Evaluation of the Role of Plasma High Sensitivity C-reactive Protein Levels as a Prognostic and Diagnostic Marker in Acute Ischemic Stroke

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Abstract

Introduction: Cerebrovascular disease is the second most common cause of death worldwide. Male gender, older age, smoking, hypertension, diabetes, and hypercholesterolemia are the well-known risk factors for carotid disease as well as for stroke. An increasing body of evidence has linked inflammation with the pathogenesis of atherothrombotic stroke. C-reactive protein (CRP), one of the acute phase reactants, is an indicator of the underlying systemic inflammation and a novel plasma marker of atherothrombotic disease. Hence, the measurement of plasma high sensitivity CRP (hs-CRP) levels can be useful in stroke patients.

Materials and Methods: 60 patients with either hypertension or diabetes or both or none without thrombolysis with the first ever acute ischemic stroke patients were examined with the exclusion from the exclusion criteria. Plasma hs-CRP level was determined within 72 h of onset of symptoms in all computed tomography-confirmed ischemic stroke patients. This clinical study was performed during July 2013 to July 2014. hs-CRP was randomly measured in 60 age- and sex-matched individuals admitted in other wards of the hospital matched in all possible criteria expect the disease under study as a control group.

Results: The hs-CRP concentration was significantly elevated in acute ischemic stroke as compared to control group and it was more between 51 and 70 years of age group and almost equal in both genders. Only 54 of the 60 ischemic strokes patients had hs-CRP value >3 mg/L and only six patients had <3 mg/L (P < 0.001), which is statistically significant. Only 7 of the 60 control group patients had hs-CRP >3 mg/L, which is insignificant.

Conclusion: The hs-CRP level is significantly higher in ischemic strokes and by its elevation within 72 h of symptom onset was a bad prognostic indicator. Elevated hs-CRP values were a risk factor in association with other risk factors such as diabetes/hypertension.

Key words: C-reactive protein, Acute phase reactant, Ischemic stroke, Prognostic indicator

INTRODUCTION

Stroke or cerebrovascular accident is defined by the abrupt onset of a neurologic deficit that is attributable to a focal vascular cause and is the leading cause of death and disability worldwide. Ischemic stroke results from decreased blood flow, caused by blockage, to the portion of the brain with consequent cell death. Hemorrhagic stroke, on the other hand, is a result of bleeding into the brain. Ischemic stroke is far more common and potentially treatable with thrombolytic therapy. Some hemorrhagic strokes are benefited from neurosurgery.¹⁵

An increasing body of evidence has linked inflammation with the pathogenesis of atherothrombotic stroke. Infections and inflammation may promote atherosclerosis and thrombosis by elevating the serum levels of fibrinogen, leukocytes, clotting factors, and cytokines, and by altering the metabolism and functions of endothelial cells and monocyte macrophages. Low-grade infections, reflected
in elevated levels of various acute-phase proteins, might be partly responsible for the inflammatory processes observed in atherosclerotic lesions, which in turn may relate to the occurrence of ischemic symptoms. Several clinical trials have showed an association between the high concentration of serum high sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) and ischemic strokes.\textsuperscript{6,7}

CRP and ESR are acute-phase reactants, are indicators of underlying systemic inflammation, and a novel plasma markers for atherothrombotic disease. There is some difference in the test values of conventional CRP and hs-CRP. Both tests measure the same molecule in blood. The hs-CRP test measures very small amount of CRP in blood. It measures CRP in the range from 0.5 to 10 mg/L. The regular CRP is ordered for patient at risk for infection or chronic inflammatory disease. It measures CRP in the range from 10 to 1000 mg/L. The recent use of highly sensitive hs-CRP assays, with international reference standards set by the World Health Organization (WHO), has enhanced the usefulness of hs-CRP as a reliable predictor of cardiovascular events. A strong and consistent association between the clinical manifestations of atherothrombotic disease and baseline hs-CRP levels has been described in epidemiological studies of patients with acute myocardial ischemia or myocardial infarction, stable and unstable angina pectoris, and myocardial infarction or recurrent ischemia among those hospitalized with angina pectoris.\textsuperscript{8}

**MATERIALS AND METHODS**

The present study, “Plasma hs-CRP levels as a prognostic and diagnostic marker in acute ischemic stroke” was carried out in the Department of Medicine, S.R.N. Hospital, Allahabad, during a period of 1-year from July 2013 to July 2014.

The study was undertaken with the following aims.
1. To observe plasma hs-CRP levels in acute ischemic stroke
2. To evaluate the role of hs-CRP as a prognostic and diagnostic aid in acute ischemic stroke
3. To evaluate the role of hs-CRP as a risk factor in acute ischemic stroke.

