



REEMERGENCE OF A FORGOTTEN ENEMY: LIPOPROTEIN(A) IN ISCHEMIC STROKE – A PROSPECTIVE CASE-CONTROL STUDY FROM SOUTH INDIA.

Neurology

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ABSTRACT

Background: Elevated Lipoprotein(a) [Lp(a)] is an established risk factor for atherothrombosis, but data from India remain limited. **Objective:** To assess the association between Lp(a) levels and acute ischemic stroke (AIS) and evaluate relationships with stroke subtype, severity, and outcome. **Methods:** In this prospective case-control study (September 2022–September 2023), 73 first-ever AIS patients and 33 age- and sex-matched controls were enrolled. Lp(a) was measured by immunoturbidimetry. Elevated Lp(a) was defined as >74 nmol/L and high-risk levels as >125 nmol/L. Stroke subtype was classified using TOAST criteria, while severity and outcome were assessed using NIHSS and mRS. **Results:** Mean Lp(a) levels were significantly higher in AIS patients than controls (116.7 ± 79.2 vs 70.3 ± 69.0 nmol/L; $p=0.005$). High-risk Lp(a) levels were more frequent among cases (31.5% vs 15.2%; $p<0.01$). Lp(a) showed no significant association with TOAST subtype, carotid stenosis, LDL levels, stroke laterality, circulation territory, NIHSS, or discharge mRS. Hypertension was the only vascular risk factor significantly associated with stroke. **Conclusion:** Elevated Lp(a) is significantly associated with AIS in South Indians, independent of conventional vascular risk factors. Its lack of association with stroke severity and outcome may reflect limited sample size. Given emerging Lp(a)-lowering therapies, larger multicenter studies are needed to define its prognostic and therapeutic role in stroke prevention.

KEYWORDS

Acute Ischemic Stroke ,NIHSS, Lipoprotein (a) ,South India ,Biomarker .

INTRODUCTION

Lipoprotein A (Lp(a)) was initially described in 1963. It is a low-density lipoprotein (LDL)-like particle synthesized from hepatocytes that contains an additional apolipoprotein, Apo [A], attached to the Apo B 100 component of LDL via a disulfide bond.^[1]

Its phylogenetic role in the human body is believed to be the reduction of bleeding during childbirth, the prevention of cancer dissemination, and the promotion of wound healing.^[2] Lp(a) is expressed as an autosomal codominant factor located on chromosome 6q 27.^[3] Its peak plasma levels are typically attained by the age of five (ranging from 0.2 to 200 mg). Furthermore, Lp(a) serves as an acute inflammatory marker.

There are three distinct forms of Lp(a): the native form, the oxidized form, and the glycated form. The native form possesses thrombogenic, pro-inflammatory, antifibrinolytic, and chemoattractant functions. The oxidized form is a result of the oxidation of Lp(a) particles. The third type is the glycated Lp(a), which is formed through the non-enzymatic glycation of Lp(a) in type 2 diabetes (T2DM). This process subsequently enhances its atherogenic properties. The glycated Lp(a) is a result of increased facilitation of plasminogen activator inhibitor-1, leading to a subsequent attenuation of tissue plasminogen activator (tPA).

Population studies have demonstrated a 1.6-fold increase in the risk of stroke among individuals with elevated Lp(a) levels.^[4] Elevated Lp(a) is defined as greater than 75 nmol/L or 30 mg/dl, and values exceeding 125 nmol/L or 50 mg/dl are considered high risk, as per the 2022 European atherosclerosis society consensus statement^[5]

