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A Study of C - reactive protein in Acute Ischemic Stroke.

Anusha Reddy[1], Vijaykumar.G. Warad[2], S.S Devarmani[3], Ravi Kattimani[4], Syed Afaque Hyder Inamdar[4]

[1]Junior Resident, Department Of Medicine, Shri B M Patil Medical College, BLDE (Deemed To Be University), Vijayapura, Karnataka, India.
[2]Professor, Department Of Medicine, Shri B M Patil Medical College, BLDE (Deemed To Be University), Vijayapura, Karnataka, India.
[3]Professor, Department Of Medicine, Shri B M Patil Medical College, BLDE (Deemed To Be University), Vijayapura, Karnataka, India.
[4]Assistant Professor, Department Of Medicine, Shri B M Patil Medical College, BLDE (Deemed To Be University), Vijayapura, Karnataka, India.

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ABSTRACT

Background: The role of the inflammation in the causation of the atherosclerotic changes has been proved. Various studies done have showed the role of C reactive protein as an early inflammatory mediator and its association with the stroke and its outcome has been done and is under research. Hence we evaluated the role of C reactive protein in acute ischemic stroke within 72hrs of the onset of the symptoms. **Methods:** We studied prospectively 60 patients of stroke who were admitted in Shri B M Patil Medical College hospital who were diagnosed and admitted with ischemic stroke on the basis of the History, Clinical examination and proved on CT scan. CRP was measured on admission within 72hrs of the onset of the symptoms and patients were selected on the basis of the inclusion and exclusion criteria. This study was conducted between September 2017 to July 2019 .60 age and sex matched controls were considered for the study for comparison and these were patients admitted in the other wards of the hospital after matching the inclusion and exclusion criteria. **Results:** The CRP value in our study was maximum in age group of 51-60yrs of age.Males were 39 cases and 21 were females. The mean age in females was 63.7±11.6 yrs and in Males was 60.4±9.3 i.e mean age was higher in females compared to males. The mean CRP among cases was 42.4±32.6 and among controls was 11.6±16.1 which showed a P value of <0.001 which was statistically significant.85% of the cases had elevated CRP and only 20% had normal values which was significant. **Conclusion:** CRP was elevated in patients with stroke when compared to controls and it was associated with poor outcome and was a poor prognostic indicator and patients with elevated CRP had increased risk of mortality.

Keywords: C-reactive protein, Ischemic stroke, CT scan.

INTRODUCTION

Stroke is an important cause of mortality in elderly and increased rate of morbidity in elderly patients. In spite of understanding the physiology, pathology and incidence of cardiovascular and cerebrovascular disease developing advances in prevention and treatment, the burden of disease is increasing. Furthermore chronic conditions such as Diabetes mellitus and Hypertension which are considered as risk factor for stroke do not explain the occurrence of cardiovascular diseases and cerebrovascular disease in the different population groups.

There is no surprise that extensive research study is necessary for potential risk factors.

At the start of 20th century, Sir Williams Osler (1908) and Ophulus (1921) proposed that infection could be association in pathogenesis of atherosclerosis. In fact, research of more than a century has indicated various microorganisms as significant link between inflammation and the pathogenesis of atherosclerosis. Recent research show atherosclerosis as one of the cause of inflammation1. Researchers found a protein in the study of patients with cardiovascular and cerebrovascular disease which was named as C-reactive protein. C-reactive protein value estimation may help in the assessment of Atherosclerosis of vessels in healthy persons. Limited research has been done in our country despite of the increasing incidence of the cerebrovascular disease.

Name & Address of Corresponding Author
Dr. Anusha Reddy,
Junior Resident
Department of Medicine,
Shri B M Patil Medical College,
BLDE (Deemed To Be University), Vijayapura,
Karnataka, India.

MATERIALS AND METHODS

The study "C Reactive protein in acute ischemic stroke" was conducted in Shri B M Patil Medical college Vijayapura, during the period from October 2017 to July 2019.

The study was done with the following aims.

1. To study Plasma CRP levels in acute ischemic stroke.
2. To evaluate the role of CRP in acute ischemic stroke

Selection of cases: The study was done in patients admitted and diagnosed with acute ischemic stroke in Shri B M Patil Medical College Vijayapura

Period of Study: From October 2017 to July 2019.

Sample Size: 60 patients who were age and sex matched among cases and controls admitted in Shri B M Patil Medical College

Study subjects: 60 cases of acute ischemic stroke admitted during the period of December 2017 to July 2019 Controls: 60 controls will be selected from the patients admitted in hospital, which were compared with study subjects in all factors except the disease under study.

