STUDY OF GENETIC, METABOLIC AND INFLAMMATORY RISK FACTORS IN PATIENTS OF ACUTE ISCHEMIC STROKE

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ABSTRACT

Stroke is the third leading cause of death and foremost cause of disability. Based on studies in CAD patients, a focus has been shifted on genetic and inflammatory markers as risk factors for stroke besides deranged lipid profile. The present study was aimed to ascertain the role of Lipoprotein (a), C-Reactive protein (CRP) levels and lipids in patients of ischemic stroke. The study was done in 82 subjects including 40 Computerized Tomography (CT) proven patients of ischemic stroke and 42 age and sex matched controls. Complete biochemical parameters including lipid profile were carried out on autoanalyzer using standard kits and reagents. Lipoprotein (a) [Lp(a)] was determined by immunoturbidimetric assay. Atherogenic indices (Total cholesterol/HDL, LDL/HDL and Lipid Tetrad Index) were calculated using these lipid parameters. The CRP levels were measured semi-quantitatively by latex agglutination test method. Out of 40 stroke patients, 38 had abnormalities in lipid profile (As per ATP III guidelines). A significant difference was seen in serum cholesterol, LDL cholesterol and atherogenic indices between the patients and controls. The difference in CRP levels in cases and control subjects was highly significant (4.78 ± 0.72 mg/dl vs 0.76 ± 0.70 , $p < 0.001$). 96.5% of patients with raised CRP had abnormal lipid levels also. CRP levels in stroke patients showed significant correlation with total cholesterol and LDL ($p < 0.001$), Lp (a) ($p = 0.002$) and atherogenic indices ($p < 0.05$). Raised CRP levels in stroke patients were significantly associated with large territory infarcts, severe disability and poor functional outcome ($p < 0.05$). Genetic [Lp(a)], metabolic (deranged Lipid profile) and inflammatory factors (CRP) together are instrumental in causing cerebrovascular arteriosclerosis leading to ischaemic stroke and can be used as important markers to identify patients at risk of severe stroke and to institute aggressive preventive strategies.

KEY WORDS

Ischemic stroke, C - reactive protein, Lipid profile, Atherogenic Indices, Lipoprotein (a).

INTRODUCTION

Stroke is defined by the National Institute of Neurological Disorders and Stroke (NINDS), as a sudden loss of brain function resulting from an interference with the blood supply to the brain (1). Stroke is the third most common cause of death in the developed countries (2). It ranked as the sixth leading cause of Disability Adjusted Life Years (DALY; one

DALY being equal to one year of health lost due to disease) in 1990 and is projected to rank fourth by the year 2020 (1). Annually, 15 million people worldwide suffer a stroke. Of these approximately 5 million die and another 5 million are left permanently disabled, placing a great socio-economic burden on the family and society (3). Thus, stroke results in substantial health-care expenditures; the mean lifetime cost resulting from an ischemic stroke is estimated at \$140,000 per patient (2). Though, the incidence of stroke is declining in many developed countries but the absolute number of strokes continues to increase due to ageing population (3).

India will soon have to bear an enormous socioeconomic burden due to the costs of the rehabilitation of stroke survivors; this is because the population is now surviving through the peak years (age 55-65) for the occurrence of stroke or

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cerebrovascular accident (CVA). Community surveys from many regions show crude prevalence rates for stroke (presumed to be of vascular origin) in the range of 90-222 per 100,000 persons (4). It is important to reduce the impact of stroke in communities by both primary as well as secondary preventive strategies, which include identifying people at risk and thereby appropriate risk factor management.

