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PLASMA C-REACTIVE PROTEIN LEVELS AS A PROGNOSTIC AND DIAGNOSTIC MARKER IN FIRST EVER ACUTE ISCHEMIC STROKE

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ABSTRACT: BACKGROUND AND PURPOSE: The measurement of markers of inflammation or thrombosis has been proposed as a method to improve the prediction of risk in patients with vascular disease. The role of C-Reactive protein (CRP) as a novel plasma marker of atherothrombotic disease is currently under investigation. We related plasma CRP levels to first ever ischemic stroke and its role as a diagnostic aid. **METHODS:** Sixty patients with either hypertension or diabetes or both or none without thrombolysis with first ever acute ischemic stroke patients were examined with the exclusion from the exclusion criteria. CT scan of brain was done after 24 hours of onset of symptoms to confirm the diagnosis. Plasma CRP level was determined after 12 hours and before 72 hours of onset of symptoms in all CT confirmed ischemic stroke patients. CRP was randomly measured in 60 age and sex matched individuals admitted in other wards of the hospital matched in all possible criteria except the disease under study as a control group. **RESULTS:** The CRP concentration in ischemic strokes independent of infarction site, the value was more between 51-70 years of age group and almost equal in both gender. 54 of the 60 ischemic strokes studied had CRP value >6mg/l and only 6 patients had <6mg/l ($p < 0.001$), chi square test value is $\chi^2 = 73.65$ which is statistically significant. Only 7 of the 60 control group had CRP >6mg/l, which is insignificant. **CONCLUSION:** The CRP level is significantly higher in ischemic strokes and by its elevation between 12-72 hours of symptom onset was a bad prognostic indicator. An elevated CRP value was a risk factor in association with other risk factors like diabetes/hypertension.

KEYWORDS: C-reactive protein, Ischemic stroke, Diagnostic marker.

INTRODUCTION: Stroke remains the major cause of human mortality and morbidity. Cardiovascular and cerebrovascular diseases appear to be frequently encountered now and are responsible for morbidity. In spite of our increasing understanding of the pathophysiology and epidemiology of cardiovascular diseases and stroke the burden of above said diseases are high.

Furthermore atherogenic risk factors such as hypertension, smoking, hyperlipidemia, and diabetes mellitus do not fully account for the clinical occurrence of CHD and stroke in different populations. Extensive search/ study are necessary for potential risk factors. Indeed atherosclerosis is now accepted as an inflammatory disease, possible infections include chlamydia, H-pylori, Herpes and CMV.

Avery and his collaborators characterized the C-reactive material as a protein which required calcium ions for its reaction with CPS and introduced the term "acute phase" to refer to serum from patients acutely ill with infectious diseases and containing the C-reactive protein.^{1,2}

C-reactive protein (CRP), an acute phase reactant and a marker for underlying systemic inflammation has been reported to be elevated in acute coronary syndromes.^{3,4} Several studies show that in the first attack of myocardial infarction or Stroke there is rise of C-reactive protein.⁵

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Apparently measuring C-reactive protein might provide novel method to detect level of atherosclerosis in otherwise healthy persons.⁶ this new finding assumed importance to researchers as they raised the possibility that atherosclerosis may be at least partly and inflammatory process disease.⁷ Antimicrobial and antiviral therapy may someday become the part and parcel of therapies to prevent heart attack and stroke. Limited works have been published on CRP changes in stroke in India despite high incidence of CVA in India.

Concentrations of CRP are directly correlated with the presence and severity of coronary, cerebral and peripheral arterial atherosclerosis.⁸

In view of the different observations by various works about the source of inflammatory stimulus and significance of value of C-reactive protein in thrombotic stroke and relation between different risk factors, the present study was undertaken with the following aims and objectives:

1. To observe plasma CRP levels in acute ischemic stroke.
2. To evaluate the role of CRP as a prognostic and diagnostic aid in acute ischemic stroke.
3. To evaluate CRP levels as a risk factor in acute ischemic stroke.