Inclusion criteria:

1. Male and Female patients of 20-80yrs of age
2. CT scan show ischemia

Exclusion Criteria:

1. Other than age in inclusion criteria i.e. age <20yrs or >80yrs
2. Patients with history of cardiac disease such as myocardial ischemia, myocarditis and valvular heart disease
3. Any patient with previously diagnosed with TIA or stroke
4. Any patient having autoimmune disease, collagen vascular diseases
5. Patients with history of hemorrhage, tumors
6. Patient with RTA and head injury
7. Patients whose CT scan is normal
8. Patients with CNS infection that can alter the values of CRP.

Protocol of the Study

History was taken from patient and the attenders and important history regarding onset, duration of weakness any slurring of speech, deviation of angle of mouth any associated history of headache, vomiting, convulsions was taken.

- Past history regarding the presence of risk factors of the diabetes and hypertension in the past was taken.
- Personal history related to addictive habits was also taken. Examination done according to proforma.

All the routine investigation including the complete blood counts, renal profile, urine routine, chest X-ray and ECG done. CT scan was done at the time of the admission to hospital and C-reactive protein levels were done on admission.

CT in cerebral infarction:

Hyper acute infarct (<12 hours): Normal in large cases around 50%, hyper dense area may be seen in about few cases Acute (12 to 24 hours): Low density areas, loss of grey- white matter differentiation, sulcal effacement.

1 to 3 days: low density involving both grey and white matter.

4 to 7 days: mass effect and edema may be seen and sulci and gyri are enhancing.

1 to 8 weeks: mass effect is absent, chronic enhancement as hyper intensity is present

Months to years: Encephalomalacic change, volume loss

CRP Estimation: CRP estimation is done using the following VITRIOS chemistry products

VITRIOS CRP slides provided

1FS and 4600 Chemistry Systems

Calibrator kit 7 on VITRIOS 250/350/950/5 and VITRIOS 5600 integrated system text.

Sample: 5 ml of patient blood was collected into the plane vial and centrifuged within 4hrs of collection and plasma separated Reagents

Statastics: Chi-square ($\chi 2$) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance. ROC analysis for Sensitivity- specificity was done to check relative efficiency. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant.

RESULTS

Table 1: Distribution of Age between Cases and Controls

Age (Yrs)	Cases		Controls	
	N	%	N	%
21-30	1	1.7%	1	1.7%
31-40	2	3.3%	2	3.3%
41-50	5	8.3%	5	8.3%
51-60	25	41.7%	25	41.7%
61-70	19	31.7%	19	31.7%
>70	8	13.3%	8	13.3%
Total	60	100.0%	60	100.0%

Mean±SD of age 61.6±10.3 years

Table 2: Association of Age and Gender among both Cases and Controls

Age (Yrs)	Male		Female		p value
	N	%	N	%	
21-30	0	0.0%	1	4.8%	0.394
31-40	2	5.1%	0	0.0%	
41-50	4	10.3%	1	4.8%	
51-60	18	46.2%	7	33.3%	
61-70	11	28.2%	8	38.1%	
>70	4	10.3%	4	19.0%	
Total	39	100.0%	21	100.0%	

Our study is a hospital based case control study of 6o patients with acute ischemic stroke and 60 age and sex matched controls admitted in Shri B M Patil medical college Vijayapura between the period of September 2017 to July 2019 Summary of results