The increased incidence of atherosclerosis has been reported to be particularly high in Indian population whether in India or else where (5). This Asian Indian "paradox" reflects the perception that this population has an attributable risk higher than anticipated, despite the appearance of low risk by traditional risk factors (dyslipidemia, non-vegetarian diet, smoking and hypertension), which may be related to demographic profile, transition in economy and lifestyle changes predisposing to increased atherogenic risk (6). Considering that the risk factors for stroke are similar to those of coronary heart disease, only 50% of stroke could be attributed to conventional risk factors (dyslipidemia, high blood pressure, smoking) thus, leaving a substantial void in the current understanding of the pathogenesis of stroke. This perceived void has led to considerable research on nontraditional risk factors and genetic causes of stroke.

In recent years there has been greater emphasis on homocysteine, lipoprotein (a), Fibrinogen, TNF, IL, D- Dimer, Serum amyloid A and C - reactive protein (CRP) as newer markers for CAD and associated cerebrovascular disorders. CRP is an acute-phase reactant that has been shown in prospective cohort studies to be a reliable measure of underlying systemic inflammation, and levels in the high-normal range were found to predict future cardiovascular events (7). Several prospective studies examined the association between CRP and incident ischemic stroke, primarily among apparently healthy adults. Most studies (8-10), although not all (11), found a significant independent association between CRP and the risk of incident stroke. A meta-analysis of studies with long-term follow-up showed that the risk for stroke in healthy individuals with the highest quartile of CRP concentrations increased nearly 1.7-fold compared with those with the lowest quartile (12).

Many studies indicate that Lp(a) is related to CAD and stroke, and a recent meta-analysis indicates that elevated Lp(a) increases the risk of vascular events by 30% in secondary prevention studies and by 70% in primary prevention studies (13). Lp (a) consists of LDL particle attached with the apo (a) protein by a disulfide bridge. The apo (a) moiety has structural similarities to plasminogen. Thus, with its lipid and

plasminogen-like component, Lp (a) may provide a link between atherothrombosis and atherosclerosis (14). The atherogenicity of Lp(a) is 10-fold higher than LDL. Lp(a) is also highly thrombogenic and antifibrinolytic, by virtue of its homology to plasminogen (15). More than 10 angiographic and case-control studies in India have shown elevated Lp(a) levels to be a powerful risk factor for premature atherosclerosis, especially under the age of 40 years (16,17).

Plasma lipid ratios that include both an atherogenic and an anti-atherogenic lipid component (e.g. total cholesterol/ high density lipoprotein cholesterol ratio, Low Density Lipoprotein/ HDL ratio) have been found to be strong predictors of coronary artery disease (18). A comprehensive Lipid Tetrad Index has been described as the single best predictor of CAD risks in diverse populations, especially Asian Indians. This index reflects the total burden of dyslipidemia and is derived by multiplying three proatherogenic lipids [cholesterol, triglycerides and Lp(a)] and dividing the result by HDL values [total cholesterol (TC) x triglycerides (TG) x Lp (a)/HDL] (19).

It has been shown that if CRP is measured along with lipids, it can have better predictive value in cases of atherosclerotic coronary artery disease than when used alone thus signifying their interaction in atherogenesis (20, 21). This study was hence done to evaluate the cumulative roles of dyslipidemia, CRP and genetic factors like Lp(a) in ischemic stroke as their correlation has not been extensively studied in North Indian population.

MATERIALS AND METHODS

A total of 82 subjects including 40 cases of acute ischemic stroke of various age groups and both sex admitted between Feb. 2002 and April 2003 were included in the study. The acute ischemic stroke was diagnosed by WHO definition of stroke and confirmed by CT scan of head. 42 age and sex matched controls (hospital employees and healthy attendants of patients of non vascular diseases) were also included in the study. Ischemic stroke patients were enrolled in this study with inclusion criteria i.e. CT scans showing cerebral infarction and patient admitted within 12 hours of ischemic stroke.

Patients with Diabetes Mellitus and recent myocardial infarction, within 6 weeks, recurrent Stroke, any infective / inflammatory and neoplastic process that is known to be associated with raised C-reactive protein levels, renal, hepatic, neurodegenerative and collagen vascular diseases were excluded from the study. Similar exclusion criteria were also applied for healthy controls.

