Research Article

iMedPub Journals
www.imedpub.com

Stroke Research and Theraphy

2021
Vol.5 No.6: 132

The Role of Lipoprotein (a) in Intracranial Atherosclerotic Disease: A Hospital Based Cross Sectional Study from India

Dnyaneshwar Asole[1*], Ashok PP[1] and Mahendra Thakre[2]

[1]Department of Neurology, PD Hinduja National Hospital & Research Centre, Mahim, Mumbai

[2]Department of Neurology, Lokmanya Tilak Municipal General Hospital and Medical College, Sion, Mumbai

[*]**Corresponding author:** Dnyaneshwar Asole, Department of Neurology, PD Hinduja National Hospital & Research Centre, Mahim, Mumbai, E-mail: dcastle1980@gmail.com

Received date: December 6, 2021; **Accepted date:** December 20, 2021**; Published date:** December 27, 2021.

Citation: Asole D, Ashok PP, Thakre M (2021) The Role of Lipoprotein (a) in Intracranial Atherosclerotic Disease: A Hospital Based Cross Sectional Study from India. Stroke Res Ther Vol.5 No.6:132.

Abstract

Introduction: The goal of this study was to compare elevated levels of Lipoprotein (a) in ischemic stroke patients with extracranial atherosclerotic stenosis (ECAS) and intracranial atherosclerotic stenosis (ICAS), in order to determine whether there was a link between elevated Lp (a) levels and ICAS in Indian patients.

Methodology: The present cross-sectional study was conducted in the Department of Neurology, PD Hinduja National Hospital and Medical Research Centre, Mumbai from January to December 2016. Various clinical, laboratory and radiological parameters including Lp (a) were compared between patients with ECAS and ICAS stroke.

Results: During the study period, ECAS group included 110 patients while ICAS group included 40 patients. We observed that mean Lp (a) levels were 38.7 mg/dl in the ECAS group and 28.4 mg/dl in the ICAS group. It was found to be high in 60% of the ECAS patients and 45% of the ICAS group, with no significant difference between the two groups (p value=0.11). There was no statistical difference on caparison of clinical risk factor profile between ECAS and ICAS patients. Hemispheric large cortical plus subcortical infarcts (53%) and cerebellar infarcts (20%) were more common in ICAS group (p values of <0.05 for both). Whereas cortical watershed (37%) and deep watershed (33%) infarcts were more common in the ECAS group (p values of <0.001 and <0.05 respectively).

Conclusions: Lp (a) levels were not significantly different between ECAS and ICAS patients presenting with acute ischemic stroke.

Keywords: Lipoprotein (a); Risk factors; Intracranial Atherosclerosis; Stroke

Introduction

The atherosclerotic plaque develops due to the accumulation of lipids, inflammatory cells, smooth muscle cells, and extracellular matrix in the sub-endothelial space over time. Atherosclerotic plaques are mainly found at arterial bifurcations, branch points and vessel curvatures, whereas straight non branching arterial segments are generally spared [1]. Stroke is a major cause of mortality and morbidity worldwide, with ischemic stroke being the predominant type (approximately 80%) found in stroke patients [2]. With the current ageing population, the number of people suffering from stroke will inevitably escalate leading to increasing demand for more effective prevention, diagnosis and treatment strategies. As one of the most common causes of ischemic stroke worldwide [3], Intracranial Atherosclerosis (ICAS) accounts for about 30-50% of ischemic stroke or transient ischemic attacks in Asia, 15-29% in Africa, and 5-10% in Europe or North America [4]. Exploring the distribution of risk factors among these subtypes is essential for understanding potential pathogenic mechanisms of stroke and targeting preventive treatments. This will also influence choices for management. In this regard, Lipoprotein (a) (Lp (a)) is a Low-Density Lipid (LDL)-particle which is composed of apolipoprotein B-100 to which apolipoprotein (a) is covalently bound. Recently, Lp (a) has been recognized as a potentially important risk factor for atherosclerotic disease. To the best of our knowledge, there is no study from India which has compared Lp (a) levels between ECAS and ICAS patients. This led us to undertake the present study to find out whether raised Lp (a) is linked to increased incidence of intracranial atherosclerosis in Indians.

