Original Research Article

Study of C-Reactive Protein Level in Patients of Acute Ischemic Stroke and Its Correlation With Serum Lipid Profile

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ABSTRACT

Objective: To study the level of C- reactive protein as an independent risk factor in patients of ischemic stroke taking into account other risk factors and to correlate the concentration of CRP with serum lipids in ischemic stroke. **Research Design and Methods:** C- reactive protein, Total cholesterol (TC), LDL-Cholesterol, HDL cholesterol, triglycerides and prevalence of hypertension were assessed in 100 cases of ischemic stroke and TIA admitted in various medical wards of a tertiary care hospital included in this study in 2010-2011. **Results:** There was a statistically significant positive crude correlation between C-reactive protein and TC, TG and LDL-Cholesterol (all $P < 0.001$). A negative correlation was found between C-reactive protein and HDL cholesterol, $P<0.001$). Out of 100 patients of acute ischemic stroke, 70% of patients had raised CRP while 30% of patients had low level of CRP. **Conclusions:** The finding of the present study clearly reveals that increased level of C-reactive protein is associated with increased risk of ischemic stroke. Thus C-reactive protein levels may be taken up as an important laboratory marker in determining the future risk of cerebrovascular accident.
Key words: acute ischemic stroke, C- reactive protein, Serum lipid profile

INTRODUCTION

Stroke is a worldwide health problem. It makes an important role to morbidity, mortality and disability in developed as well as developing countries. Stroke is one of the leading causes of death after heart disease and malignant diseases. [1]

A stroke, also known as cerebrovascular accident is an acute neurological injury whereby the blood supply to a part of the brain is interrupted either by a clot in the artery or if the artery bursts.

On comparison of stroke rates in India and other countries, it was found that

rates are two to three times higher in India. [2] Some predisposing cause of stroke like rheumatic heart disease, cortical venous thrombosis in postpartum period is seen more often in India than in western countries. [1]

Rapid advancement is taking place in the diagnosis of stroke. Initially angiography was used to determine the type of stroke as well as vessel involved. Computerized tomography demonstrates precisely about the type, site and size of stroke, AV malformation and ventricular deformities. Hematoma in CT scan is hyper dense shadow, in case of infarction there is silent period of 1-2 days before hypo dense area is seen in brain or may not be visible on CT scan.[3] MRI will demonstrate these lesions. [3] High speed digital subtraction angiography (DSA) and magnetic resonance angiography (MRA) visualizes the cervical and basal intracranial arteries. [4]

CRP is an acute phase reactant synthesized in liver in response to cytokine interleukin-6, is also a factor in development of atherosclerotic plaque. Although hs-CRP was initially believed to be only a marker of vascular inflammation but recent researches indicates that it also plays an active role in atherogenesis. [5] It is detectable in early stage of plaque development and is believed to be involved throughout the atherogenic process. [6]

The median value in healthy adult is 800 ng/ml, 90% were less than 3 µg/ml and 99% less than 10 µg/ml. The rate of C-reactive protein synthesis and secretion increase within hours of an acute injury or onset of inflammation like acute myocardial infarction, bacterial infection, stroke , acute rheumatic fever, probably under the influence of humoral mediator such as leukocyte endogenous mediator and prostaglandins. [7] Increased CRP level have also been described in smokers, sedentary and obese persons, malignancy, type 2 diabetes, gestational diabetes and metabolic syndrome persons. [8]

Recent evidence gathered in seemingly healthy adults using high sensitive CRP (hs-CRP) method indicates that hs-CRP is a strong independent risk factor for subsequent development of stroke, myocardial infarction, peripheral vascular disease and diabetes mellitus. [7, 8, 9, 10]

Earlier studies have examined CRP concentration during the course of acute myocardial infarction and angina. In recent years, several studies have reported that the risk for cardiovascular disease was positively associated with base line CRP concentration. This association has been interpreted as confirmation of the role of inflammation in the pathogenesis of coronary heart disease but any contribution of CRP to pathogenesis of stroke has received little attention. So present work is planned to address the role of inflammation (by CRP concentration) in pathogenesis of stroke and to correlate the level of serum lipids with CRP.

MATERIAL AND METHODS

The present study was conducted on patients of acute ischemic stroke admitted in various medical wards of a tertiary care hospital. A total of 100 cases of ischemic stroke and TIA were included in this study.