**Selection of Patients**
The study was conducted on patients admitted with clinically first attack of stroke to medicine ward in the S.R.N. Hospital, Allahabad.

**Period of Study**
The study period was from July 2013 to July 2014.

**Sample Size**
100 patients admitted with stroke (computed tomography [CT] proved) were selected for the study; of this, 80 patients had thrombotic stroke. Of this, 60 were selected after exclusion of patients having heart disease, infection, tuberculosis, malignancies anywhere in the body, previous history of stroke, transient ischemic attack (TIA), and other factors known to alter hs-CRP value as the study group. 60 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 the 100 stroke patients, 60 were selected as the study group strictly adhering to the inclusion criteria.

**Inclusion Criteria**
Patients presenting with focal neurological deficit of acute onset with vascular origin, in the form of hemiparesis, hemianesthesia or aphasia, or having evidence of the presence of ischemia in CT scan of brain admitted in the ward of medicine department within 72 h.

**Exclusion Criteria**
1. Patients with a history of heart disease: Any valvular heart disease, infective endocarditis, and myocardial infarction
2. Patients with a previous history of stroke or TIA
3. Patients with collagen vascular diseases, active tuberculosis, and arteritis
4. Patients with hemorrhagic stroke, tumor, and subarachnoid hemorrhage
5. Patients with head injury within the past 3 months
6. Patients with meningitis, brain abscess, or any infection that affect hs-CRP value.

**Study Protocol**
Clinical history was taken from either the patient or his/her relatives or attendant, whereas taking history importance was given regarding the presence or absence of vomiting, headache, and convulsions. Past history of hypertension, diabetes, coronary artery disease, rheumatic heart disease, TIA, collagen diseases, meningitis, tuberculosis, endocrine disorders, and congenital disorders was taken. Personal history regarding dietary habits, smoking, alcohol consumption, and tobacco chewing was noted. The National Institutes of Health Stroke Scale (NIHSS) was assessed in all patients to assess the neurological disability and its prognosis.

Detailed neurological examination was done based on pro forma. All the other systems such as cardiovascular system, gastrointestinal system, and respiratory system were examined in detail. Detailed investigations including blood
hemoglobin, total leukocyte count, differential count, liver function tests, kidney function test, urine routine, fasting blood sugar, lipid profile, electrocardiogram, chest X-ray, and 2D-ECHO were done.

CT scan: In all the cases, only plain CT was done.

**Test Principle for hs-CRP**
The assay is based on a latex-enhanced turbidimetric immunoassay method. When an antigen-antibody reaction occurs between CRP in a sample and anti-CRP antibody which has been sensitized to latex particles, agglutination results. This agglutination is detected as an absorbance change (570 nm), with the magnitude of the change being proportional to the quantity of CRP in the sample. The actual concentration is then determined by interpolation from a calibration curve prepared from calibrators of known concentration.\(^9,10\) As per the current literature, the cardiovascular risk is determined as low risk with hs-CRP levels <1.0 mg/L, medium risk if 1.0-3.0 mg/L, and high risk when >3.0 mg/L. For our study, we considered hs-CRP level of ≥3 mg/L as high risk and ≤3 mg/L as low risk.

**NIHSS**
NIHSS is a tool used by health-care providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, whereas a higher score is indicative of some level of impairment.\(^11\) The individual scores from each item are summed to calculate a patient’s total NIHSS score. The maximum possible score is 42, with the minimum score being 0.\(^12,13\) The NIHSS has been repeatedly validated as a tool for assessing stroke severity and as an excellent predictor for patient outcomes.\(^14-16\)

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stroke symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to severe stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe stroke</td>
</tr>
</tbody>
</table>

**Statistics**
Data were presented as mean ± standard deviation. Values were considered significant if \( P < 0.005.\)

The Chi-square test and t-test for independent samples were used in most cases to compare frequency distribution.

**RESULTS**
We studied 100 cases of the first episode stroke admitted in Medicine Department, S.R.N Hospital, Allahabad, from July 2013 to July 2014.

Among these patients, 80 cases were CT-proved ischemic stroke and 20 cases constituted hemorrhagic stroke which included intracerebral and subarachnoid hemorrhage. Of these 80 ischemic stroke patients, 60 cases were studied after excluding the patients using the exclusion criteria. We also studied 60 age- and sex-matched controls as the control group. Among the 60 stroke patients, 44 patients had cortical infarction whereas 14 patients had subcortical or lacunar infarction.
Table 1 shows that similar age- and sex-matched controls were taken for the study as the hs-CRP level increases with age.

