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Dr. Samina Tarannum
Associate Professor, Department of General Medicine, Osmania Medical College, Hyderabad, Telangana, India

Corresponding Author:
Dr. Samina Tarannum
Associate Professor, Department of General Medicine, Osmania Medical College, Hyderabad, Telangana, India

Serum lipoprotein (a) levels as an independent risk factor for ischemic stroke

Dr. Samina Tarannum

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Abstract
Background: Increased plasma concentrations of atherogenic lipoproteins, especially Lp (a) play an important role in the development of atherosclerosis leading to premature myocaridial infarction and stroke. Lp (a) is a novel risk factor for atherosclerosis, whose role in multiracial populations has been debated. The significance of different lipid variables in cardiovascular disease and cerebrovascular disease has been extensively studied but the role of Lp (a) in Indian population is yet to be determined.
Objective: To determine the role of Lipoprotein (a) as a marker for ischemic stroke, with regard to Indian scenario.
Design: This is a case-control study.
Duration: One year (2019-2020).
Setting: Department of Medicine, Osmania General Hospital, Hyderabad.
Participants: Hundred patients admitted in Osmania General Hospital, Hyderabad.
Methods: Diagnosis of ischemic stroke was based on clinical evidence of ischemic stroke and CT scan/MRI. Some exclusions were made. 50 age and sex matched healthy subjects were used as controls. In all patients, a detailed history, general physical examination, a detailed neurological examination and other risk factor variables were entered on a pre-designed proforma. SBP ≥140mm Hg, DBP ≥90mm Hg were considered hypertensive levels; any patient with FBS ≥126mg/dl (or) RBS ≥200mg/dl was defined diabetic. Each case underwent the investigations – Plasma Lipoprotein (a) Levels, Lipid Profile, Complete Hemogram, Complete Urine Examination, Blood Sugars, Renal Function Tests, Serum Electrolytes, ECG, Echocardiography*, X-Ray, CT-Brain*, MRI-Brain*. Lp (a) was measured by a Hitachi model 717 (7160) automated analyser using Lp (a) Latex DIACHI kit. *Denotes whenever required.
Results: In the present study, cases of ischemic stroke (n = 100) had a mean plasma Lp (a) value of 38.034 mg/dl with a S.D. of 17.423, which was significantly higher (p = 0.001) than in healthy controls, in whom it was 24.308 mg/dl with a S.D. of 11.469, indicating that serum lipoprotein (a) levels are a risk factor of ischemic stroke.
Conclusion: Elevated serum Lp (a) is an independent risk factor of ischemic stroke. Measurement of serum Lp (a) has to be considered as a screening tool for the risk of vascular events in patients with various known risk factors. It is imperative to strictly control additional risk factors in individuals with elevated Lp (a).

Keywords: lipoprotein a, ischemic stroke, risk factors, screening

Introduction
Stroke is defined as rapidly developing clinical symptoms and/or signs of focal or at times global loss of cerebral function with symptoms lasting more than 24 hours or leading to death with no other apparent reason other than that of vascular origin. Strokes (cerebrovascular accidents) are considered to be one of the most common causes of life threatening neurological disease, causing mortality and long term severe disability in people [1].

It continues to be the third leading cause of death after heart disease and cancer. Stroke occurs most frequently in hour or two after awakening in the morning and mortality is higher in winter than in summer months. WHO defined stroke as sudden onset of focal or at times global loss of cerebral function with symptoms lasting more than 24 hours or leading to death with no other apparent reason other than that of vascular accident *viz*. lesion of vessel wall, occlusion by thrombus or embolus, ruptured or altered permeability of vessel wall [2].
The blood supply of brain is derived from two internal Carotid arteries and two vertebral arteries which anastomose at the base of the brain to Circle of Willis.

The Carotid arteries supply anterior portion of the brain while the vertebrobasilar system supplies the posterior portion of the brain. At rest, the brain receives 20% of cardiac output and consumes about 20% of total inspired oxygen [3]. The cerebral blood flow is about 50ml/100gm of brain tissue. Metabolic failure of brain tissue ensues within seconds after cerebral blood flow ceases. Values less than 16-18 ml/100gm of tissue/minute causes infarction of brain tissue [4]. Values more than 20ml/100gm of tissue/minute causes ischemia without infarction. A fall in cerebral blood flow to zero causes death of brain tissue within 4-10 minutes [5]. Auto regulation is a prominent feature of brain circulation [6-8].