Criteria for designation of stroke:
After a detail history from all patients they were accordingly designated
1. Transient ischemic attack (TIA)
2. Reversible ischemic neurological deficit (RIND)
3. Complete stroke.

A computerized tomographic scan and/or magnetic resonance imaging of the brain were done in all patients to rule out

hemorrhagic cause of stroke. Patients were designated as having ischemic stroke by the following criteria:

1. Patient having stroke as detected on clinical examination and CT SCAN/MRI documented infarction in the form of hypodensity.

2. Patient having stroke as detected by clinical examination but with a normal CT scan (hemorrhage ruled out)

Detailed clinical profile of the subject was recorded on separate performa regarding general information i.e. age, sex, present and past history; history of systemic illness and a thorough clinical examination including detailed neurological examination was done. All cases were evaluated clinically including diabetes mellitus, hypertension, ischemic heart disease, previous history of stroke, alcohol intake and smoking. Patient's routine hematological investigations including hemoglobin, total and differential leukocyte counts, peripheral blood film examination, urine examination, blood sugar, urea, lipid profile, electrocardiogram, X-Ray chest and computerized tomogram and/or MRI was performed.

Blood pressure was measured in both upper limbs in sitting position after a rest of 30 minutes with random mercury sphygmomanometer.

Fasting venous blood sample (defined as no caloric intake for at least 8 hours) was obtained for fasting plasma glucose and serum lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride). Postprandial plasma glucose was collected 2 hours after morning meal.

In this study, estimation of C-reactive protein level was done by immumoturbidimetry using a buffer and anti-CRP coated latex as reagent. We measured CRP concentration in acute ischemic stroke patients and those who were having CRP level more than 3 mg/L were considered as raised CRP.

RESULTS

In present study 100 patients were included who suffered from acute ischemic stroke confirmed by clinical examination and CT scan and/or MRI. The concentration of C-reactive protein was measured in all patients.

Table no.1 showing that majority of patients belonged to 5th to 7th decade however stroke, in patients more than 70 years of age had elevated level of CRP.

67% of patients with history of hypertension and 57% of patients with no history of hypertension had raised CRP.75.6% of patients with history of diabetes and 52% of patients with no history of diabetes had raised CRP.75% patients with history of diabetes and hypertension (both) and 45% patients with no history of hypertension and diabetes had raised CRP.

74% patients who were having serum cholesterol more than 200 mg% had raised CRP while 57.5% patients who had serum cholesterol less than 200 mg% had raised CRP.78.7% patients who had LDL-C level more than 130 mg% had raised CRP while 47.1% patients who had LDL-C less than 130mg% had raised CRP.80% patients who had triglyceride more than 150 mg% had raised CRP while 51.4% patients who were having triglyceride <150 mg% had raised CRP.

87% patients who had HDL-C level less than 40 mg% had raised CRP while 50% patients who had HDL-C more than 40 mg% had raised CRP.

Table no.1 showing percentage of high CRP level with different groups of acute ischemic stroke patients

AGE	TOTAL NO	NO CASES CRP > 3mg/dl	% OF CASES CRP> 3 mg/dl
>75	20	16	80
<75	80	46	56
Female	37	25	67
Male	63	37	58.7
Smoker	36	23	63.8
Nonsmoker	64	38	59
HTN	46	31	67
Non-HTN	54	31	57
DM	41	31	75.6
Non DM	59	31	52
DM,HTN	20	15	75
Non DM,non HTN	33	15	45
> 126 Blood Sugar	35	26	74.2
< 126 Blood Sugar	65	36	55.3
UNCON	32	28	87
CON	68	34	50
>200 Total cholesterol	27	20	74
<200 Total cholesterol	73	42	57.5
>130 LDL	47	37	78.7
<130 LDL	53	25	47.1
> 150 Total triglyceride	30	24	80
< 150Total triglyceride	70	36	51.4
HDL <40	32	28	87
HDL>40	68	34	50

Gray shads shows higher percentage of high CRP patients with risk factor of Acute ischemic stroke

Table no. 2 showing that CRP level was statistically higher (P< 0.001) in patients who were having raised total cholesterol , LDL - cholesterol , triglyceride when compared to patients who were having normal total cholesterol, LDL – cholesterol and triglyceride.