Beyond stroke, several meta-analyses have revealed an increased risk of myocardial infarction (MI), calcific aortic valve stenosis, carotid stenosis, ischemic stroke, femoral artery stenosis, and a generalized increase in all-cause mortality by 1.2 fold with elevated Lp(a) levels.^[6] Drugs designed to reduce dyslipidemia have been demonstrated to have no impact on Lp(a) levels, paradoxically statin use has been associated with an increase in Lp(a) levels in few studies^[7]. Given that Lp(a) levels are predominantly determined by genetic factors, there is a lack of clarity regarding screening protocols. Furthermore, there is a lack of effective therapies to reduce Lp(a), which presents an ethical dilemma in the process of screening. However, it is undeniable that Lp(a) is rapidly emerging as an economical stroke biomarker, and there are a few promising treatment options emerging with multiple ongoing trials regarding the same. An exhaustive meta-analysis

conducted by the neurology department at AIIMS Delhi revealed, among other findings, that most of the studies did not consider the TOAST classification while analyzing stroke cases^[8]. Additionally, an analysis of Indian studies demonstrated that most of them were conducted by broad specialties and non-clinical departments, resulting in the exclusion of a substantial amount of clinical information. To address these shortcomings, we initiated this study to analyze the incidence of elevated Lp(a) in our stroke population between September 2023 and September 2024. Our objective was to mitigate the limitations identified in previous Indian studies by incorporating the TOAST groups, NIHSS score at admission, and MRS at discharge, in addition to routine laboratory and diagnostic tests performed for stroke.

METHODOLOGY

We conducted an observational prospective case-control study spanning from September 2022 to September 2023. The initial consecutive 73 cases of ischemic stroke admitted to our tertiary care hospital, meeting the inclusion criteria, were included in the study after obtaining written consent and Institutional Review Board (IEC) approval. Thirty-three age- and gender-matched controls were selected from the medicine wards admitted for non-vascular diseases.

Inclusion criteria:

- Cases: Patients admitted to the neurology and medical wards with the first attack of ischemic stroke, as defined by the American Heart Association.^[9]
- Controls: Patients admitted to medical wards for non-vascular diseases without a prior history of CAD, PVOD, CVA or TIA.

Exclusion Criteria:

- Hemorrhagic stroke
- Previous history of stroke or TIA
- Patients on statins or other lipid-lowering agents

Evaluation and Treatment Protocol: Patients underwent clinical examinations, biochemical studies, and supportive radiological investigations as per the established evaluation and treatment protocol for ischemic stroke. The NIHSS score was recorded at admission to assess the severity of the stroke^[10]. Scores less than 5 were classified as minor strokes, 5-15 as moderate strokes, 16-20 as moderate-severe strokes, and greater than 20 as severe strokes. The type of stroke was determined using the TOAST classification^[11]. The Modified Rankin Score was noted at the time of discharge. Comorbidities were

documented according to standard international definitions (e.g., diabetes WHO criteria, hypertension JNC VII). Significant history of smoking and alcohol use was considered to be at least 1 year of use. Lipoprotein A levels were measured using immune turbimetry in mg/dl. Elevated values were defined as greater than 74 nmol/L (30 mg/dl), and high-risk values were defined as greater than 125 nmol/L (50 mg/dl). Statistical analyses were performed using SPSS, and p values less than 0.05 were considered statistically significant.

RESULTS:

Our study included 73 cases and 33 controls selected consecutively after applying inclusion and exclusion criteria. The mean age in the cases was 60.14 (12.194), while the mean age in the controls was 57.88 (12.903). There was no significant statistical difference between the two groups ($P=0.388$).

Gender Distribution:

69% of the cases were males and 67% of the controls were male, and the gender difference was not significant between both groups.

The most common presenting complaint was limb weakness (60.82%), followed by ipsilateral upper motor neuron facial weakness in 34 patients (46.6%). 15 patients (20.5%) had language abnormalities, with Broca's aphasia being the most common form. 25 patients (34.2%) had dysarthria, which was predominantly labial (15), followed by mixed (6) and lingual (4) types. 3 patients (4.1%) had visual field defects, all of whom had PCA territory strokes with occipital lobe infarcts and corresponding homonymous hemianopia. 3 patients (4.1%) had other cognitive abnormalities, such as hemineglect (2) and simultanagnosia (1).

