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Research Article

High sensitivity C-reactive protein as a prognostic marker in ischaemic and haemorrhagic stroke

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ABSTRACT

Background: Stroke is the leading cause of death worldwide and one of the main causes of long-term disability. Many patients with elevated CRP levels within 72 hours of stroke have an increased risk of death. However, vascular inflammation is more related to high-sensitivity CRP (hsCRP).There is a distinct possibility that elevated hsCRP may be a direct response to the extent of cerebral tissue injury. The aim of this study was to compare the high sensitivity C-reactive protein (hsCRP) level in patients of stroke and assess its utility in predicting the functional outcome.
Methods: A prospective study of 50 patients presenting with a history of focal neurological deficit of acute onset in the form of hemiparesis/hemianaesthesia and having evidence of presence of infarct/haemorrhage in CT/MRI scan of brain and 50 age and sex matched healthy controls was done. In all patients hsCRP levels were measured within 24 hours of presentation. Admission hsCRP levels were then compared to the scandinavian stroke scale scores.
Results: Mean hsCRP levels were significantly higher in patients with stroke than controls. Patients with a good long term outcome had a statistically significant lower hsCRP levels. 8 patients died during follow/hospitalisation. They had higher hsCRP levels than patients who survived. hsCRP levels and scandinavian score showed a significant correlation both with ischemic and haemorrhagic stroke.
Conclusion: hsCRP can be used as a marker for prognosis in cases with stroke. hsCRP levels are higher in ischemic stroke than in haemorrhagic stroke.

Keywords: Stroke, hsCRP level, Scandinavian stroke scale

INTRODUCTION

Stroke is the leading cause of death worldwide and one of the main causes of long-term disability. According to the World Health Organization, 15 million people suffer from stroke each year. About 87% of all strokes are due to ischaemia. There is increasing evidence that inflammatory processes are involved in cerebral ischaemia.[1-3] Ischaemic brain injury is characterized by acute local inflammation and changes in levels of inflammatory cytokines, notably C reactive protein (CRP). Elevated stroke risk has been linked to high levels of CRP. Many patients with elevated CRP levels within 72 hours of stroke have an increased risk of death.[4] CRP serves as biomarker for systemic inflammation. However, vascular inflammation is more related to high-sensitivity CRP (hsCRP).[5] The association between hsCRP and a high stroke severity remains unexplained .There is a distinct possibility that elevated hsCRP may be a direct response to the extent of cerebral tissue injury.

hsCRP is an acute- phase reactant produced by the liver under the control of interleukin-6. Almost certainly the primary circulating physiological mediator, because most other cytokines rarely reach effective concentrations in plasma (its normal level in plasma is 6mg/dl).[6] Levels of hsCRP measured shortly after stroke predicted complementary aspects of prognosis.

During approximately 4 years of follow up, hsCRP levels were associated with increased mortality.[7] Leukocyte count predicts recurrent stroke or death after first stroke within 6 months.

This study was undertaken to study the high sensitivity C-reactive protein (hsCRP) level in Indian patients with stroke and to evaluate the hsCRP level as a prognostic marker in cases of different types of stroke.

This study was aimed to assess hsCRP as a prognostic marker by comparing with scandinavian stroke scale score and to compare levels in ischaemic and haemorrhagic stroke.

METHODS

We conducted a prospective observational study in 50 patients aged above 40 years admitted to CSSH Hospital, Meerut presenting with history of focal neurological deficit of acute onset in the form of hemiparesis, hemi anaesthesia or aphasia and having evidence of the presence of stroke (ischaemic/haemorrhagic) in CT/MRI scan of the brain. 50 age and sex matched controls were also taken to compare hsCRP levels. Patients qualifying all inclusion and exclusion criteria were enrolled in the study. Patients with history of recent MI/ACS (within last 3 months), arthritis, known case of cancer, hepatic failure, patients on steroids and oral contraceptives, patients with renal disorder (s. creatinine >1.2),major trauma (within last 6 months)or recent Surgery (within last 6 months) were excluded.

Stroke severity and outcome as well as improvement or worsening of neurological status was assessed on admission and after 6 months using the scandinavian stroke scale.

Brain imaging was done by non-contrast CT or MRI. And patients were classified into haemorrhagic or ischaemic stroke. Blood samples were drawn within 24 hours of admission for hsCRP along with urea, creatinine, complete blood count, liver function tests and blood sugar.

hs-CRP estimation

hsCRP was assayed using the solid phase enzyme immunoassay (ELISA). This immunoassay kit allows for the in vitro quantitative determination of human hsCRP concentration in serum, plasma and biological fluids. The minimum detectable value of CRP for ELISA test is typically less than 0.156 ng/ml.