An elevated Lp (a) level presents the option to raise a person's risk and to target the person for a more aggressive treatment. The optimal level should be no greater than 20mg/dl, especially in Indian population [9, 10].

Materials and Methods

The present study was conducted in the department of Medicine, Osmania General Hospital, Hyderabad, for a period of one year from 2019-2020. In this study, we recruited 100 patients, survivors of ischemic non-cardio embolic stroke with history of sudden onset of focal neurological deficit persisting beyond 24 hours from the emergency wards and the general wards of Osmania General Hospital, Hyderabad.

Diagnosis of ischemic stroke was based on the following criteria (Inclusion criteria)

1. Clinical evidence of ischemic stroke.
2. Cranial Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) consistent with ischemic stroke.
3. Absence of major predisposing factors to cardiogenic stroke.

Exclusion criteria

1. Patients with radio-imaging showing intra-cerebral hemorrhage, tumor, or other mass lesion.
2. Patients with Coronary Artery Disease.
3. Patients with vasculitis.
4. Patients with other endocrine, liver and renal diseases.
5. Patients taking drugs which may alter lipid and lipoprotein profiles.
6. Women on contraceptive pills.
7. Sepsis.
8. Malignancy.
9. Active collagen vascular disease.

50 age and sex matched healthy subjects were used as controls. In all patients, a detailed history, general physical examination, a detailed neurological examination and other risk factor variables were entered on a pre-designed proforma. SBP ≥140mm Hg, DBP ≥90mm Hg were considered hypertensive levels; any patient with FBS ≥126mg/dl (or) RBS ≥200mg/dl was defined diabetic. Each case underwent the investigations – Plasma Lipoprotein (a) Levels, Lipid Profile, Complete Hemogram, Complete Urine Examination, Blood Sugars, Renal Function Tests, Serum Electrolytes, ECG, Echocardiography*, X-Ray, CT-Brain*, MRI-Brain*. Lp (a) was measured by a Hitachi model 717 (7160) automated analyser using Lp (a) Latex DIACHI kit which allows easy and accurate measurement of Lp (a) in serum or plasma via a latex agglutination turbidimetric method. *Denotes whenever required.

Observations and Results

Gender distribution

Gender distribution between the cases and controls is depicted in table 2.

Table 1: Gender distribution of both the cases and controls

Gender	Case	Control	Total
Male	49 (49%)	32 (64%)	81 (54%)
Female	51 (51%)	18 (36%)	69 (46%)
Total	100 (100%)	50 (100%)	150 (100%)
History of HTN			
Non HTN	28 (28%)	20 (40%)	48 (32%)
HTN	72 (72%)	30 (60%)	102 (68%)
Total	100 (100%)	50 (100%)	150 (100%)
History of DM			
Non DM	64 (64%)	33 (66%)	97 (64.7%)
DM	36 (36%)	17 (34%)	53 (35.3%)
Total	100 (100%)	50 (100%)	150 (100%)
History of smoking			
Non Smokers	45 (45%)	20 (40%)	65 (43.3%)
Smokers	55 (55%)	30 (60%)	85 (56.7%)
Total	100 (100%)	50 (100%)	150 (100%)
History of alcohol			
Non Alcoholic	45 (45%)	22 (44%)	67 (44.7%)
Alcoholic	55 (55%)	28 (56%)	83 (55.3%)
Total	100 (100%)	50 (100%)	150 (100%)
History of diet			
Mixed Diet	88 (88%)	43 (86%)	131 (87.3%)
Veg diet	12 (12%)	7 (14%)	19 (12.5%)
Total	100 (100%)	50 (100%)	150 (100%)
	Case	**Control**	**Total**
No Family History	95 (95%)	50 (100%)	145 (96.7%)
Family History	5 (5%)	0 (0%)	5 (3.3%)
Total	100 (100%)	50 (100%)	150 (100%)

Table 1. Gender distribution and other symptoms and history of both the cases and controls

As evident from table 1, among cases, 49 were males and 51 were females. Among controls, 32 were males and 18 were females.