MATERIALS AND METHODS: This prospective cross-sectional study was conducted for 15 months i.e. from January 2008 to June 2009 at medicine department (BTGH), attached to M.R. Medical College, Gulbarga. The patients were recruited after obtaining their informed consent. The study protocol was approved by the Institutional Ethics Committee of M. R. Medical College, Gulbarga.

Selection of Patients: The study was conducted on patients admitted with clinically first attack of stroke to medicine intensive care unit or acute medical ward of BTGH, Gulbarga.

Sample Size: 250 patients admitted with stroke (CT proved) were selected for the study, of this 200 patients had thrombotic stroke. Out of this 60 were selected after exclusion of patients having heart disease, infection, tuberculosis, malignancies anywhere in the body, previous history of stroke, TIA and other factors known to alter CRP value as the study group. 60years of age and sex matched control subjects were selected from patients in other wards matched in every possible aspect except for the disease under study.

Study Group: Of 200 stroke patients, 60 were selected as the study group strictly adhering to the inclusion criteria.

Inclusion Criteria:

1. Age group 20-80 years.
2. Patients with either or both type 2 diabetes mellitus and hypertension.
3. Ischemia proved by CT scan brain, in all cases of the study.

Exclusion Criteria:

1. Age >80 and <20 years.
2. Patients with history of heart disease-any valvular heart disease, Infective Endocarditis, myocardial infarction.
3. Patients with previous history of stroke or TIA.
4. Patient's collagen vascular diseases, Active tuberculosis, Arteritis.

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5. Patients with hemorrhagic stroke, tumor, subarachnoid hemorrhage.
6. Patients with head injury within past 3 months.
7. CT negative stroke.
8. Patients with meningitis, brain abscess or any chronic infection that affect CRP value.

Study Protocol: Clinical history was taken from either the patient or his/ her relatives or attender, while taking history importance was given regarding presence or absence of vomiting, headache and convulsions. Past history of hypertension, diabetes, CAD, RHD, TIA, Collagen diseases, Meningitis, Tuberculosis, Endocrine disorders and congenital disorders were taken. Personal history regarding dietary habits, Smoking, Alcohol consumption and tobacco chewing were noted.

NIH stroke scale was assessed in all patients to assess the neurological disability and its prognosis. Detailed neurological examination was done based on preform. All other systems like CVS, GIT and RS Systems were examined in detail. Detailed investigations including Hb%, TC, DC, urine routine, FBS, lipid profile, ECG, chest X-ray, 2D-ECHO were done.

CT scan after 24 hours after onset of symptoms and C-reactive protein estimation was done anytime between 12-72 hours of symptom onset.

CT Scan Findings in Cerebral Infarct:

- Hyper acute (<12 hours): Normal (50-60%).
- Hyper dense MCA artery (25-90%).
- Obscuration of lentiform nuclei.
- Acute (12-24 hrs.) Low density basal ganglia.
- Loss of gray white matter interface.
- (Insular ribbon sign).
- Sulcal effacement.
- 1-7 days Mass effect.
- Wedge shaped low-density area involving white grey matter.
- Gyral effacement.
- 1-8 weeks Contrast enhancement persist.
- Mass effect resolves.
- Months to years Encephalomalacia.
- Volume loss.
- Calcification.

CRP Estimation: CRP estimation was done with latex CRP reagent by slide agglutination as per manufacturer's recommendations, which is a qualitative and semi-quantitative rapid latex slide test.

Sample: No special preparation of the patient was required prior to sample collection, 5ml of venous blood was collected into a sterile vial without anticoagulant. Blood was allowed to clot completely and the collected serum was tested i.e., reagents as described below:

Reagents/Accessories (Supplied in the Kit):

- Reagent-1: Normal saline.
- Reagent-2: Latex CRP reagent.

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Reagent-3: Positive control serum.

Reagent-4: Negative control serum.

All reagents were stored at 2-8 degrees till the expiry date mentioned.

Statistics: Data were presented as mean $\pm$ SD values were called significant (if $p < 0.005$). The chi square test was used in most cases to compare frequency distribution.