All the patients were evaluated in a step-wise manner by means of a performa, which included detailed history, examination and investigations. Risk factors for stroke like coronary artery disease, hypertension, hyperlipidemia, smoking, and alcohol were studied. Dietary habits and socioeconomic status were also taken into account. The complete hematological and biochemical investigations including lipid profile, X-ray chest and 12-lead electrocardiogram were done in all patients. In addition, Carotid Doppler and echocardiography was also done where possible. Patients with blood pressure of more than 140/90 mm of Hg in supine position on two occasions were considered to be hypertensive where as patients with serum cholesterol of more than 200 mg/dl, LDL Cholesterol more than 100 mg/dl, serum triglycerides more than 150 mg/dl and serum HDL less than 40 mg/dl were taken as abnormal lipid levels (NCEP ATP III guidelines) (22).

CRP Estimation : A fasting venous blood sample for CRP was collected at the time of admission. The serum was separated and stored at -80°C till analyzed by latex agglutination test (Rhelax Tulip). Latex particles coated with Anti CRP monoclonal antibodies were agglutinated when mixed with samples containing CRP. Positive as well as negative controls were used. The presence of agglutination was taken as C-reactive protein levels greater than 0.6mg/dL (0.06mg/L) while absence of agglutination indicated a CRP levels less than 0.6mg/dl in the serum. Serial dilutions of the serum sample (1:2, 1:4, 1:8, 1:16, 1:32, 1:64 and so on) were prepared using isotonic saline and these dilutions were treated in a similar manner as the undiluted sample. The presence of agglutination indicated serum CRP levels of 1.2 mg/dl, 2.4mg/dl, 4.8mg/dl, 9.6mg/dl, and 19.2mg/dl and so on. Concentration of CRP was calculated as $CRP (mg/dl) = 0.6 \times D$ where D being the highest dilution of serum showing agglutination. CRP values less than 0.6 mg/dl were taken as 0.6 mg/dl for uniformity in calculations. Serum CRP levels of more than 0.6mg/dl were taken as abnormal as compared to other similar studies where cut off values of CRP were taken as 0.5mg/dl (23).

Lipid Profile : Serum cholesterol and triglycerides were estimated by enzymatic method on Beckman CX5 Clinical Chemistry Autoanalyzer using Randox (USA) kits. HDL was determined by precipitation method and LDL was calculated using Friedewald formula.

Lipoprotein (a) : Serum lipoprotein (a) was determined by immunoturbidimetric immunoassay on Beckman CX5 Clinical Chemistry Autoanalyzer using commercial kit by CLONITAL.

Statistical Analysis : Data are expressed in Mean $\pm$ Standard Error of Mean. Statistical Analysis was done using SPSS statistical software. For categorical variables, ANOVA was applied. For continuous variables Student's t-test was applied. p-values < 0.05 were considered significant. Pearson's correlation was used to find out significant correlation between two variables.

RESULT

Patient Population : The baseline characteristics of study and the control group were found to be similar (age 56.48 ± 2.03 years vs 54.40 ± 1.80 years and male to female ratio of 1.22 vs 1.21). The clinical characteristics of stroke patients included in the study are shown in Table 1. In the study group, 25% patients were less than 40 years (young strokes) while maximum number (55%) were in age group of more than 60 years. Eleven patients (27.5 %) had lacunar infarcts where as 29 (72.5%) had cortical infarcts. Six (15%) patients died during hospitalization.