CRP level was statistically significantly higher (P<0.001) in patients who were having low HDL-C when

compared to patients who were having normal HDL-C.

Table no.2 showing significance of CRP with risk factor of acute ischemic attack

Sr.No	AGE	Total no	Mean crp	t value	p value	significance
1	< 75	80	4.67± 2.87	3.34	0.0012	Yes
2	> 75	20	7.20±3.61			
3	Male	63	5.20 ± 3.28	0.0755	0.9400	Not
4	Female	37	5.15 ±3.05			
5	Smoker	36	5.41 ±3.07	0.5411	0.5897	Not
6	Nonsmoker	64	5.05 ± 3.26			
7	HTN	46	5.61 ±3.18	1.2581	0.2113	Not
8	Non-HTN	54	4.81± 3.16			
9	DM	41	5.72 ±2.62	1.4301	0.1559	Not
10	Non DM	59	4.80 ±3.49			
11	DM,HTN	20	6.29 ±2.71	1.8535	0.0696	Not
12	Non DM,non HTN	33	4.58 ± 3.54			
13	> 126 Blood Sugar	35	6.11± 2.48	2.1869	0.0311	Yes
14	< 126 Blood Sugar	65	4.68 ±3.41			
15	CON	68	4.49±3.18	3.3091	0.0013	Very
16	UNCON	32	6.64±2.68			
17	>200 Total cholesterol	27	6.52 ±3.33	2.6489	0.0094	Very
18	<200 Total cholesterol	73	4.68 ±2.99			
19	>130 LDL	47	6.51±3.15	4.2760	0.0001	Extremely
20	<130 LDL	53	4.00 ±2.72			
21	> 150 Total triglyceride	30	7.33± 3.11	4.9169	0.0001	Extremely
22	< 150 Total triglyceride	70	4.26 ±2.75			
23	HDL <40	32	7.09± 2.69	4.5005	0.0001	Extremely
24	HDL>40	68	4.28±3.01			

DISCUSSION

Acute ischemic stroke is a major cause of disability and deaths in our country. With the advent of promising therapies for acute ischemic stroke, there is higher expectation for rapid recovery and good outcome. Despite these new therapies, poor outcome may still occur because ischemic stroke is heterogeneous disease in which outcome is influenced by many factors like extent of brain injury, severity and duration of insult. "Outcome is further influenced by genetic predisposition, temperature, blood glucose and other unknown factors. Demographic variable, risk factors, clinical examination, laboratory test results and imaging studies all provide important insight regarding CRP levels and outcome.

A biological marker c-reactive protein is an acute phase reactant and reflects activation of inflammation. [11] It has been found that stroke patients most intensely may be at greater risk for

subsequent such events. We studied the plasma concentration of C-reactive protein in patient of acute ischemic stroke and correlated its level with serum lipids. In present study 100 patients were included who suffered from acute ischemic stroke confirmed by clinical examination and CT scan and/or MRI. The concentration of C-reactive protein was measured in all patients.

In our study 80% of patients were below 75 years of age and 20% were over 75 years of age. Patients who were below 75 years of age, 57% patients had raised CRP while those who were above 75 years of age, raised CRP were found in 80% patients. Similar result were found in studies carried out by Howard et. al. [12] and Henon et. al. [13]

Regarding the influence of sex, we found that among males only 58.7% had raised CRP as compared to females where this figure was 67%.This finding is again in agreement with those of Howard et.al. [12] and Henon et. al. [13]

In relation to risk factor smoking we found that 63.8% patients in smoker group were having raised CRP while 59 % of patients in non smoker group were having raised CRP. Similar results were obtained in studies done by Tiney Hoekstra et al. [10]

Blood pressure can also influence the concentration of CRP, we found that 67% of patients in whom history of hypertension was present had raised CRP while 57% of patients in whom no history of hypertension was there had raised CRP. Mario et. al. [14] also arrived at a conclusion that increased blood pressure was significantly associated with elevated level of CRP in acute ischemic patients. [14]

In the present study, we found that 75.6% of patients having history of diabetes had raised CRP while 52% of patients not having history of diabetes had raised CRP level. This suggests that inflammation may precede atherosclerosis in diabetic patients. It is evidence by the physician health study Ridker PM et al. [15] that showed hs-CRP was elevated in diabetic mellitus patients.