Methodology

Study design

The present cross-sectional study was conducted by the Department of Neurology, PD Hinduja National Hospital & Medical Research Centre, and Mumbai in which patients with a diagnosis of ischemic stroke were included from January 2016 till December 2016. During the study duration 110 ECAS and 40 ICAS patients were included. The patients and their attendants were explained the purpose of the study and an informed consent was obtained from them or their legal representatives before enrolment in the study. The study was approved by the Institutional Ethics Committee.

Inclusion criteria and case definitions

Acute ischemic stroke patients with large artery stenosis as a mechanism of stroke were included in the study. They were classified as either as ECAS or ICAS. ICAS was defined as significant stenosis in the intracranial arteries including anterior cerebral artery, middle cerebral artery, posterior cerebral artery, basilar artery and intracranial internal carotid, vertebral artery, without significant stenosis of the extracranial carotid and vertebral arteries. ECAS was defined as significant stenosis in the common carotid, extracranial internal carotid and vertebral arteries without significant stenosis of the intracranial arteries. Significant stenosis was defined as presence of more than 50% stenosis of the arterial lumen assessed by 1.5 Tesla MR Angiography.

Exclusion criteria

We excluded patients with lacunar ischemic strokes, those with clinical evidence of cardio-embolic stroke, with clinical or serological evidence of CNS vasculitis, with clinical or biochemical evidence of liver, renal, or thyroid disease, women on contraceptive pills, those with on-going fever or presence of sepsis, with clinical or radiological evidence of malignancy, those with collagen vascular disease or those with CT or MRI Brain showing intracranial bleed. Patients with simultaneous significant (>50%) atherosclerotic stenosis of both extracranial and intracranial arteries on CT or MRI study were also excluded.

Data collection and data analysis

All patients were subject to recording of a detailed history, general physical examination, a detailed neurological examination. History regarding clinical risk factors profile such as age, sex, hypertension, diabetes mellitus, cardiovascular history, drug history, smoking habits and alcohol intake was also recorded. The following investigations were performed in each case: Complete hemogram, fasting blood sugar, postprandial blood sugar, HbA1c levels, renal function tests, lipid profile, plasma Lp (a) levels, MRI brain with angiography. CT angiography of head and neck vessel was done in selected patients to confirm presence of atherosclerotic arterial stenosis exclude non atherosclerotic disease of vessels like vasculitis.

Overnight fasting blood samples were collected for estimation of Lp (a) levels. Lp (a) estimation was done through immunoturbidimetric assay at our laboratory. Lp (a) can also be estimated by Radio Immune Assay, Rosache strips using micro-ELISA, Monoclonal antibodies. The normal values of level of serum Lp (a) are less than 30 mg/dl. The level of serum Lipoprotein (a) more than 30 mg/dl were considered as high level. Parameters of dyslipidaemias were defined according to NCEP ATP III (2005 revision) definition if total cholesterol levels were ≥ 200 mg/dl or triglyceride levels were ≥ 150 mg/dl or LDL levels were >100 mg/dl or HDL levels were <40 mg/dl [5]. Abdominal obesity was defined according to NCEP ATP III (2005 revision) definition for metabolic syndrome, if patient's waist circumference was ≥ 40 inches in men and ≥ 35 inches in women.

The data were compiled using Microsoft Excel sheet and analyzed using SPSS 23 software. Descriptive analysis for numerical data consisted of mean+SD (if normally distributed)/ median and range (if not normally distributed) and for categorical data consists of frequencies and percentage for various parameters. Normality of data was checked using Kolmogorov Smirnov test. Ap value of less than 0.05 was considered as statistically significant.