There were 72 hypertensives and 28 non-hypertensives among cases whereas there were 30 hypertensives and 20 non-hypertensives among controls.

In this study, the number of diabetics and non-diabetics among cases are 64 and 36 respectively. Whereas among controls, there number is 33 and 17 respectively.

The number of smokers in cases in this study is 55 and that of non-smokers is 45 whereas their number in control group is 30 and 20 respectively.

The number of alcoholics among cases is 55 and non-alcoholics were 45 whereas the number of alcoholics and non-alcoholics in control group is 28 and 22 respectively.

Statistical analysis shows that this variable is statistically insignificant (p = 0.728)

Positive family history of stroke could be elicited in 5 cases, with no family history in 95 cases. Among the controls, none of the subjects had a positive family history. Analysis of family history in stroke in cases and controls shows that it is statistically insignificant (p = 0.108)

Table 2: Age and BMI distribution of both the cases and controls

Age	No. of cases	Mean	Standard deviation
Cases	100	55.37	10.94
Controls	50	53.8	12.8
BMI			
Cases	100	25.89	4.24
Controls	50	24.4	3.73

As shown in table 2, the study included 100 patients of ischemic stroke and 50 healthy controls. The mean age in cases was 55.37 years with a S.D. of 10.94 and mean age in controls being 53.8 years with a S.D. of 12.8. Thus the cases and controls were comparable in respect to age.
The mean BMI in cases was 25.89 Kg/m^2 with a S.D. of 4.24 and that in controls was 24.4 Kg/m^2 with a S.D> of 3.73. On further analysis, the difference was found to be statistically significant (p = 0.037).

Peripheral pulses distribution

Table 3: Family history distribution of both the cases and controls

	Case	Control	Total
Atherosclerosis	17 (17%)	0 (0%)	17 (11.3%)
Normal	83 (83%)	50 (100%)	133 (88.7%)
Total	100 (100%)	50 (100%)	150 (100%)

On statistical analysis, this was found to be significant in respect to ischemic stroke (p = 0.002).

Table 4: Distribution based on lipid profile

Total cholesterol	No. of cases	Mean cholesterol	Standard deviation	P value
Cases	100	182.95	31.56	0.008
Controls	50	197.8	32.36	
Triglycerides				0.072
Cases	100	122.06	34.24	
Controls	50	111.96	27.4	
LDL				0.045
Cases	100	115.68	31.30	
Controls	50	106.9	21.24	
HDL				0.721
Cases	100	40.11	3.25	
Controls	50	40.30	2.64	

The mean levels of total cholesterol were 182.95 mg/dl with a S.D. of 31.56 in cases and 197.8 in controls with a S.D. of 32.36. On further analysis, this was found to be statistically significant (p = 0.008).
The mean levels of HDL cholesterol in cases and controls of this study were 40.11 with a S.D. of 3.25 and 40.30 with a S.D. of 2.64, respectively. Further statistical analysis showed that this variable was statistically insignificant (p = 0.721).

Lipoprotein (a) distribution

Lipoprotein (a) level distribution found in cases and controls of this study are depicted in table 15 and 16.

Table 5: Lp (a) distribution of both the cases and controls

Lp (a) levels	Case	Control	Total
>30mg/dl	62 (62%)	10 (20%)	72 (48%)
<30mg/dl	38 (38%)	40 (80%)	78 (52%)
Total	100 (100%)	50 (100%)	150 (100%)

Table 5 shows the distribution of Lp (A) levels with respect to normal (<30mg/dl) and abnormal levels (>30mg/dl). 62 cases and 10 control subjects enrolled in this study had Lp (A) levels >30mg/dl, whereas 38 cases and 40 control subjects had normal values <30 mg/dl.

Table 6: Lp (a) distribution of both the cases and controls

	No. of cases	Mean cholesterol	Standard deviation	P value
Cases	100	38.034	17.423	0.001
Controls	50	24.308	11.469	

As evident in table 6, the mean Lp (a) levels in cases is 38.034 mg/dl with a S.D. of 17.423 and in controls, it was 24.308 with a S.D. 11.469. On further statistical analysis, this variable was found to be statistically significant (p = 0.001).