Statistical analysis

The results obtained were subjected to standard statistical methods for analysis and relevant conclusions were drawn from them. All the data was analyzed using computer based software. Measures of the central tendency including mean and standard deviation were used to ascertain the data regarding hsCRP values and also scandinavian stroke scale score. The correlation between hsCRP on admission and prognostic scale for functional disability was analyzed with spearman's rank order correlation. The correlation of stroke severity (assessed by scandinavian stroke scale) and hsCRP was analyzed with spearman's rank order correlation. An independent t test was used to evaluate the differences between hsCRP levels and each risk factor for stroke and to compare hsCRP levels in stroke patients to healthy patients. P value of less than 0.05 was considered to be statistically significant throughout the study.

RESULTS

Out of total 50 patients of stroke, 29 (58%) patients had Ischaemic Stroke and 21 (42%) patients had haemorrhagic stroke.

Out of the total 29 patients with infarct, 19 patients were in the category of severe stroke scoring between 2 to 8 points. 5 patients each were in the moderate stroke category and minor stroke category respectively. In the 21 patients with haemorrhagic type of stroke, 7 patients were in the severe stroke group, 5 patients were in the moderate stroke group, whereas 9 patients were in the minor group (Table 1).

Table 1: Distribution of cases according to scandinavian stroke scale and type of stroke.

Score	Type of stroke	
	Infarct	Haemorrhage
2 to 8	19	7
9 to14	5	5
>14	5	9

Table 2: hsCRP and Glasgow coma scale.

GCS score	3 to 8 (group A)	9 to 12 (group B)	12 to 15 (group C)
hsCRP	30.543±16.764	7.833±6.52	7.33±0.577

The hsCRP levels were compared between the study and the control group. The mean hsCRP in the study group was 23.7±17.778 and the mean hsCRP in the control group was 0.870±0.252. Independent t test was used to compare the levels of hsCRP in both groups. On analysis a significant difference was found between the hsCRP levels of patients and healthy controls. (p value< 0.0001).

Patients were divided into 3 groups according to the Glasgow coma scale, group A (GCS of 3 to 8), group B (GCS of 9 to 12) and group C (GCS of more than 12). The mean hsCRP of study group with GCS of 3 to 8 was 30.543±16.764; the mean hsCRP of group with GCS of 9 to 12 was 7.833±6.52. The hsCRP of group with GCS of more than 12 was 7.33±0.577 (Table 2).

This was statistically significant (p value <0.001). On comparing group A and B, the difference of hsCRP was statistically significant (p value<0.001), However on comparing group B and group C, p value was 0.953 which was not statistically significant.

Table 3: hsCRP and scandinavian stroke scale score in ischaemic stroke.

hsCRP levels	Prognostic score	Long term score	6 month score
0-20	18.800±1.095	29.800±3.033	33.400±4.336
21-30	8.00±2.191	6	23.500±1.643
31-40	6.286±2.928	4.143±3.388	21.429±2.225
41-50	4.286±1.380	1.143±1.069	10.857±8.764
>50	2.00	1.500±1.0	2.0±4

Table 4: hsCRP and scandinavian stroke scale score in haemorrhagic stroke.

hsCRP levels	Prognostic score	Long term score	6 month score
0-5	19.5±0.548	31±7.668	37.5±4.93
6-10	12.33±5.745	17.22±9.011	24.556±9.825
>10	2±1	0.033±0.816	1.833±4.491

Table 5: hsCRP and functional outcome based on the scandinavian stroke scale long term score in patients with ischaemic stroke.

Outcome	Number of patients	Mean hsCRP levels
Good outcome	9	19.22±8.614
Poor outcome	17	41±2.409
Mortality	3	51.667±3.786

In patients of ischaemic stroke., it was observed that patients with a hsCRP value of 0-20 had a mean prognostic score of 18.80±1.095, patients with hsCRP value of 21-30 had a prognostic score of 8.0±2.191, patients with hsCRP value of 31-40 had a score of 6.286±2.928, patients with hsCRP level of 41-50 had a score of 4.286±1.380 and patients with hsCRP levels of >51 had the lowest prognostic score of 2 (Table 3).

This data is statistically significant with a p value of <0.001.

The long term score in patients of ischaemic stroke, with hsCRP levels in the range of 0-20 was 29.8±3.033, the score for patients of hsCRP levels in range of 21-30 was 6, score for patients with hsCRP levels 31-40 was 4.143±3.388, score for hsCRP levels 41-50 was 1.143±1.069 and long term score of patients with hsCRP value of >51 was 1.5±1 (Table 3).