On analysis of blood sugar level at the time of admission, out of patients who were having blood sugar more than 126mg%, elevated level of CRP occurred in 74.2% where as in those with blood sugar level less than 126 mg% elevated level of CRP occurred in 55.3%. Mooren M et. al. [16] and Dana E King et. al. [17] studies were also correlates with our study.

When patients have two risk factors as who had history of diabetes and hypertension both, 75% had elevated CRP level whereas in those who had no history of hypertension and diabetes, 45% patients had raised CRP. This data draw a parallel results which obtained by Mario et. al. [14] and Morren et. al. [16]

Unconsciousness is showing a severity in stroke patient. When we compare it with CRP we found that the patients who were unconscious (Glasgow coma scale < 10) at the time of admission, 87.5% had raised CRP whereas out of those who were conscious, 50% had raised CRP level. This result correlates with the observation made by Howard et. al. [12]

In our study, we found that 74 % of patients were having raised CRP level under the group having total cholesterol more than 200 mg% while 57.5% of patients were having raised CRP level under the group having serum cholesterol level less than 200 mg%. Sedreddine et. al. [18] also concluded that there is close relationship between incidence of ischemic stroke, CRP level and level of total cholesterol, triglyceride, LDL-C and HDL-C.

In our study, we found that 78.7% of patients were having raised CRP level under the group having serum LDL-C more than 130 mg% while 47.1% patients were having raised CRP level under the group having

serum LDC-C less than 130 mg% Steven et. al. [19] and Sadreddine et. al. [18] also found in their study this correlation between LDL-C and serum C-reactive protein level. Paul M et. al. [20] found that C-reactive protein and LDL cholesterol are minimally correlated but base line level of each had a strong linear relation with incidence of stroke events.

In our study we found that 80 % of patients were having elevated level of CRP under the group having serum triglyceride more than 150 mg% while 51.4% of patients were having elevated level of CRP under the group having serum triglyceride less than 150 mg%. Similar result was obtained in studies conducted by Seddreddinne et. al. [18] and Steven et. al. [19] Steven also concluded that intensive statin therapy is significantly related to greater reduction in the level of both atherogenic lipoprotein and CRP. [19]

In our study we found that 87% of patients who were having serum HDL-C less than 40 mg% had raised CRP while in those having serum HDL-C more than 40 mg%, 50% of patients had raised CRP This result also correlated with study done by Seddreddine et. al. [18] and Steven et. al. [19]

On analyzing the concentration of C-reactive protein as a risk factor in acute ischemic stroke, out of 100 patients taken up in our study, 62% of patients had raised CRP while 38% of patients had low level of CRP.

On correlating the C-reactive protein concentration with serum lipid profile in patients of ischemic stroke we found that mean±SD C-reactive protein was 6.52 ±3.33 mg/L in patients having total cholesterol more than 200 mg% while it was 4.68 ±2.99 mg/l in patients having total cholesterol less than 200 mg%. On application of `t` test we found that this results was statically very significant as the `p` value is 0.0094.

We also found that mean±SD CRP concentration was 6.51±3.15 mg/L in patients group having LDL-C level more than 130 mg% while it was 4.00 ± 2.72 mg/L in patient having serum LDL-C level less than 130 mg%. On application of `t` test we found that this results was statistically highly significant as the `p` value is <0.0001.

We found that mean±SD CRP concentration was 7.33± 3.11 mg/L in patients having triglyceride level more than 150mg%. While it was 4.26 ±2.75 mg/L in patient having triglyceride level less than 150 mg%. On application of `t` test we found that this result was statistically highly significant as the `p` value is <0.001.

We found that mean C-reactive protein was 7.09± 2.69 mg/L in patients having serum HDL-C level less than 40 mg%, while it was 4.28±3.01 mg/L in patients having serum HDL-C level more than 40 mg%. On application of `t` test, we found that this result was statistically significant as the `p` value is 0.001.

