectively, difference between the two being statistically highly significant (p=0.002).

Other risk factors i.e. homocysteine, triglyceride, cholesterol, smoking, diabetes mellitus and hypertension were positively related to carotid atherosclerosis. Association of hypertension was statistically significant [OR 2.34 (95% CI 0.99 to 5.54); p=0.05], whereas others relations were not significant statistically. Association of Lp (a) and carotid atherosclerosis was significant with adjustment for the traditional risk factors also, adjusted OR 1.026 (95% CI 1.009 to 1.043; p=0.003). Prevalence of diabetes mellitus in our young population was 31.1%.

Table 1: Relation of lipoprotein (a) levels with carotid intima medial thickness (CIMT)

Lipoprotein (a) levels (mg/dL)	CIMT <0.8mm (Normal)		CIMT ≥0.8mm (Abnormal)		Total		p-value
	No.	%	No.	%	No.	%	
Elevated (>30)	30	33.4	10	11.1	40	44.5	
Normal (≤30)	44	48.8	6	66.7	50	55.5	0.109*
Total	74	82.2	16	17.8	90	100	

Odds Ratio: 2.44 [95% CI 0.8028 to 7.443] *Not significant

Table 2: Relation of lipoprotein (a) levels with luminal stenosis

Lipoprotein (a) levels (mg/dL)	No Luminal stenosis		Luminal stenosis present		Total		p-value
	No.	%	No.	%	No.	%	
Elevated (>30)	21	23.3	19	21.1	40	44.5	
Normal (≤30)	41	45.6	09	10	50	55.5	0.003**
Total	62	68.9	28	31.1	90	100	

Odds Ratio: 4.122 [95% CI 1.5914 to 10.6753] **Highly Significant

Table 3: Relation of degree of luminal stenosis with lipoprotein (a)

Degree of stenosis	Number of Patients	%	Mean value of Lp (a) (in mg/dL)
No stenosis	62	68.9	28.93 (± 22.9)
<50%	19	21.1	49.9 (±27.33)
Stenosis 50-70%	03	3.3	34.67 (± 25.31)
>70%	06	6.7	60.16 (±28.15)
Total	90	100	35.60 (±28.09)

Table 4: Relation of lipoprotein (a) levels with carotid atherosclerosis

Lipoprotein (a) levels (mg/dL)	Group A		Group B		Total		p-value
	No.	%	No.	%	No.	%	
Elevated (>30)	16	17.8	24	26.7	40	44.5	0.001**
Normal (≤30)	37	41.1	13	14.4	50	55.5	
Total	53	58.9	37	41.1	90	100	

**Highly significant

Discussion

Stroke is an increasing public health problem, since it is a leading cause of long term disability and death especially in young adults. Early detection of risk factors and their control is a very crucial in fighting this challenging problem. Elevated lipoprotein (a) potentially increases the risk of vascular disease via prothrombotic/ antifibrinolytic effects as apolipoprotein (a) possesses structural homology with plasminogen and plasmin but has no fibrinolytic activity [6]. Another mechanism of action of lipoprotein (a) is recruitment of monocytes to the vessel wall and promotion of binding that could lead to recruitment of monocytes to the vessel wall and promotion of foam cell formation and localization of lipoprotein (a) at atherosclerotic plaques [4]. It readily oxidizes and forms highly atherogenic particles with LDL. It enhances oxidation, uptake and retention of LDL. Other mechanisms include enhancing thrombosis, decreases plasmin formation and impaired fibrinolysis. It also increases smooth muscle proliferation and migration, inhibits transforming growth factor, enhances expression of intercellular adhesion molecules and impairs formation of collateral vessels [7].

Most of the patients in the present study had left middle cerebral artery territory stroke (43.3%). About half of the patients were more than 45 years of age in the present study. Only 27.8% of the total patients were female and there was no female in the age group of 18-25 years group. In the study done by Nasr et al. [8], which had the same study population, mean age was almost same as our study (44.8 years) and males were affected more than females in the study population and the sub-group of carotid atherosclerosis. On the contrary, in the study done by Rigalet al. [3] the number of female patients was more (42%) but the mean ages were almost similar to our study, 42.3 years for men and 47.3 years for women. Even in studies with patients including all patients of stroke, irrespective of age, males were more affected than females – about 66% in total population and 65.6% in a sub-group with extracranial atherosclerosis [9,10].

Mean values of Lp (a) were high in cases of ischemic stroke as compared to controls. In a study conducted by Rigal et al. [3] in young population of stroke, Lp (a) was strongly associated with ischemic stroke in men (OR 3.54) and not in women (OR 0.31) with mean values being 41 mg/dL in males and 35 mg/ dL in females. This is contrary to our findings as in our study the mean values were higher in females.

We also considered the prevalence Lp (a) elevation (>30 mg/dl) as a parameter since mean values are sometimes affected by skewed data (very high or low values). To avoid bias and confusion, we estimated the number of patients with Lp (a) levels above the cut off levels of 30 mg/dl as well as the mean values of Lp (a). For other parameters also, comparison was done with the number of patients above the cut-off normal values. When we compared the prevalence of elevated Lp (a) (44.4%) with other traditional risk factors in our study, it was almost same or more except for smoking. Prevalence of elevated levels of homocysteine was 41.1%, cholesterol 31.3%, triglyceride 43.4%, smoking 46.7%, hypertension 44.4% and for diabetes mellitus it was 31.1%.