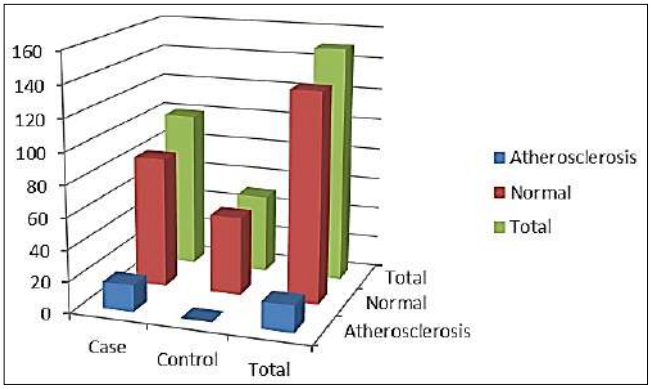

Fig 1: Peripheral pulses distribution of both the cases and controls

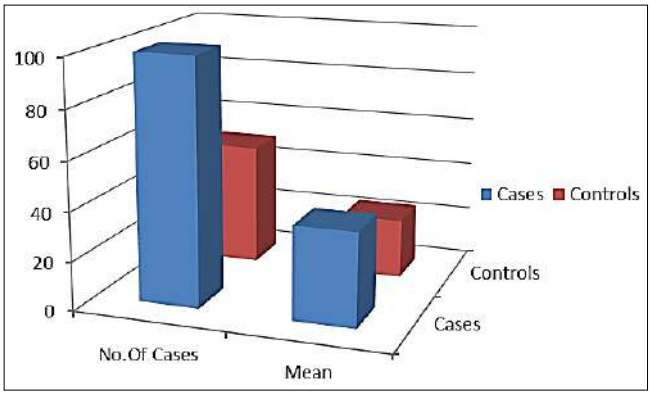

Fig 2: Lp (a) distribution of both the cases and controls

Discussion

Stroke is the most common life threatening neurological disease [11]. In spite of advances made in the diagnosis and management of stroke patients, there remains a substantial number of stroke events that cannot be explained on the basis of conventional risk factors. This study could help in understanding the pathophysiology of stroke in respect to

different risk factors, and improve the identification and selection of individuals who might benefit from individualized therapy [12]. Studies of lipoprotein (a) levels in patients of ischemic stroke were initiated to understand the etiologic role in the disease [13-15]. Elevated serum Lp (a) levels were shown to be an independent risk factor for ischemic stroke in various studies since the last 20 years, mainly in the western populations. The objective of this research was to study the role of elevated serum Lp (a) levels as an independent risk factor of ischemic stroke especially with regard to Indian population. In the present study cases of ischemic stroke (n = 100) had a mean plasma Lp (a) value of 38.043 mg/dl with a S.D. 17.423 which was statistically significantly higher (p = 0.001) than in healthy controls, in whom it was 24.308 mg/dl with a S.D. of 11.469, indicating that serum lipoprotein (a) levels are a risk factor of ischemic stroke [16]. The high discriminating power of Lp (a) serum levels in this study is probably due to the strict criteria applied to include individuals because we took extra precautions in selecting our study population [17]. Our study also indicates the role of body Mass Index (p = 0.037), peripheral vascular disease (p = 0.002), total cholesterol (p = 0.008) and LDL cholesterol levels (p = 0.045), being independent risk factors of ischemic stroke. The results of our study indicate that high Lp (a) levels are an independent risk factor for ischemic stroke and stress upon the need for further research on lipoprotein (a) and its relationship to ischemic stroke in Indian population in particular and to find novel methods for its prevention and management [18-21].

Conclusions

Elevated serum Lp (a) is an independent risk factor of ischemic stroke. Measurement of serum Lp (a) has to be considered as a screening tool for the risk of vascular events in patients with various known risk factors. It is imperative to strictly control additional risk factors in individuals with elevated Lp (a).

We stress upon the need for further research on lipoprotein (a) and its relationship to ischemic stroke in Indian population in particular and to find novel methods for its prevention and management.

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