1. Among the 60 cases, and controls 39 were males and 21 were females in the both the groups as it was age and sex matched study
2. The mean age of the both cases and controls was 61.6±10.3 years. Majority were in the age group of 51-60yrs of age as shown in [Table 1]
3. The increased incidence of thrombotic stroke in male in mean age group of 60.4±9.3 and females in the mean age group of 63.7±11.6yrs which showed that mean age was higher in females compared to males in our study as shown in [Table 2]
4. Most common addictive risk factor among the cases was smoking which constituted about 53 percent of the cases followed by multiple risk factor in 28.3 % and only alcohol in 6.7% of the cases as shown in [Figure 1]
5. Most common associated risk factor for stroke in our study among the cases was combination of the Diabetes mellitus and Hypertension which was present in 60 percent of the cases followed by hypertension only in 20% cases and only diabetes mellitus in 10% of the cases as shown in [Figure 2]
6. Our study showed study showed the mean C reactive protein among the case to be 43.4±32.6 and among the control group which showed 11.1±16.1 that there was significant elevation of the levels of the C reactive protein among the cases compared to the controls as shown in [Table 3]
7. Our study showed elevated C reactive protein in 80% of the cases and 15% of the controls hence showed a significant elevation among the cases as shown in [Figure 3]
8. Maximum number of the cases showed elevated C reactive protein level in the age group of 51-60yrs and younger cases less than 40yrs had less significant rise in the C reactive protein level as shown in [Table 4]
9. Our study showed C reactive protein levels were more in the age group of 41-6yrs of age among the cases and was less in patients with young stroke as shown in [Table 4]
10. Mortality was higher in the cases who had higher C reactive protein levels and both diabetes mellitus and hypertension as a risk factor, associated smoking and who had cortical infarcts and mixed infarcts compared to other cases
11. [Table 5] shows the results from receiver operating characteristic curve (ROC) analysis. The area under the curve (AUC) was found 86.1% for CRP values which was statistically significant.
12. AUC as shown in Figure 4 is equal to the probability that a classifier will rank a randomly chosen positive instance of mortality higher than a randomly chosen negative one. Cut off value of CRP values (more than 9.25) yields the chance of predicting the stroke cases with morbidity and mortality with sensitivity 80% and specificity 71.7%.

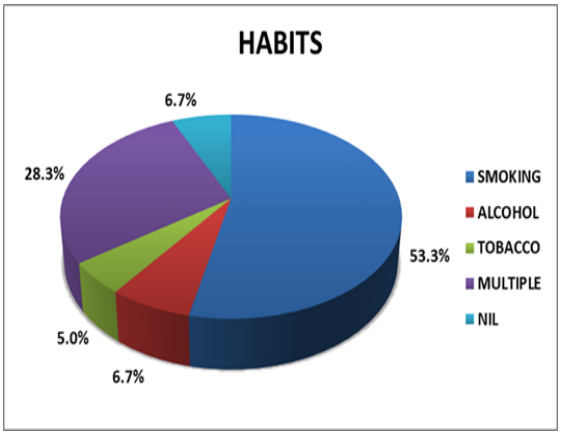

Figure 1: Showing Habits among Cases

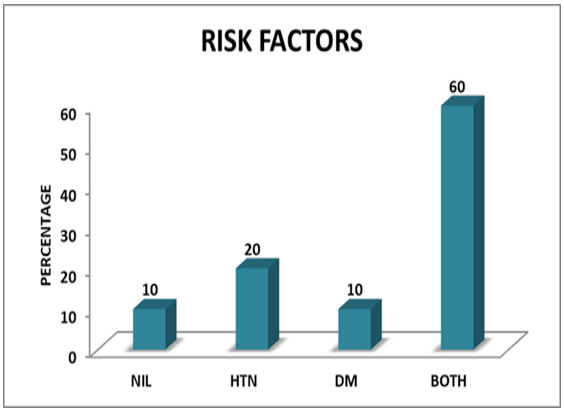

Figure 2: Risk Factors among the Cases

Table 3: Showing Mean CRP Values among Cases and Controls

Parameters	Cases		Controls		t value	p value
	Mean	SD	Mean	SD		
CRP Value	43.4	32.6	11.1	16.1	6.871	<0.001*

Table 4: Mean CRP Level between Cases and Controls By Age

Age(Yrs)	Cases		Controls		p value
	Mean CRP	SD	Mean CRP	SD	
21-30	21.1	0.0	3.0	0.0	-
31-40	50.0	14.1	0.6	0.6	0.039*
41-50	57.0	14.0	5.6	3.9	0.010*
51-60	48.8	10.8	7.7	6.9	<0.001*
61-70	34.6	14.7	8.5	7.2	0.003*
>70	42.1	14.4	6.1	3.3	0.011*
TOTAL	43.4	32.6	11.1	16.1	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Table 5: ROC Analysis of CRP Value between Cases and Controls

Parameters	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
CRP Value	0.861	0.035	<0.001*	0.792	0.93

Note: * significant at 5% level of significance (p<0.05)

Parameters	Positive if greater than or Equal to	Sensitivity	Specificity
CRP Value	9.25	80.0%	71.7%