The distribution of various comorbidities among cases and controls is provided below. Only hypertension was significantly different between the two groups; the rest of the comorbidities were similar in distribution. Table (1)

The mean duration of admission since day of stroke was 2.84 (SD=2.768, 24 (32.9%) presenting on the first day of stroke. The mean MRS score at discharge was 2.41 with SD of 1.603.

Stroke severity was assessed with NIHSS, with 53.4% presenting with moderate stroke and 8.2% presenting with moderate to severe stroke, and remaining 38.4% with minor stroke.

8 (11%) patients were thrombolysed. MRI brain was done in 73 patients, the distribution of mean Lp(a) values in all groups were similar [$p=0.34$], and there was no gender difference in distribution of MRI findings. [$p=0.166$]

CV doppler was done in 66 patients of which 36 had normal study, 6 patients had severe stenosis and 24 patients had varying amounts of non significant atherosclerosis.

Comparison of routine lab values between cases and controls is as follows

Table 2. Except for total cholesterol, LDL SGOT all other lab parameters have no significant difference between cases and controls.

Table 3 The mean serum lipoprotein A levels in the stroke cases was 116.65 (SD =79.22) nmol/L as opposed to 70.32 (SD=68.95) in the controls and the difference was statistically very significant with a p value of 0.005

We divided the lipoprotein levels into three risk levels and compared both groups which revealed a highly significant difference between the risk levels between cases and controls. 78.8% controls had lipoprotein levels in the low risk range as opposed to 35.6% in cases. 31.5% cases had lipoprotein A levels in high risk range.

The TOAST classification of the cases shows predominance of small vessel occlusion as the etiology of stroke, followed by large artery atherosclerosis.

We evaluated the correlation between lipoprotein A levels and TOAST groups, but no significant association was detected ($p=0.732$). Additionally, we assessed the relationship between large artery

atherosclerosis, as assessed by carotid Doppler, and lipoprotein levels, but no significant association was observed ($p=0.757$).

We also studied the correlation between LDL levels and Lp(a) levels which did not reveal any significant association [$p=0.6$]

Of the 37 cases, 35 were right-sided, and 1 case had bilateral stroke. Notably, patients with right hemispheric strokes exhibited higher lipoprotein levels (40% with high-risk levels), while 48.6% of cases had lipoprotein levels within normal limits. However, this difference was not statistically significant ($p=0.099$). Furthermore, we analyzed the association between Lp(a) levels in the territory of stroke. The mean Lp(a) value in anterior circulation stroke was 116.7, while in posterior circulation stroke, it was 116.2. Both values were comparable, and no statistical significance was observed ($p=0.97$).

DISCUSSION

The mean age of our stroke cases was 60.13 (SD=12.19), while the controls were 57.8 (SD12.9). There was no significant difference between the groups ($p=0.385$), which is similar to most Asian studies [12],[13],[14].

Lipoprotein A (Lp(a)) and Stroke Incidence

Our study revealed significantly elevated Lp(a) levels in stroke cases (116.65 (SD =79.22) nmol/L or 54.24 [36.837] mg/dl) compared to controls. 31.5% of stroke cases had Lp(a) levels above 125 nmol/L (50 mg/dl), which is considered high risk as compared to 15.2% of controls, implying a potential role in the occurrence of AIS. A large-scale Indian study revealed a mean admission serum Lp(a) level of 82.3 [SD= 52.9] mg/dl (equivalent to 177 nmol/L). None of the studies were undertaken by neurology departments, and only one study studied a correlation with TOAST classifications. However, all the studies except two found a significant statistical correlation with elevated Lp(a) and AIS incidence. Of the two studies that did not, one had a very low sample size, and the second did not assess the significance. Table 4