CRP Levels : CRP levels of more that 0.6 mg/dl were found in 42.68% of the total subjects. Group-wise distribution showed

Table 1: Demographic Profile of stroke cases included in the study

		MALES (N=18)	FEMALES (N=22)
AGE (Years)	= 40	2	8
	41-60	7	5
	> 60	9	9
ESR (mm in first hour)		11	12
DIET	Vegetarian	14	10
LITERACY (N=22)		15	7
LOWER SOCIOECONOMIC STATUS (N=26)		10	16
H/O SMOKING (N=18)		14	4
HYPERTENSION (N=16)		8	8
PREVIOUS HISTORY OF CAD		2	4
TYPE OF INFARCT	Lacunar	3	6
	Lobar	15	16
ABNORMAL SPEECH (N=18)		8	10

that 72.5% patients and 11.9 % normal subjects had raised CRP (Figure 1). The difference in C –reactive protein levels in cases and controls were highly significant by ANOVA ($p<0.001$). Fourteen out of 16 hypertensive patients had raised CRP. The correlation between presence of hypertension and raised CRP levels was significant ($p= 0.029$). CRP levels were also found to be higher in 88.8% smokers. The correlation between smoking and raised CRP levels was highly significant ($p=0.007$).

with abnormal CRP levels had abnormal values of one or more lipid parameters [cholesterol, triglycerides, HDL, LDL, Lp(a)] also . A highly significant correlation was observed between raised CRP levels and abnormal serum cholesterol ($p<0.001$), serum LDL- C ($p<0.001$) and serum Lp (a) ($p=0.002$). However, no significant correlation was observed between raised CRP levels and decreased HDL levels (Figure 2). A significant positive correlation was observed between raised CRP and all atherogenic indices (Table 3).

Lipid Profile : Abnormal lipid levels were found in 95% stroke patients and 23.81% subjects in control group. Mean levels of total serum cholesterol in patients and controls was 173.98 ± 4.99 mg/dl and 159.21 ± 2.68 mg /dl respectively ($p=0.01$). The mean levels of lipoprotein (a) in stroke cases and control group were 55.70 ± 4.98 and 24.67 ± 1.69 mg/dl respectively. The difference in values of HDL, LDL and Lipoprotein (a) in stroke cases and control group was highly significant ($p<0.01$) (Table 2).

Correlation between type of Stroke and CRP, Lp(a), Atherogenic Indices : Type of stroke (lacunar/ cortical) did not show any significant correlation with Lipid and lipoprotein levels including Lp(a) in patients, whereas highly significant correlation was observed with CRP values. Patients presenting with lacunar infarction generally had CRP levels less than

Table 2: CRP values and lipid profile in Stroke cases and controls.

	Stroke Cases	Control	p-value
CRP Levels mg/dl	4.78 ± 0.72	0.76 ± 0.70	<0.001
Serum Cholesterol	173.98 ± 4.99	159.21 ± 2.68	0.010
Serum Triglycerides	102.65 ± 5.67	98.19 ± 4.36	0.533
HDL Cholesterol	35.25 ± 1.27	39.19 ± 1.05	0.019
LDL Cholesterol	110.15 ± 5.04	95.29 ± 2.75	0.010
Lipoprotein (a) levels	55.70 ± 4.98	24.67 ± 1.69	<0.001

28 out of 29 (96.5%) patients and 60% of control subjects

Table 3 : Correlation between Raised CRP levels and Atherogenic Indices

	Mean Value in Stroke Patients	Pearson Coefficient Value	p-value
Total Cholesterol (TC)	173.98 ± 4.99	0.599	<0.001
Triglycerides (TG)	102.65 ± 5.67	-0.044	0.788
HDL	35.25 ± 1.27	0.051	0.755
LDL	110.15 ± 5.04	0.591	<0.001
Lipoprotein (a)	55.70 ± 4.98	0.478	0.002
TC/HDL Ratio	5.21 ± 0.26	0.318	0.046
LDL/HDL Ratio	3.35 ± 0.24	0.375	0.017
Lipid Tetrad Index	31287 ± 3960	0.374	0.017

0.6mg/dl. In fact all but one patient with CRP levels more than 4.8 mg/dl had cortical infarction (Table 4). This difference was highly significant statistically ($p < 0.005$).