At 6 months follow up, patients were assessed with the long term score and it was found that, patients with hsCRP levels of 0-20 had a score of 33.40±4.336, patients with hsCRP levels of 21-30 had a score of 23.5±1.643, patients with hsCRP level of 31-40 had a score of 21.429±2.225, patients with hsCRP levels of 41-50 scored 10.857±8.764 and patients with hsCRP level of >51 had a mean score of 2 (Table 3).

We conclude that, hsCRP levels strongly correlate with the prognostic score, long term score, and 6 month score in ischaemic stroke.

The patients with haemorrhagic stroke, a hsCRP level between 0 and 5 had a prognostic score of 19.5±0.548, patients with an hsCRP of 6-10 had a prognostic score of 12.33±5.745 and patients whose hsCRP was >10 had a mean prognostic score of 2±1.0. This data is statistically significant with a p value of <0.001 (Table 4).

Patients of haemorrhagic stroke with hsCRP level of 0-5 had a long term score of 31±7.668, patients with hsCRP level between 6 to 10 had a long term score of 17.22±9.011, whereas patients with hsCRP level of more than 10 had a mean long term score of 0.033±0.816. (Table 4).

On follow up, patients with a hsCRP level of 5-10 had a 6 month score of 37.5±4.93, patients with hsCRP level of 6-10 had a mean 6 month score of 24.556±9.825, whereas patients with hsCRP of more than 10, had the lowest mean 6 month score of 1.833±4.491 (Table 4). Here also the inverse correlation was statistically significant (p value<0.01)

Poor outcome on the scandinavian stroke scale is defined by a long term score at 6 months, A score of less than 25 is classified into a poor outcome, whereas a score of more than 25 is defined a good outcome. Patients of ischaemic stroke with a good long term outcome had a mean hsCRP level of 19.22±8.614, patients with a poor outcome had a mean hsCRP level of 41±2.409 and 3 patients died during follow/hospitalisation had the highest mean hsCRP level of 51.667±3.786. It was statistically significant (p<0.001) (Table 5).

It was conferred that in ischaemic stroke, higher hsCRP levels at admission are associated with higher morbidity and mortality.

Table 6: hsCRP and functional outcome based on the scandinavian stroke scale long term score in patients of haemorrhagic stroke.

Outcome	Number of patients	Mean hsCRP levels
Good outcome	13	5.538±2.367
Poor outcome	3	10.667±2.309
Mortality	5	11.2±1.924

In the haemorrhagic stroke cohort, the patients with good outcome had a mean hsCRP level of 5.538±2.367, patients with poor outcome had a mean hsCRP level of

10.667±2.309 and patients who died had the highest hsCRP level of 11.2±1.924. It was statistically significant (p<.05) (Table 6).

Higher values of hsCRP at admission correlate with the functional outcome of patients with haemorrhagic stroke.

DISCUSSION

This study was designed to correlate the hsCRP levels at the time of admission with the prognosis. Scandinavian Stroke Scale was used for prognostication by calculating the score at the time of admission and after 6 months.

In the study there was a significant difference between hsCRP levels between patients of stroke and the control group. The mean hsCRP of the patients in the study group was 23.77±17.778 and the mean hsCRP in the control group was 0.870±0.252. This difference was statistically significant. Previous studies also reported that hsCRP levels were higher in patients of stroke than in patients who did not have stroke. Other studies have shown varying prevalence. In a study by Di Napoli et al from Italy, 95 patients (74.2%) with acute ischaemic stroke had high CRP levels (>0.5 mg/dl) at admission.[8] Muir et al had detected elevated CRP (>10 mg/L) levels in 96 out of the 228 (42.1%) patients admitted with acute ischaemic stroke in the UK.[9] In a study by Elkind M et al, it was found that levels of hsCRP are higher in stroke patients than in stroke free patients, supporting our findings.[10]

We also found a significant difference of hsCRP values in patients of Ischaemic stroke and patients of haemorrhagic stroke. The mean hsCRP level in the patients of ischaemic stroke was 35.345±14.495 whereas the mean hsCRP level in patients of haemorrhagic stroke was 7.619±3.471. This difference was statistically significant and shows that the mean hsCRP level is higher in patients of ischaemic stroke than in patients of haemorrhagic stroke. This finding of ours is supported by previous studies. In a study by Roudbary et al hsCRP level was more in the ischaemic stroke subset as compared to the haemorrhagic subset.[11] Serum level of hsCRP in Ischaemic patients was 18.92±11.28 and in hemorrhagic group was 2.65±1.70. In another study by Talreja et al, hsCRP levels were found to be higher in patients of haemorrhagic stroke than in ischaemic stroke. This may be due to large haemorrhage causing ischaemia and raising levels of hsCRP.[12]