The mean duration since stroke onset in our cases was 2.84 days, which was similar to the study by Chakraborty et al [20] which collected the first value within 2 days of stroke onset. Lp(a), being an acute phase reactant, was considered a confounding factor in analyzing its relevance. It demonstrated a serial decrease over days and months. However, given our resource-constrained setting, serial assays would have added to the cost burden on patients and were not deemed justified. Nevertheless, the same study noted a negative correlation between serum albumin levels less than 3.5 gm and Lp(a). In this context, albumin was a negative biomarker, while Lp(a) was a positive biomarker of inflammation in stroke. In our study, none of the patients had albumin levels less than 3.5 gm. None of our patients exhibited alterations of other markers of inflammation, such as thrombocytosis, elevated ESR, or CRP. Consequently, we presume that the elevated Lp(a) levels indicate a genetically mediated risk factor rather than a transient marker of inflammation. Notably, the South Indian studies did not measure Lp(a) serially. [15],[16],[19] However, there remains scope for further research in this regard within the South Indian population.

The stroke severity did not correlate with Lp(a) levels, unlike the aforementioned study where an association was observed. We investigated the association between different TOAST categories and Lp(a) levels, which was also not significant. These findings were consistent with those observed by the aforementioned study [20] both of which are in contrast to other international studies where a significant association was found [21],[22],[23]. This discrepancy can be attributed to the smaller case numbers in the Indian studies.

MRI brain lesions were categorized and compared with lipoprotein A (Lp(a)) values. The mean Lp(a) levels were comparable across all groups. Notably, there was no significant difference in Lp(a) levels between anterior and posterior circulation strokes, a finding corroborated by More study [17]

Laboratory parameters were comparable between the stroke patients, controls, and healthy individuals with the exception of total cholesterol and LDL which was significantly reduced in controls. There was no negative association between LDL and Lp(a) levels as was found in several international studies [7]. We had excluded all patients on statins and this effect appears to be statin mediated probably resulting in this lack of correlation.

In our study, only two patients had elevated Lp(a) as the sole risk factor, both of whom had Lp(a) levels exceeding 80-90 nmol/L. Four patients only had dyslipidemia as a risk factor, with three of them having elevated Lp(a) levels (70-75 nmol/L, 102 nmol/L, and 260 nmol/L). Five patients had diabetes as the sole risk factor, and six patients had hypertension as the sole risk factor. Cardiovascular risk factors in both the stroke patients and controls were comparable ($p>0.05$).

A higher potential predilection for right-sided strokes was observed in patients with elevated Lp(a) levels, although this finding was statistically insignificant and not replicated in any international or regional studies.

CONCLUSION

In conclusion, as with previous Indian and international studies, our study demonstrated a clear elevation of serum lipoprotein A in stroke cases. We found two cases whose only risk factor was elevated Lp(a). In the light of studies showing counterproductive effect of LDL lowering therapies on Lp(a), we need to think beyond treatment of conventional risk factors. However, none of the guidelines on dyslipidemia recommend discontinuing statins or other LDL-lowering agents because the benefits clearly outweigh the risks.

Contrary to international studies, in our study there was no significant association between Lp(a) levels and the severity of stroke or long-term outcome, which may be attributed to the low sample size.

Our study had many shortcomings including a low sample size, its observational nature and logistical limitations in carrying out serial Lp(a) measurements.

All the aforementioned studies have established Lp(a) as a definite risk factor of acute ischemic stroke. It is also cost-effective, maintains stability across age distributions, and is genetically determined.

However we must exercise more caution in labelling it as a stroke biomarker as only one Indian study has found association with stroke severity and none of them were interventional studies. As reiterated in multiple previous Indian studies, a multi-center randomized controlled trial in this subject is the need of the hour.

In the therapeutic frontier, there is newfound hope in the form of numerous ongoing drug trials investigating the effects of various therapeutic options, such as PCSK inhibitors^[24], ASOs^[25], and RNAi therapy^[26], in beneficially reducing Lp(a) levels. Of these, PCSK inhibitors are of particular interest because they reduce both LDL and Lp(a).

From the first decade of its description we have sought to understand its significance and find ways to meaningfully alter it and met with disappointing results. It was that positive test you didn't have a treatment for. But with the current breakthroughs, and in the words of Don P Wilson^[27] its time may finally come.