OBSERVATIONS: There were 250 cases of first episode stroke in BTGH Of those 200 cases were CT proved ischemic stroke. Of those 60 cases were studied after excluding the patients using the exclusion criteria. 60 age and sex matched controls were studied as the control group.

Type of stroke	No. of Cases	Percentage
Ischemic stroke	200	80%
Hemorrhagic	50	20%
Total	250	100%

Table 1: Type of Stroke CT Evaluated (N = 250)

The above table shows that 80% of cases were ischemic strokes while only 20% constituted hemorrhagic stroke which included intracerebral and sub Arachnoid hemorrhage.

Type of Stroke	No. of Cases	Percentage
Hemorrhagic (ICH + SAH)	50	42
RHD Cases (embolic)	15	12.5
Old IHD	10	8.3
Infections (TB, Malaria, Sepsis, Pneumonia)	20	16.6
Malignancies	5	4.2
Previous stroke	20	16.4

Table 2: Exclusion Group (N = 120)

Table 2: Provides information about the exclusion of patients who did not fit into the study, as they would have altered the CRP values. It shows that 42% of patients were eliminated from study because of hemorrhagic stroke, while 12.5% case were due to emboli from cardiac source 8.3% were excluded because they had old history of ischemic heart disease. 16.6% had some infective foci, 4.2% were having malignant disease and 16.4% were having previous history of stroke/ TIA.

Sex	Total	Percentage
Males	37	61.6%
Females	23	38.4%

Table 3: Sex Distribution in Study Group (N = 60)

Table 3: Shows sex distribution of the study group where 61.6% were males and 38.4% were females.

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Age in Years	No. of Patients				Total	Percentage
	Male	Percentage	Female	Percentage		
21 – 30	0	0	0	0	0	0
31 – 40	4	10.8	0	0	4	6.6
41 – 50	6	16.2	6	28.1	12	20.0
51 – 60	8	21.6	4	17.4	12	20.0
61 – 70	10	27.0	8	37.8	18	30.0
71 – 80	9	24.4	5	21.7	14	23.4

Table 4: Age and Sex Distribution in Study Group (N = 60)

Table 4: Shows maximum thrombotic stroke patients were in the age group of 61-70 constituting 30% of the study population. Young stroke (age <40 years) were found only in 6.6% (Ratio of 1:15) of cases all of whom were males. Women <50 years accounted only for 6 cases i.e. 10% of the total cases.

Age in years	No. of Patients				Total	Percentage
	Male	Percentage	Female	Percentage		
21 – 30	0	0	0	0	0	0
31 – 40	4	10.8	0	0	4	6.6
41 – 50	6	16.2	6	28.1	12	20.0
51 – 60	8	21.6	4	17.4	12	20.0
61 – 70	10	27.0	8	37.8	18	30.0
71 – 80	9	24.4	5	21.7	14	23.4

Table 5: Age and Sex Distribution of Control Group (N = 60)

Table 5: Shows that similar age and sex matched controls were taken for the study as CRP increases with age.

	No. of Cases	Percentage
Mode of onset		
Sudden (within minutes)	49	82.0
Gradual (within hours)	11	18
Level of consciousness		
Alert	36	60.0
Drowsy	16	26.6
Comatose	8	13.4
Convulsions		
Present	10	16.6
Absent	50	83.4
Headache/ vomiting		
Present	14	23.3
Absent	46	76.7

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Facial weakness		
Present	20	33.3%
Absent	40	66.7%
Dysarthria		
Present	18	30%
Absent	42	70%
Table 6: Clinical Picture (N=60)		

Table 6: Shows the clinical presentation, 82% of patients had sudden onset of symptoms while 11% developed the symptoms gradually. 60% were alert at the time of presentation while 26.6% were drowsy and 13.4% were comatose. Convulsions were present in 16.6% and head ache/ vomiting in 23.3% of the cases. 33.3% had facial weakness while 30% of the patients had dysarthria at admission.