Results

During the study period, 110 patients were included in ECAS and 40 in ICAS group. The median age of patients was 62 years with a range of 31-89 years and 67 years with a range of 34-87 years in ECAS and ICAS groups respectively (p value=0.59). In the ECAS group, there were 76 males and 34 females, compared to 34 and 6 in the IACS group (p value=0.051). Hypertension was found in 72 (65%) in ECAS and 30 (75%) in ICAS group (p value=0.26). Diabetes mellitus was found in 52 (47%) in ECAS and 22 (55%) in ICAS group (p value=0.41). Abdominal obesity was found in 45 (41%) in ECAS and 19 (48%) in ICAS group (p value=0.47). There were 15 (14%) smokers in ECAS group as compared to 9 (23%) in ICAS group (p value=0.19). Significant alcohol intake was present in 13 (12%) and 9 (23%) patients of ECAS and ICAS groups respectively (p value=0.11). Thus age, gender, and the occurrence of hypertension, diabetes mellitus, smoking, and significant alcohol consumption were not statistically different between the ECAS and ICAS groups as shown in **Table 1.**

Table 1: Comparison of clinical profile between Extracranial (ECAS) and Intracranial Stenosis (ICAS) patients.

Clinical variables	ECAS (n=110)		ICAS (n=40)	p value	
	N	%	N	%	
Gender					
Females	34	31%	6	15%	0.051
Males	76	69%	34	85%	
Past medical history					
Hypertension	72	65%	30	75%	0.26
Diabetes mellitus	52	47%	22	55%	0.41
Smoking	15	14%	9	23%	0.19
Alcohol	13	12%	9	23%	0.11
Abdominal obesity	45	41%	19	48%	0.47
Age	**ECAS (n=110)**		**ICAS (n=40)**	**p value**	
Median value	62 years		67 years	0.593	
Range	31-89		34-87		

Hemispheric large cortical plus subcortical infarcts (53%) and cerebellar infarcts (20%) were more common in ICAS group (p values of <0.05 for both). Whereas cortical watershed (37%) and deep watershed (33%) infarcts were more common in the ECAS group (p values of <0.001 and <0.05 respectively) as shown in **Table 2.**

Table 2: Comparison of radiological profile between extracranial (ECAS) and intracranial stenosis (ICAS) patients

Sites of infarction	ECAS (n=110)		ICAS (n=40)		p value
	N	%	N	%	
Hemispheric large cortical plus subcortical infarcts	29	26%	21	53%	<0.05
Cortical watershed	41	37%	1	3%	<0.001
Deep watershed	36	33%	5	13%	<0.05
Cerebellar	3	3%	8	20%	<0.05
Brainstem	3	3%	5	13%	0.06

The blood sugar profile was similar in the two study groups and the values were statistically not significant. High FBS was seen in 47 (43%) of the ECAS and 17 (43%) of the ICAS group (p value=0.98), whereas high PLBS was seen in 46 (42%) of the ECAS and 17 (43%) of the ICAS group (p value=0.94). Similarly high HbA1c levels were seen in 38 (35%) of the ECAS and 12 (30%) of the ICAS group (p value=0.61). Lipid profile was also found to be similar in the two study groups, except low HDL, which was observed in 70 (64%) of the ECAS patients as compared to 17 (43%) of the ICAS patients. This was statistically significant with a p value of <0.05 as shown in **Table 3.**

Table 3: Comparison of laboratory profile between extracranial (ECAS) and intracranial stenosis (ICAS) patients

Laboratory variables	ECAS (n=110)		ICAS (n=40)		p value
	N	%	N	%	
Blood sugar profile					
High fasting blood sugar	47	43%	17	43%	0.98
High post-prandial blood sugar	46	42%	17	43%	0.94
High HbA1c	38	35%	12	30%	0.61
Lipid profile					
High Cholesterol	30	27%	8	20%	0.36
High low-density lipoprotein	35	32%	8	20%	0.15
Low high-density lipoprotein	70	64%	17	43%	<0.05
High very low-density lipoprotein	26	24%	5	13%	0.26
High triglyceride	25	23%	5	13%	0.31