Patients in whom statin therapy resulted in CRP levels less than 1 mg/L had better clinical outcome regardless of LDL-C level, These data provide evidence that reducing inflammation particularly CRP level have a role in altering the atherothrombic process so during statin therapy in addition to monitoring LDL-C, CRP value also should be monitored. [19, 20, 21] Napoli et al also found that there was increased probability of deaths or new vascular events in patients with increased C-reactive protein level. [20]

CRP concentration may reflect that the degree of stroke severity, co-relating with the degree of inflammation directly consequent to cerebral infarction. CRP concentration may indicate underlying unstable atherosclerotic disease. CRP may reflect the response of patient inflammation system.

CONCLUSION

In conclusion, the finding of the present study clearly reveals that increased level of C-reactive protein is associated with increased risk of ischemic stroke. Thus C-reactive protein levels may be taken up as an imperative laboratory marker in determining the future risk of cerebrovascular accident.

REFERENCES

1. Park K. Park`s Text Book of Preventive and Social Medicine. 21th ed., Banarsidas Bhanot publishers,Jabalpur, 2011; 348.
2. Prasad K. Epidemiology of cerebrovascular disease in India. Recent concept in stroke. 1st edition, Mumbai Indian College of Physician, 1999; 11-19.
3. H.R.Jager Diagnosis of stroke with advanced CT and MR imagingBritish Medical Bulletin 2000, 56 (No 2) 318-333
4. Andrew R. X.,Adnan I. Q., Jawad F.K.,Abutaher M. Yahia, Rohit Bakshi, Neuroimaging of Stroke: A Review: Computed Tomography; Posted: 05/12/2003; South Med J. 2003;96(4) © 2003 LWW, http://www.medscape.com/viewarticle/452843
5. Blake GJ, Ridker PM. CRP and other inflammatory risk marker in acute coronary syndrome. Jr. of AM College Cardiology, 2003;3 75-425.
6. Ridker PM et al. CRP and risk of cardiovascular disease. Curr Atheroscler Rep, 2003
7. Pepys MB. C-reactive protein fifty year on Lancet March 21, 1981:653-656.
8. American Heart Association. Inflammation, heart disease and —'
9. Bamford J, Sanderecock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project, 1981-86, J Neurology, Neurosurgery, Psychiatry, 1990; 53:16-22.
10. Tiny Hoekstra, Johanna M, Geleijuse, Evert G. Schonfen. Smoking and CRP : result of the Am hem elderly study. CRP, 2001; 1: 018.
11. Rost NS, Wolf PA, Kasa CS, Hayes MK, Massaro JM et al. Plasma concentrate of C-reactive protein and risk of ischemic stroke and transient ischemic attack, the Framingham Study. Stroke, 2001; 32:2575-579.
12. Howard G, Walker MD. Community hospital based stroke programme factor influencing survival after stroke. Arch Neurology, 1996; 17:294-299.
13. Henon H, Vehier FM, Luca SC. Early predictors of death and disability after acute cerebral ischemic event. Stroke, 1995; 26:392-398.
14. Mario Di Napoli, Francesca Papa. Association between blood pressure and C-reactive protein level in acute ischemic stroke. From the Neurological Section. Hypertension 2003; 42 : 1117, American Heart Association.
15. Ridker PM, Hennekens GH. CRP adds to prediction value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation, 1998; 47: 2007-2011.
16. Rodriquez Moren M et. al. Increased level of CRP in non L controlled DM subject. Jr. Diabetes Complication.

stroke : Role of C-reactive protein, 2006; 152-157.

17. Arch G. Mainos, Dana E King et. al. C-reactive protein and glycemic control in adult with diabetes. ADA Diabetes Care, 2003; 26: 1536-1539.
18. Sadreddinni, Abolfathni AA, Lakien A. C-reactive protein, fibrinogen level, Lp(a), lipid profile and platelet count in patient with ischemic stroke. Pak J Neurological Sci, Jun 2006; 1(1) 7-13.
19. Steven E Nissen et al. Stanin therapy, LDL cholesterol, CRP and coronary artery disease. NEJM, 2005, Jan 6; 352:29-38.
20. Napoli MD, Papa F, Bocola. Prognostic influence of increased C-reactive protein and fibrinogen level in ischemic stroke. Stroke, 2001; 32:133.
21. Nissen et al. The effect of stanin treatment is not only due to lipid lowering. JAMA, 2004, 291:1071-1080.

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