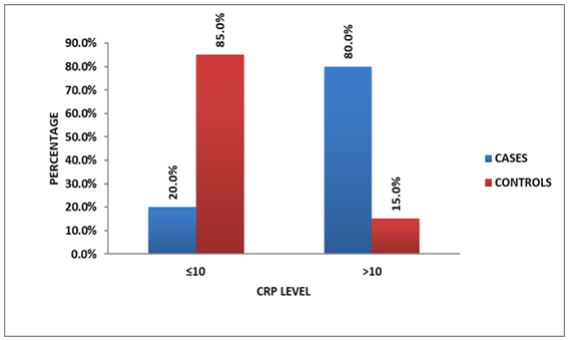

Figure 3: CRP Level between Cases and Controls

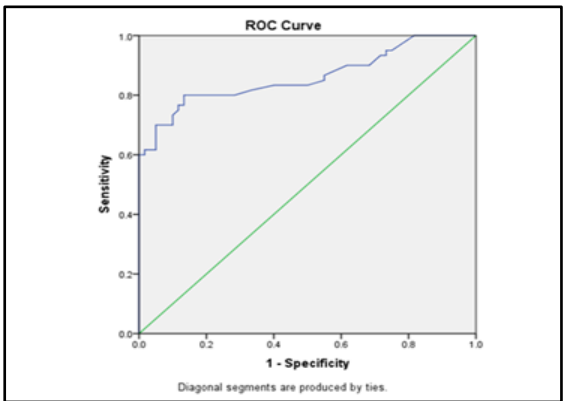

Figure 4: ROC Curve of CRP Value between Cases and Controls

DISCUSSION

In our present study mean age of cases and contols was 61±10yrs of age which was comparable with David curb et al,[1] which showed mean age among cases 58.1±5.7yrs and among controls 55.8±5.4yrs, Agarwal et al,[2] having shown 65.3±9.07yrs and 65.3±8.88yrs, Dhamija R K et al,[3] showing 56.48yrs and 54.20yrs, respectively among the cases and the controls, Natalia Rose et al,[4] showing 69.7yrs.

In our present study incidence of stroke among the young patients was about 5.1 percent which was in comparision to studies done by Kristensen B et al,[5] which showed 5 percent and T song Hai Lee et al,[6] which showed about 6.8 percent of the cases.

The greater incidence of stroke among men compared to women is well established. But according to recent studies emphasis has been made upon the increasing incidence of stroke in women with respect to the age.[7] Entire life time risk 16% of women & 8 % men die of stroke Knowledge of the difference in the sex incidence is of importance for the management of the admitted patients with the stroke.[8] Our study showed the increased incidence of thrombotic stroke in male in mean age group of 60.4±9.3 and females in the mean age group of 63.7±11. 6yrs showing highest incidence which was comparable with the study done by James Roquer et al.[9] Who documented mean age of stroke was higher in females than compared to males Smoking is considered as a risk factor for acute stroke in the population. smoking is considered to affect the cerebral circulation through the mechanism of arterial vasoconstriction and increased platelet aggregation.

Smokers in our study were 53.3 % of the cases which was comparable to the study done by J David Curb et al,[1] which showed 54.4 % of the cases in the study to be smokers and study done by Natalia S Rost et al,[4] which showed 22.7 percent of the smokers among the study group. Hence smoking was an important risk factor for occurance of stroke

Our study showed that both hypertension and diabetes mellitus increased the incidence if the stroke independently and having been diagnosed with both diabetes mellitus and hypertension together increased the risk dramatically this was in accordance with the study by Gang Hu et al,[10] which was one of the fewer studies which showed the combined effect of the diabetes mellitus and hypertension occurring concomitantly, Kissela B M et al,[11] also studied the concomitant effect of diabetes mellitus and hypertension in patients with ischemic stroke in North kentuky stroke study.

In our study cases diagnosed with both diabetes mellitus and hypertension with ischemic infarct showed 9 deaths among the total 13 deaths which further indicates the increased risk of mortality of patients with both the risk factors of hypertension and diabetes mellitus which was in accordance with the study done by Gang Hu et al,[10] Kissela B M et al,[11] which showed increased incidence and mortality among patients diagnosed with both diabetes mellitus and hypertension rather than either diabetes mellitus or hypertension alone and this may be because of the undiagnosed disorder of glucose metabolism in patients diagnosed with hypertension.

Our study showed that the cases had a significant lesser HDL levels compared to the controls with a p value being significant of p<0.001 which was in accordance to the studies done by Samantha A Reina MS et al,[12] which showed that lower level of HDL was associated with elevated risk of stroke.

However, our study did not notice any significant difference in the Total cholesterol, LDL and triglycerides among the cases and the controls.