	No. of Cases	Percentage
Cortical	4	3
Frontal	8	13.4
Parietal	20	33.3
Temporal	2	3.3
Parietotemporal	6	10.0
Front parietal	8	13.4
Sub cortical	4	6.6
Basal ganglia, Thalamus	12	20.0
Internal capsule	4	6.6
Table 7: Localization of Lesions on CT scan (N=60)		

Cortical infarction constituted 73.4% of cases in which maximum cases (33.3%) had infarction in the parietal lobe, followed by frontal and fronto-parietal areas which had 13.4% each. Sub cortical infarction constituted 26.6% with basal ganglia and/ or thalamus involved in 20% cases.

NIH Scale	No. of Patients		Total	Percentage
	Male	Female		
Minor Stroke (1-4)	8	2	10	16.6
Moderate Stroke (5-15)	18	15	33	55
Moderate - Severe Stroke (16-20)	10	4	14	23.4
Severe Stroke (> 20)	1	2	3	5
Table 8: NIH Stroke Scale (N=60)				

Minor stroke accounted for 16.6% cases, while most patients (both male and female) 55% had moderate stroke, only 5% cases had severe stroke, whilst 23.4% had moderate to severe stroke.

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	C - reactive protein Levels			
	< 6mg/ dl	Percentage	> 6mg/dl	Percentage
Study group (N=60)	6	10	54	90
Control (N=60)	53	88	7	12

Table 9: C-reactive protein level in CT proved ischemic stroke patients

$$X^2 = 73.65, p < 0.001$$

Table 9: Shows CRP values of CT evaluated ischemic stroke patients after admission, > 12 hours < 72 hours after the symptoms onset 54 of the 60 thrombotic stroke patients had CRP >6 mg/dl only 6 patients had CRP<6mg/dl (P <0.001). Chi-square test value was 73.65, which is statistically very significant. Only 7 patients in the control group had CRP>6mg/dl.

Age in Years	CRP Values		Total
	> 6mg/dl	< 6mg/dl	
21 – 30	0	0	0
31 – 40	2	2	4
41 – 50	11	1	12
51 – 60	11	1	12
61 – 70	16	2	18
71 – 80	12	2	14

Table 10: CRP levels in relation to age (N = 60)

Table 10: Shows the relation of CRP values with age, i.e. CRP level is more between the age group of 61 – 70 and is less in young adults (< 40 years of age).

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DISCUSSION: Strokes kill ≈ 5 million people each year. Cerebrovascular disease is the second cause of death worldwide.⁹ Kristensen B.¹⁰ et al documented young ischemic strokes occurring in patients younger than 45 years old was rare and less than 5 percent of all cerebral infarctions. A recent stroke registry study by T. Song – Hai Lee.¹¹ et al revealed that the incidence of young stroke was 6.8% of all strokes.

In our study young ischemic stroke less than 40 years of age constitutes 6.6% of all strokes and highest incidence in males was noticed after the age of 61-70 years i.e., 27% and in females also the incidence was highest in the age group of 61-70 years i.e. 37.8%. The greater prevalence of stroke in men is well known, but recent issues emphasize the importance of stroke in women.¹²

Over the entire life time, $\approx 16\%$ of women but only 8% of men will die of stroke.¹³ Knowledge of sex differences might be of interest in improving preventive strategies and the in-hospital management of stroke patients. Jaume Roquer et al.¹⁴ documented mean age for stroke was higher in women than in men.

In contrast to above studies, we documented the increased incidence of acute thrombotic stroke in both males and females after the age of 60 years with slight predominance in males. We also documented the incidence of thrombotic stroke after 60 years of age in males and females were 73% and 76.9% respectively.

Smoking is widely accepted as one of the risk factors for cerebral infarction in western populations. Smoking is thought to affect lacunar infarction mainly through reversible factors, such as increased platelet aggregation and arterial vasoconstriction induced by sympathetic activity rather than through atherogenic factors and this relationship has not been observed in most Japanese epidemiological studies.¹⁵

Contrary to the above study, the above relation of smoking with acute ischemic stroke is not observed in our population. Manson JE et al.¹⁶ In their study had proved that stroke in diabetics is more likely to be fatal, when compared to any other novel risk factors.