Table 4 : Observed CRP levels and Type of Infarction in Stroke cases

CRP (mg/dl)	Number of Patients	Lacunar Infarction	Cortical Infarction	P-Value
≤0.6	11	8	3	<0.005
>0.6-4.8	15	2	13	
>4.8	14	1	13	

Correlation between Outcome of stroke and CRP, Lp(a) and atherogenic indices : 15% of stroke patients died during the hospitalization while 85% were discharged with either partial or full recovery. Out of the survivors, 27.5 % of patients made full recovery, whereas 57.5% of patients had partial recovery. Patients' lipid and lipoprotein parameters did not correlate significantly with the disease outcome. However, most of patients who recovered fully had CRP levels less than 0.6mg/dl where as 83.3% of patients who died had CRP levels of more than 4.8mg/dl at the time of admission. Correlation between CRP levels and outcome (Table 5) was very highly significant ($p < 0.001$).

Table 5 : Correlation between CRP levels and outcome after Acute Ischemic Stroke

CRP (mg/dl)	Patients	Died	Partial Recovery	Full Recovery	P-value
≤0.6	11	-	4	7	<0.001
>0.6-4.8	15	1	11	3	
>4.8	14	5	8	1	

DISCUSSION

Stroke is one of most common neurological disorder met in clinical practice that destroys body and mind alike. The best strategy for reducing its burden is prevention by targeting population at risk for primary prevention and risk factor management to prevent its recurrence. The present study is a hospital based case control study to determine correlation of lipids, lipoprotein (a) and CRP in patients of ischemic stroke.

The present study had about 25% patients with young stroke presenting before the age of 40 years. This observation is peculiar to our population as reported by many studies done in Asia (24). However this study included more number of women than men which is unusual as it has been reported

that incidence of athero-thrombotic cerebrovascular disease is about 30% higher in males as compared to females (25). This could be because of our hospital being women diseases hospital with more women being treated as compared to men on year-to-year basis.

In the present study significantly higher levels of serum cholesterol, LDL-cholesterol, Lipoprotein (a) and lower HDL - Cholesterol were observed in stroke patients as compared to control group. The significant decrease in HDL along with increased cholesterol, LDL and lipoprotein (a) explains the significant differences observed in the studied atherogenic indices. Similar results have been observed in a prospective cohort study in apparently healthy US women, where total cholesterol, low-density lipoprotein cholesterol, the total cholesterol to high-density lipoprotein cholesterol ratio, and non-high-density lipoprotein cholesterol were significantly associated with increased risk of ischemic stroke during 11 years follow-up (26) and another study where low HDL was associated with an increased risk of ischemic stroke with an odds ratio of 3.09 (27).

In the present study, CRP levels were significantly higher in around three fourth patients of stroke as compared to their age and sex matched controls. Elevated levels of CRP have been shown in multiple cohort studies to correlate with increased incidence of stroke (28). It has also been postulated as a significant predictor of future TIA and Stroke in Framingham study (29). This observation is crucial in our population, where high prevalence of adiposity and basal CRP levels in young adults in India could be important factor for the development of atherosclerosis (30). The observed normal CRP levels in 27.5% of stroke patients in the present study can be partly explained by the fact that small ischemic strokes do not always induce complete and full acute phase response. Similar observations in patients of ischemic stroke with normal CRP levels have been reported in other studies also (23). These changes in CRP may be consistent with the "inflammation theory of atherosclerosis". CRP not only is a marker of inflammation but also proinflammatory, pro-atherosclerotic and pro-thrombotic in nature. It interacts with endothelial cells and stimulates the production of cytokines like IL-6, IL-1b, TNF, ET-1 and upregulates the expression of adhesion molecules (ICAM and VCAM). CRP also directly enhances the production of MCP-1, enhances monocyte recruitment, activates the complement and promotes macrophage LDL uptake, increases the production of tissue factor from monocytes (31).