We observed that median Lp (a) levels were 38.7 mg/dl (range: 2.1-201 mg/dl) in the ECAS group and 28.4 mg/dl (range: 1.9 to 222 mg/dl) in the ICAS group (p value=0.42). It was also found to be high in 66 (60%) of the ECAS patients and 18 (45%) of the ICAS group, with no significant statistical difference between the two groups (p value=0.11) as shown in **Table 4.**

Table 4: Comparison of Lipoprotein (a) levels between Extracranial (ECAS) and intracranial stenosis (ICAS) patients

Lipoprotein(a) levels	ECAS (n=110)		ICAS (n=40)		p value
	N	%	N	%	
High	66	60%	18	45%	0.11
Normal	44	40%	22	55%	
Median value	38.7 mg/dl		28.4 mg/dl	0.42	
Range	2.1-201 mg/dl		1.9-222 mg/dl		

Discussion

The present study was done to compare the clinical risk factor and biochemical variables between ECAS and ICAS stroke patients and assess the association of raised Lp (a) with ICAS. We also compared the radiological profile among these groups. In our study of 150 stroke patients, 73% had ECAS and 27% had ICAS. Previous reports have observed that ICAS is a more common cause of stroke than ECAS in Asian populations. ICAS accounts for about 33%–50% of ischemic strokes and >50% of Transient Ischemic Attacks (TIAs) in these populations [6]. ICAS was the most common stroke mechanism in the Hyderabad Stroke Registry reported by Kaul, et al. [7]. As the majority of the world's population is represented by Asians, ICAS is thus the most common vascular lesion in stroke patients worldwide. However, new studies have indicated increase in ECAS among Asian stroke patients, and though this difference may be lost in the future [8]. Another reason for the lower number of patients with ICAS in our study could be due to the exclusion of patients with simultaneous significant (>50%) atherosclerotic stenosis of both extracranial and intracranial arteries.

In the present study, the median age of patients was 62 years with a range of 31-89 years and 67 years with a range of 34-87 years in ECAS and ICAS groups respectively. Srivastva, et al. observed that intracranial stenosis is more commonly associated with younger age (age<60 years) while extracranial stenosis with older age group (age>60 years) [9]. However, a study by Uehara, et al found that older age is risk factor for both extracranial and intracranial stenosis [10].

We observed that 76 (69%) of the ECAS and 34 (85%) of the ICAS were males, however this observation was statistically not significant. Li, et al. showed men had a higher risk of suffering from ICAS with acute ischemic strokes than women, demonstrating that a sex difference existed in ICAS with anterior circulation stroke. This may be due to the fact that males are the bread winners in majority of India and they are more likely to seek medical care, which suggests cultural bias. In addition, this association of male gender with ECAS could be explained by the fact that men tended to have habits of smoking, alcohol use, and a high calorie and fat intake [11]. Kim, et al. investigated differences in risk factors between patients with ICAS and ECAS and found patients with ICAS were more often young (65.92 ± 11.50) and female (42%) as compared to that in ECAS group (mean age 68.08 ± 9.42 and 21% females)[12].