In terms with that of the above study, we also observed that mortality was highest among the diabetic group when compared to hypertensive group or diabetic and hypertensive group.

Thomas S. Bowman et al.¹⁷ documented that TC, HDL and Triglyceride level were not independent risk factors for ischemic stroke and TC: HDL ratio did not have a linear association with the risk of ischemic stroke.

In contrast to the above study we did notice the much significance rise in TC, LDL and TG and decrease in HDL in relation to ischemic stroke when compared to controls in our study.

CRP, one of the acute phase reactants, is an indicator of underlying systemic inflammation.¹⁷ and a novel plasma marker of atherothrombotic disease.¹⁸ It is likely that CRP has many pathophysiological roles in the inflammatory process, including binding of phosphocholine and recognition of foreign pathogens and phospholipid constituents of damaged cells.¹⁷

Kerstin win beck et al.¹⁹ study documents, rised CRP in 127 patients without thrombolysis with a first ischemic stroke no more than 12 hours after symptom onset. In contrast, a CRP increase between 12 and 24 hours after symptom onset predicts an unfavorable outcome and is not a best parameter to predict outcome which is estimated before 12 hours of onset of symptoms.

In the present study, CRP was measured only after CT image confirmation of infarction which was done after 24 hours of onset of symptoms. So CRP level was estimated after CT confirmation and before 72 hours of onset of symptoms. In the present study, CRP was elevated in 54 patients out of 60 study group which is statistically significant.

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Mario Di Napoli et al.²⁰ studied, the risk of CRP in 72% of patients ($P < 0.0001$) out of 473 first ever ischemic patients and suggested the CRP as a independent marker of underlying chronic inflammatory process in atherosclerosis. Montaner et al.²¹ described a peak level of interleukin-6 after 24 hours of symptom onset. Recently, Di Napoli.²² observed an increase of CRP within 3 hours after stroke compared with the prestroke value. Mahapatra SC et al.²³ observed CRP value 76mg/L in 64 patients out of 80 total thrombotic stroke patients ($P < 0.001$). The study was undertaken to assess the role of inflammation in pathogenesis of ischemic stroke.

Rathore HS et al.²⁴ performed a study to measure and compare CRP levels in the cortical and lacunar infarct and to find out their diagnostic importance at an early stage of stroke. CRP was estimated in 25 cases of lacunar and 25 cases of cortical infarct. The CRP was considered positive if its value was more than 6mg/L, observed rise of CRP in 12% cases of lacunar infarct and 88% cases of cortical infarct. In the present study the CRP rise was 82.4% in cortical and 26.6 in subcortical. It was clearly observed in our study that CRP was raised in all subtypes of cerebral infarct without much difference.

In Irene M et al.²⁵ study, CRP levels were measured in a random sample of 773 subjects ≥ 55 years of age and follow-up was done for the next 6.5 years. They documented the progression of subclinical atherosclerosis and CRP predicts myocardial infarction and stroke.

In our control study involved age and sex matched healthy individuals; the rise of CRP level was noted in 12% of cases. The prediction of myocardial infarction and stroke couldn't be done since it needs longer follow-up.

In L. Masoti et al.²⁶ study they retrospectively measured CRP values in 196 elderly patients for relationship between CRP and short term prognosis and concluded that elevation of CRP could represent a negative prognosis in elderly patients with ischaemic stroke, in particular, for short term prognosis. In the present study, there were 14 deaths, 10 were males and 4 were females and in all of them CRP $> 6\text{mg/dl}$ which is in terms with that of the above study reiterating that elevated CRP levels were a bad prognostic indicator.

CONCLUSION: C- reactive protein levels were significantly higher in patients with ischemic stroke when compared to controls. It is also observed that by elevated C-reactive protein in ischemic stroke can be diagnosed positively but subtypes (Cortical, subcortical) of cerebral infarction cannot be differentiated at the time of early diagnosis. C-reactive protein levels being raised within 72 hours of an acute ischemic stroke is poor prognostic indicator.

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