Table 1

	Cases	Control	P value
comorbidity			
diabetes	44(60.3%)	14(42.4%)	0.050
hypertension	46(63%)	13(39.4%)	0.027
CAD	13(17.8%)	9(27.3%)	0.266
Dyslipidemia	42(57.55)	23(69.75)	0.234
ethanol	15(20.5%)	6(18.25)	0.777
CKD	11(15.1%)	6(18.2%)	0.860
Smoking	11(15.1%)	17(16%)	0.886
obesity	2(2.7%)	2(6.1%)	0.406

Table 2. lab parameters of patients and controls

	total count	hb	platelets [lakhs]	FBS	PPBS		
Mean	10187.14	12.9157	2.5650	141.61	202.61		
Std. Deviation	3526.419	2.22812	.61826	66.089	90.545		
group		N	Mean	Std. Deviation	Std. Error Mean	t	P VALUE
bun	Case	73	30.64	12.62	1.48	0.969	0.335

	Control	33	34.91	32.74	5.70		
creat	Case	73	1.00	0.37	0.04	1.620	0.108
	Control	33	1.27	1.30	0.23		
total cholesterol	Case	70	170.97	39.81	4.76	2.979	0.004
	Control	33	143.21	52.23	9.09		
Triglycerides	Case	70	149.63	71.38	8.53	1.574	0.119
	Control	33	125.58	74.39	12.95		
LDL	Case	70	100.52	30.56	3.65	2.782	0.006
	Control	33	80.98	38.45	6.69		
HDL	Case	70	36.70	10.18	1.22	0.161	0.872
	Control	33	37.12	16.21	2.82		
VLDL	Case	68	26.32	17.03	2.07	0.347	0.729
	Control	33	25.12	14.88	2.59		
HBA1C	Case	59	8.04	2.64	0.34	2.047	0.044
	Control	31	6.93	2.03	0.36		
uric acid	Case	72	4.97	1.68	0.20	0.263	0.793
	Control	33	4.87	2.25	0.39		
sgpt	Case	71	20.46	17.32	2.06	1.735	0.086
	Control	33	30.27	40.49	7.05		
sgot	Case	71	20.95	13.32	1.58	2.894	0.005
	Control	33	35.82	38.83	6.76		
TB	Case	71	0.60	0.60	0.07	0.213	0.831
	Control	33	0.63	0.52	0.09		
albumin	Case	71	3.27	1.38	0.16	1.096	0.276
	Control	33	3.55	0.60	0.10		
TP	Case	71	6.11	2.41	0.29	1.731	0.086
	Control	33	6.85	0.79	0.14		
DB	Case	71	0.26	0.35	0.04	0.724	0.471
	Control	33	0.31	0.32	0.06		
alkaline phosphatase	Case	71	87.16	30.75	3.65	1.988	0.049
	Control	33	156.39	291.61	50.76		

Table 3: serum lipoprotein A

		N	Mean	Std. Deviation	Std. Error Mean	t	P VALUE
Lipoprotein A	Case	73	116.65	79.22	9.27	2.898	0.005
	Control	33	70.32	68.95	12.00		

TABLE 4. INDIAN STUDIES ON LIPOPROTEIN A AND ISCHEMIC STROKE.

Study	Year of publication	State	Sample size	Mean Lp(a) [SD] in mg/dl	Statistical significance
Our study		Tamil Nadu	73	54.24 [36.837]	Significant
Dhamija RK et al [18]	2007	New Delhi	40	55.70 + 4.98[2SD]	Significant
Nagaraj SK et al [16]	2011	Karnataka	21	27.43 ± 1.32 (3.26)[2SD]	Non significant
More P et al [17]	2017	Maharashtra	100	42.68 [28.25]	Significant
Natesan C et al [19]	2018	Tamil Nadu	100	28.45 [13.06]	Not assessed
Tammineni et al [15]		Andhra Pradesh	62	62.5 [18.3]	Significant
Chakraborty et al [20]	2013	New Delhi	100	82.36 [52.9]	Significant

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