As regards to Glasgow coma scale (GCS) in our study, we found that patients with GCS of less than 8 had a higher hsCRP level and higher mortality and morbidity rates. This was in agreement of the results of Teasdale et al, and Burtin et al.[13,14] This reflects the importance of GCS for assessing the severity of neurological condition.

hsCRP as a marker for severity of stroke

In our study there was a positive correlation between prognostic score of the scandinavian stroke scale and hsCRP level. We also found a significant difference in the mean value of the serum hsCRP in patients categorized as minor, moderate and severe stroke according to the scandinavian stroke scale. The mean value of hsCRP was 7.785±6.0 in the minor stroke category, 18.2±11.84 in the moderate stroke category and 34.384±16.659 in the severe category. We found the difference in the mean values of hsCRP between categories to be statistically significant. Various studies in the literature show results that support our observations. In the Bergen stroke study with a sample size of 498 patients, Idicula et al, reported that higher hsCRP levels were independently associated with greater stroke severity and mortality among patients with stroke.[15] In a prospective cohort study comprising of 1462 individuals, Rost et al, reported that 196 patients developed stroke.[16] Using Cox proportional hazard models, it was found that participants with higher levels of hsCRP showed higher relative risk ratios. In another study by Elkind et al, it was concluded that levels of hsCRP, an acute phase reactant increases with stroke severity and may be associated with mortality to a greater extent than recurrence.[10]

hsCRP as a long term prognostic marker

We found that the hsCRP level in patients who had a good outcome was 11.136±16.80 and level of hsCRP in patients with a poor outcome was 33.57±8.88. In order to establish the significance of these results, we further applied the Spearman's correlation coefficient to study the relationship between hsCRP level at admission and long term outcome assessed by the scandinavian stroke scale at 6 months. It was found that inverse correlation existed between the levels of hsCRP and the scandinavian stroke scale at 6 months (correlation coefficient of -0.672). These results indicate an inverse relation between hsCRP level and long term scandinavian stroke scale, meaning higher hsCRP levels correlate with lower scandinavian scores indicating a poorer long term prognosis. Previous studies also reported that in stroke patients the measurement of hsCRP within 24 hours of stroke symptoms can be an independent predictor of prognosis. Arenillas et al, in their study showed that a hsCRP level above the receiver operating characteristic curve cut off value of 1.41 mg/dL emerged as an independent predictor of ischaemic events in first ever transient ischaemic attack or ischaemic stroke patients with intracranial stenosis.[17] Another report concluded that hsCRP levels were most markedly elevated in patients with stroke caused by large artery disease, which tends to cause larger infarct and greater disability and they were significantly lower in patients with stroke caused by small artery disease which cause small infarcts.[18] Winbeck et al observed that an increase in CRP level between 12 and 24 hours after the onset of symptoms

predicts an unfavourable outcome and is associated with an increase in incidence of cerebrovascular and cardiovascular events.[19]

Although infarct size and stroke severity are major determinants of short- term prognosis after ischaemic stroke, hsCRP predicts prognosis, in particular mortality or new vascular events during the first year independent of infarct size and stroke severity.[20] hsCRP can predict recurrent cardiovascular disease, stroke and death in different settings and high levels of hsCRP consistently predict new events in these patients. Higher hsCRP levels also are associated with lower survival rate of these people.[7] Idicula et al suggested that measurement of hsCRP at entry and when possible at discharge, 1 to 3 months later may be useful, because it is likely that higher risk of future events is confined to patients with persistently elevated levels of hsCRP.[15]

CONCLUSION

These findings clearly indicate that levels of hsCRP can be used as a marker to predict the long term prognosis of patients with stoke. hsCRP levels are higher in ischemic stroke than haemorrhagic stroke. Lower admission levels of hsCRP seem to confer a protective advantage on the long term outcomes being associated with higher long term scores on the scandinavian stroke scale, indicating a better outcome in these patients. Similarly, patients with higher hsCRP levels are expected to have lower scores indicating a poor prognosis. hsCRP levels are higher in ischemic stroke than haemorrhagic stroke. hsCRP is emerging as a prognostic marker in stroke. It will be a great help for clinicians if we can have a test which not just predicts the outcome but also diagnose patients at risk for stroke so that a timely intervention can subvert that risk.

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