Hypertension was found to be the most common past medical history, irrespective of the location of stenosis. It was observed that 72 (65%) of the ECAS and 30 (75%) of the ICAS were hypertensive. Diabetes mellitus was seen in 52 (47%) of ECAS and 22 (55%) of ICAS groups making it the next most common risk in our study, followed by abdominal obesity. It should be noted that we could not find a significant association of any comorbid conditions with both ECAS and ICAS. Keheya, et al. found the most prevalent risk factors in their study population to be hypertension (77.4%) and reported that hypertension, was non-significantly more prevalent in ECAS patients [13]. In a similar study, Li, et al. reported that ECAS had more frequent hypertension (67.5% vs. 53.8% p <0.001) than the patients with ICAS [14]. Jin, et al. reported that hypertension (56.9% in ICAS vs. 28.6% in ECAS) was significant risk factors for ICAS [15]. Keheya, et al. found DM in 53.9% of their patients and found it to be more common in ICAS patients (55.2%) as compared to ECAS (52.6%), though the difference was not statistically significant [13]. In the study by Kim, et al. DM was diagnosed DM in 35.5% with ICAS, 35.8% with ECAS and 36.6% in both ICAS & ECAS, p value=0.9 [12]. NOMASS, Barcelona-ASIA and some other studies have reported DM as more prevalent and important for prognosis in ICAS, but it has not been supported by our or by other studies [16]. DM, a major component of metabolic syndrome, is an established risk factor for ECAS [17]. However, its role in ICAS is yet to be elucidated, and previous studies have yielded controversial results [18]. In the present study, abdominal obesity was found to be present in 41% of ECAS and 48% of ICAS patients, with no statistical difference between them. Jin et al also found no significant difference regarding BMI and waistline between ICAS or non-ICAS groups [15]. Obesity is an established risk factor for stroke, but no other studies have evaluated its association with ICAS or ECAS. Future studies should investigate this association, as South-East Asian population is at a higher risk for metabolic syndrome.

Lee, et al. described the possible mechanisms of stroke associated with large-artery intracranial atherosclerotic stenosis (ICAS) as artery-to-artery embolism, hypoperfusion, branch occlusive disease and a combination of these mechanisms [18-22]. This was similar our study, where hemispheric large cortical plus subcortical and cerebellar infarcts were observed to be significantly more in ICAS group. The likely mechanism being branch occlusive disease. Derdeyn, et al. demonstrated a link between extracranial carotid occlusive disease and hemodynamic impairment, which leads to cortical and internal watershed infarcts, which is consistent with our findings, in which cortical and deep (internal) watershed infarcts are significantly more common in the ECAS group [23].

We observed that serum Lp (a) levels were also found to be similar among ECAS and ICAS patients. Thus, we did not find any correlation between Lp (a) levels and predilection towards ICAS in our study population. Kim, et al. observed that the median serum Lp (a) levels of the ICAS (32.0, 21.5-48.9 mg/dL), ECAS (35.0, 23.9-48.6 mg/dL), and combined intra and extracranial stenosis (39.3, 21.4-67.0 mg/dL) group were significantly higher than that of the non-cerebral stenosis group (25.3, 13.1-43.7 mg/dL) (p<0.001, respectively), and there was a significant difference of lipoprotein levels between the ICAS and combined group (p=0.047) [21]. The underlying mechanism of involvement of Lp (a) is not clearly understood. It is known that apolipoprotein (a) has a tendency to bind with connective tissue elements, and Lp(a) particle is vulnerable to oxidative modification and scavenger receptor uptake. As a result, Lp(a) could actively promote atherosclerosis [22]. In addition, Lp(a) is associated with endothelial dysfunction [23]. However, these mechanisms need to be verified from future bench research.

Conclusion

There are a few limitations of the study. This was a hospital-based study. This might introduce some sampling bias. We excluded patients with simultaneous presence of significant (>50%) extracranial and intracranial stenosis. Our sample did not include asymptomatic patients with cerebral artery stenosis. Thus, the results might not be extrapolatable to the general public. Second, the patients were not followed up to analyse the clinical outcome and recurrence of events.

The levels of increased Lp (a) were not significantly different in ECAS and ICAS patients with acute ischemic stroke, as per this study. Thus, we did not find correlation between Lp (a) levels and predilection towards ICAS in our study population.

Reference

1. Warboys CM, Amini N, Luca A, Evans PC (2011) The role of blood flow in determining the sites of atherosclerotic plaques. F1000 Med Rep 3: 5-9.