Our study showed the mean C reactive protein among the case to be 42.4±32.6 11.1±16.1 among the control group which showed that there was significant elevation of the levels of the C reactive protein among the cases compared to the controls which was comparable to the study done by Agarwal et al,[13] which showed 25±24.78 among the cases and 4.00±1.48 among the controls, J David curb et al,[1] showed values of 14.3 among the cases and 11.6 among the controls which was comparable with our study, Natalia S Rose et al,[4] showed the values of 5.8±7.8 among the cases.

Our study showed 85% of the cases had elevated C reactive protein and 15 % of the controls had the elevated values which was comparable to the study done by Dhamaja R K et al,[3] which showed 77.3% of the cases had raised values and 12.54% of controls had elevated values, S C Mahapatra et al,[14] showed 80 percent of the cases had raised values and 1o percent of the controls had elevated values.

Mario Di Napoli et al,[15] studied the values of C reactive protein levels in 473 patients of acute ischemic stroke and showed that 72% had an elevated value of the C reactive protein and showed the association of C reactive protein as a marker of the underlying inflammatory process leading to athero thrombotic event.

A study done by Montanear et al,[16] showed the rise of the acute inflammatory mediators such as interleukin-6 after the onset of the ischemic stroke.

Mahapatra SC et al,[14] did a study on 80 of the thrombotic stroke patients and showed that 64 patients had an elevated value of the C reactive protein. The purpose of the study done was to assess the role of the underlying inflammation in the pathogenesis of the stroke.

Rathore HS et al,[17] did a study on the in the ischemic infarct patients consisting of the lacunar and cortical infarct and the role of the early inflammatory mediators in these patients of stroke and showed that the C reactive protein levels was raised in about 80 percent of the cortical infarcts and 12 percent of the lacunar infarcts and this was carried out in 25 each cases of the cortical and lacunar infarct patients.

In a study done by L Masoti et al,[18] they measured C reactive protein values in 196 elderly patients and observed the short term prognosis in these patients with stroke and they observed that elevated C reactive protein levels was associated with the poorer prognosis.

In our study C reactive protein was measured in the patients admitted and who were proven to be having ischemia by CT scan which was done at the time of the admission to the hospital and the levels of CRP was estimated after 12hrs and within 72 hrs of the onset of the symptoms.

This observation was in accordance to the study done by Kerstin winbeck et al,[19] who did study on 127 patients of stroke and showed that CRP levels estimated between 12-24hrs of the onset of the symptoms indicates poor prognosis and estimation before 12hrs did not show any significant changes.

Our study showed that 66.7 % cases with elevated CRP levels had cortical infarcts, 27.1% cases with subcortical infarct had elevated CRP levels and 6.3% cases with elevated CRP levels had both cortical and subcortical level.

In study done by Irene et al120 study, CRP levels was measured in 773 cases who were more than 55yrs of age and these cases were followed up for the next 6.5yrs The study documented the progression of the atherosclerotic changes and the change in the values of the CRP observed in them which predicted the risk of stroke or cardiovascular diseases in these individuals.

In our study the control group showed an elevation in the C reactive protein in about 15 percent of them the further risk prediction of myocardial infarction and the risk of stroke could not be assessed in these people because our study didn't do follow up of these patients which needed a longer duration for the follow up.

In our study 13 deaths occurred in which 9 were males and 4 were females and in this 6 had cortical infarcts and 4 patients had both cortical and subcortical infarcts and 3 patients had subcortical infarct. All patients who died showed an elevated levels of C reactive protein and elevated levels showed a bad prognostic indicator.

In our study 40 patients had cortical infarction out of which 6 patients expired and 16 patients had subcortical infarct out of which 3 patients expired and 4 patients had both cortical and subcortical infarcts out of which all the patients expired. This was compared to the study done by Sukdeb Das et al21 on the short term mortality prediction in patients with stroke which showed that 30% of the cortical lesion contributed for mortality and 22 % for subcortical and 32% were combined overall it showed that mortality increases when it is combined whether it is ischemic or haemorrhagic stroke which was similar to our study.

CONCLUSION

1. Our study showed that the C reactive protein was elevated in patients diagnosed with stroke when it was compared with the control group
2. Our study also showed that elevated C reactive protein was associated with the poor outcome in patients with acute ischemic stroke and is poor prognostic indicator.
3. Our study also showed that the mortality in the study group of patient who died with acute ischemic stroke in them all had elevated values of C reactive protein.

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