In the present study, no correlation of lipid and lipoproteins

was observed with the severity and outcome of the disease indicating that these factors could only be responsible for increased risk of stroke by virtue of their contribution to atherosclerotic process. However, the acute episode may be triggered by other factors like inflammation. A highly significant correlation was seen between raised CRP levels and type of infarction as well as the outcome of the disease state. The patients with higher levels of CRP also had more severe infarction (as evidenced by cortical or large territory infarcts) and adverse outcome (death or partial recovery) than patients with lower values of CRP. This finding is in accordance with similar studies, which show that ischemic stroke patients with abnormal CRP levels had higher percentage of large territory infarction than lacunar infarction (32, 33). This implies that serum CRP levels are predictor of functional disability in acute ischemic stroke and its levels correspond with the degree of inflammation and hence the outcome of the disease. It may be involved in the earliest stages of stroke. Monitoring the levels of CRP may help in the prevention and treatment of stroke. These observations are consistent with results from similar studies from West (23, 34-36).

The present study also aimed to find out any correlation between C Reactive levels and various atherogenic indices in stroke patients in view of lack of any data on this correlation in our region. It was interesting to note positive correlation of total Cholesterol, LDL, Lipoprotein (a) to CRP levels indicating a potential role of CRP in atherogenesis with concomitant deranged lipid profile and vice-versa. The same results have also been reported in a population-based study of CRP and its relation to cardiovascular risk factors particular to lipids (37, 38). Several studies also support the role of CRP as a marker of cerebrovascular atherosclerosis as evident by efficacy of statins and antiplatelet therapy in decreasing the CRP levels in patients with ischaemic stroke (39,40). Several animal models of atherosclerosis have shown that signs of inflammation occur hand-in-hand with incipient lipid accumulation in the artery wall. A plausible model linking lipids and inflammation to atherogenesis proposes that low-density lipoprotein (LDL) retained in the intima undergoes oxidative modification to form lipid hydroperoxides, lysophospholipids, carbonyl compounds, and other biologically active moieties in the lipid fraction of atheroma. These modified lipids can induce the expression of adhesion molecules, chemokines, proinflammatory cytokines, and other mediators of inflammation in macrophages and vascular wall cells. The apoprotein moieties of the lipoprotein particles can also undergo modification in the artery wall, rendering them antigenic and capable of inciting T-cell responses, thus activating the antigen-specific adaptive limb of the immune

response (31). Another possible mechanism of link between raised CRP and stroke may be explained by the finding that inflammation tends to trigger or perpetuate atrial fibrillation, which may predispose to stroke (41,42).

There are several limitations to this analysis. This study is a cross sectional study of patients admitted with stroke in our hospital and not a long term follow up prospective study and as such is limited by biases. However our subjects represented a heterogeneous population at risk with exclusion of all those in which there were known factors to increase CRP levels. Secondly it is a small study involving 82 subjects and using semi-quantitative method of CRP estimation, which was easy to use, relatively cheap and easy to carry out.

We can therefore conclude from the study that lipid derangements lead to increased risk of stroke by promoting cerebral atherogenesis. The increased atherogenesis may lead to acute events when inflammatory changes occur in these atheromas. The severity and hence the disease outcome depends on the acute phase proteins (like CRP) released during this inflammatory process. Positive correlation between high CRP levels and lipid levels particularly total cholesterol; LDL and Lp (a) levels indicate an interdependent role of all these factors in cerebral atherosclerosis. However further long-term prospective population based studies are required to establish this relationship.

CRP levels do not replace lipid evaluation, but must be considered as an adjunct to lipid evaluation in stroke patients. A complete analysis of blood lipids in patients who survive ischemic stroke helps the physician to plan the future treatment so as to prevent the recurrence of stroke. An adequate therapy of such patients may significantly improve prognosis for those who survived ischemic stroke and, in some cases, prevent its development. Statins or fibrates may be used, which are helpful in controlling, both dyslipidemia and elevated CRP.

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