2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V (2009) Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. Lancet Neurol 8: 355-369.
3. Pu Y, Dou X, Liu L (2014) Natural history of intracranial atherosclerotic disease. Front Neurol 5: 125-129.
4. Leng X, Wong KS, Liebeskind DS (2014) Evaluating intracranial atherosclerosis rather than intracranial stenosis. Stroke 45: 645-651.
5. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 106: 3143-3421.
6. Sada S, Reddy Y, Rao S, Alladi S, Kaul S (2014) Prevalence of middle cerebral artery stenosis in asymptomatic subjects of more than 40 years age group: A transcranial doppler study. Neurol India 62: 510-515.
7. Kaul S, Sunitha P, Suvarna A, Meena AK, Uma M, et al. (2002) Subtypes of ischemic stroke in a metropolitan city of South India (one year data from a hospital based stroke registry). Neurol India 50: 8-14.
8. Tsai CF, Thomas B, Sudlow CL (2013) Epidemiology of stroke and its subtypes in Chinese vs. white populations: A systematic review. Neurology 81: 264-272.
9. Srivastava T, Kumar S, Sardana V, Ojha P, Maheshwari D, et al. (2017) Extracranial and intracranial arterial stenoocclusive disease in acute ischemic stroke patients: A study from north India-evaluation with MR angiography. IJN 3: 21-25.
10. Uehara T, Tabuchi M, Mori E (1997) Occlusive lesions of carotid and intracranial arteries in patients with symptomatic lacunar infarction-evaluation by MR angiography. Rinsho Shinkeigaku 37: 796-801.
11. Mathiesen EB, Joakimsen O, Bonaa KH (2001) Prevalence of and risk factors associated with carotid artery stenosis: The tromso study. Cerebrovasc Dis 12: 44-51.
12. Kim JS, Nah HW, Park SM, Kim SK, Cho KH et al. (2012) Risk factors and stroke mechanisms in atherosclerotic stroke: Intracranial compared with extracranial and anterior compared with posterior circulation disease. Stroke 43: 3313-3318.
13. Keheya S, Tekatas A, Aynacı Ö, Utku U, Solmaz V (2016) A comparison of risk factors and prognosis between intra and extracranial acute atherosclerotic stroke in the Turkish population: A prospective study. Neurological Res 38: 864-870.
14. Li Y, Cai Y, Zhao M, Sun J (2017) Risk factors between intracranial-extracranial atherosclerosis and anterior-posterior circulation stroke in ischaemic stroke. Neurol Res 39: 30-35.
15. Jin H, Peng Q, Nan D, Lv P, Liu R, et al. (2017) Prevalence and risk factors of intracranial and extracranial artery stenosis in asymptomatic rural residents of 13 villages in China. BMC Neurol 17: 136-138.
16. Rincon F, Sacco RL, Kranwinkel G, Xu Q, Paik MC, et al. (2009) Incidence and risk factors of intracranial atherosclerotic stroke: The northern Manhattan stroke study. Cerebrovasc Dis 28: 65-71.
17. Meschia JF, Bushnell C, Albala B, Braun LT, Bravata DM, et al. (2014) Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American Heart Association. Stroke 45: 3754-3832.
18. Lee SJ, Cho SJ, Moon HS, Shon YM, Lee KH, et al. (2003) Combined extracranial and intracranial atherosclerosis in Korean patients. Arch Neurol 60: 1561-1564.
19. Schlaich MP, John S, Langenfeld MR, Lackner KJ, Schmitz G, et al. (1998) Does lipoprotein (a) impair endothelial function? J Am Coll Cardiol 31: 359-365.
20. Utermann G (1989) The mysteries of lipoprotein (a). Science 246: 904-910.
21. Kim BS, Jung HS, Bang OY, Chung CS, Lee KH, et al. (2010) Elevated serum lipoprotein (a) as a potential predictor for combined intracranial and extracranial artery stenosis in patients with ischemic stroke. Atherosclerosis 212: 682-688.
22. Lee DK, Kim JS, Kwon SU, Yoo SH, Kang DW (2005) Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease: Early diffusion-weighted imaging study. Stroke 36: 2583-2588.
23. Derdeyn CP, Khosla A, Videen TO, Fritsch SM, Carpenter DL, et al. (2001) Severe hemodynamic impairment and border zone-region infarction. Radiology 220: 195-201.