Prevalence of carotid atherosclerosis in young population of ischemic stroke patients in our studywas much higher than the study done by Kim et al. [9] where only 15% patients had carotid atherosclerosis. The reason being that the modality usedwas magnetic resonance angiography and they considered only carotid stenosis as parameter and not plaques or CIMT. Result of our study is similarto Nasr et al. [8], whereinprevalence of carotid atherosclerosis was 40% in young stroke patients.

In the present study, out of the 37 patients, 24.3% (n=9) patients had only increased CIMT, 56.8% (n=21) had only luminal stenosis and 18.9% (n=7) patients had both increased CIMT and luminal stenosis. Prevalence of luminal stenosis in our study was 31.1%, similar to the study conducted by Razzaq et al. [11]. Most of the studies considered either of the two parameters (CIMT or carotid stenosis), but in our study we considered both the parameters asit has was postulated by Lp (a)

is differently related to plaque area and degree of stenosis [12].

Carotid atherosclerosis is an important risk factor for stroke even in young patients, though not as strong as old patients. Reason being that there are many other important causes of stroke in young population *e.g.* cardio-embolic stroke, RHD etc. which dilute the association and atherosclerosis is progressive and increases with age – a trend which we saw in our study also, as most of the patients with carotid atherosclerosis were in the age group of 45-55 years in our study.

Lp (a) levels were strongly associated with carotid atherosclerosis with OR of 4.269 (CI 1.74 to 10.44; p=0.001). The difference was statistically significant **(**p=0.002) between the mean values of Group A and Group B. This association was stronger than all other traditional risk factors (diabetes mellitus, hypertension, smoking, triglycerides and cholesterol) suggesting that Lp (a) is the most important risk factor which predicts atherosclerosis in young patients of ischemic stroke. This association could be due to pro-atherogenic and anti-fibrinolytic effects of Lp (a).

This association has been studied in few studies in the past, but with the same target population in one study only [8]. The results in this study were similar to the present study with OR 3.11 for stenosis <50% and 7.44 for stenosis >50% (p<0.001). Association was positive and significant (p=0.006) in another study where the target population was CABG patients with mean values 31.8 mg/dL in carotid stenosis <50% and 41.7 mg/dL in carotid stenosis >50% (15).Another study by Kim et al. [9] yielded similar results where extra-cranial atherosclerosis was found to be strongly associated with lipoprotein (a) with OR 4.82 (95% CI 1.96 to 11.88**)**. The study done by Rafieian-Kopaei and Nasri [14] also showed positive association of CIMT with Lp (a) irrespective of diabetes mellitus in hemodialysis patients. But in our study the association with CIMT alone was not significant, although correlation was positive with OR 2.44 (95% CI 0.8 to 7.44), when CIMT ≥0.8mm was taken as abnormal. However, the association of carotid stenosis alone with Lp (a) levels was significant in our study with OR 4.121 (95% CI 1.59 to 10.6; p=0.003). Also, the relation was graded. Though the number of patients with moderate stenosis was only 3 (mean value 34.64 mg/dL), the mean value of Lp(a) was lowest (28.9 mg/dL) in the group with no stenosis. In mild stenosis group it was 49.9 mg/dL and in severe stenosis 60.12 mg/dL. But if we consider the subgroup carotid stenosis >50% including both moderate and severe stenosis, mean value was 51.6 (±27.9) mg/dL which is greater than the mild stenosis group which makes the stenosis graded. This finding was similar to the studies by Nasr et al. [8] and Klein et al. [15] where this association was strong, graded and independent of traditional risk factors. Thus in the present study, elevated Lp (a) levels predicted carotid stenosis and occlusion in stroke patients but CIMT did not. It has been hypothesized that the effect of Lp (a) on atherogenesis and vascular risk is largely related to thrombosis and impaired fibrinolysis. Stenosis and occlusion may not be attributed to plaque progression but to plaque rupture and thrombosis [15]. This could apply to stroke as well. Gendi et al. [16] postulated that there was no association of carotid atherosclerosis with Lp (a). It could be possible due to the fact that CIMT was taken as parameter in that study and not stenosis. But in studies done by Rafieian-Kopaei and Nasri [14] and Yamamoto et al. [17] CIMT was proportional to Lp (a) levels. However in these studies, the target population was different. So it could be possible that Lp (a) has some different mechanism of action in stroke patients when compared with NIDDM and CABG patients.

Thus in our study, carotid atherosclerosis especially the carotid stenosis correlated positively with Lp (a) levels in strong and graded manner in a population of young patients of ischemic stroke. CIMT although was positively associated but the association was not statistically significant.

Conclusions

Lipoprotein (a) is strongly associated with carotid atherosclerosis (especially carotid stenosis) in young patients with ischemic stroke and the association is independent of the traditional risk factors.

Recommendations

Lipoprotein (a) levels should be done in all patients of stroke especially the young stroke to identify the risk factors of stroke. Since it is strongly associated with carotid atherosclerosis, so it can be used as a screening test for identifying carotid atherosclerosis (especially carotid stenosis) in populations having high risk of having ischemic stroke *e.g.* family members of stroke patients and patients with metabolic syndrome.

Lp (a) is a potentially modifiable risk factor

with niacin, statins, etc. The strong association of Lp (a) with carotid atherosclerosis in young stroke suggests that further studies are needed to determine the role of various drugs in lowering the levels of lipoprotein (a) in young stroke population in Indian and other non-Caucasian populations.

Key Messages

Lipoprotein (a) can be used as a screening test for identifying carotid atherosclerosis in populations having high risk of having ischemic. Lp (a) is a potentially modifiable risk factor. The strong association of Lp (a) with carotid atherosclerosis in young stroke suggests that further studies are needed to determine the role of various drugs in lowering the levels of lipoprotein (a) in young stroke.

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