Table 2 shows hs-CRP values of CT-evaluated ischemic stroke patients after admission, within 72 h after the onset of symptoms. It shows that 54 of the 60 thrombotic stroke patients had hs-CRP >3 mg/L and only 6 patients had hs-CRP<3 mg/L (P < 0.001). Chi-square test value was 73.65, which is statistically very significant. Only 7 patients in the control group had hs-CRP>3mg/L.

Table 3 shows the relation of hs-CRP values with age, i.e., hs-CRP level is more in older age group (>40 years) and values are highest in the age group of 61-70 years and is less in young adults (<40 years of age).

Table 4 shows that there are 10 cases of NIHS scale with minor stroke, 33 cases of moderate stroke, 14 cases of moderate to severe stroke, and 3 cases of severe stroke. In minor stroke group patients, 7 cases had hs-CRP >3 mg/L and rest 3 cases had hs-CRP <3 mg/L. While with moderate to severe stroke of total 14 cases, all the cases had hs-CRP >3 mg/L.

Table 5 shows the relation of hs-CRP levels with mortality, i.e., mortality is more with the increasing hs-CRP levels. About 14 patients expired and 46 patients improved and discharged from the hospital. All the 14 patients who expired had hs-CRP levels more than 3 mg/L. There were no mortality in patients with hs-CRP level <3 mg/L.

**DISCUSSION**

Stroke kills around 5 million people each year. Cerebrovascular disease is the second most common cause of death worldwide. Male gender, older age, smoking, hypertension, diabetes, and hypercholesterolemia are the well-known risk factors for carotid disease as well as for stroke. An increasing body of evidence has linked inflammation with the pathogenesis of atherothrombotic stroke. CRP, one of the acute phase reactants, is an indicator of underlying systemic inflammation and a novel plasma marker of atherothrombotic disease. 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.

In the present study, hs-CRP was measured after CT confirmation and within 72 h of onset of symptoms, we found that hs-CRP was elevated in 54 (90%) patients out of 60 study group patients, which is statistically significant. A study by Winbeck et al. documented raised CRP in 127 patients without thrombolysis with a first ischemic stroke no more than 12 h after the symptom onset. They also noticed a CRP increase between 12 and 24 h after symptom onset predicts an unfavorable outcome.
Table 5: hs-CRP levels in relation with mortality

<table>
<thead>
<tr>
<th>hs-CRP levels</th>
<th>Mortality (n=14)</th>
<th>Improved and discharged (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP&lt;3 mg/dl (n=6)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>hs-CRP&gt;3 mg/dl (n=54)</td>
<td>14</td>
<td>40</td>
</tr>
</tbody>
</table>

P<0.001, hs-CRP: High sensitivity C-reactive protein

Napoli and Papa\(^23\) studied the risk of CRP in 72% of the patients (P < 0.0001) of 473 first-ever ischemic patients and suggested the CRP as an independent marker of ongoing chronic inflammatory process in atherosclerosis. Montaner et al.\(^26\) described a peak level of interleukin-6 after 24 h of symptom onset. Recently, Di Napoli\(^27\) observed an increase of CRP within 3 h after stroke compared with the prestroke value. Mahapatra et al.\(^28\) observed CRP value of 76 mg/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 the pathogenesis of ischemic stroke. Rathore et al.\(^29\) 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 6 mg/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 66.6% in subcortical infarction. It was clearly observed in our study that CRP was raised in all the subtypes of cerebral infarct without much difference.

In Van Der Meer et al.\(^30\) 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 which predicts myocardial infarction and stroke.

In our control study that involved age- and sex-matched healthy individuals, the rise of CRP level was noted in 12% of the cases. The prediction of myocardial infarction and stroke could not be done, as it needs a longer follow-up.

In a study by Masoti et al.,\(^19\) 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 ischemic stroke, in particular, for the short-term prognosis.

In the present study, there were 14 deaths, 10 were males and 4 were females, and in all of them, CRP >3 mg/L which is in line with that of the above study reiterating that elevated CRP levels were a bad prognostic indicator. The mortality rate was significantly higher in our patients with high hs-CRP. Studies in Nepal, Norway, and China had similar findings.\(^31-33\) Furthermore, the impact of CRP on mortality seems to be long term. A recent study showed that elevated CRP levels in young patients with ischemic stroke were associated with an increased risk of mortality, even 12 years after the CRP measurements.\(^34\)

**Limitations of the Study**

1. To assess the role of hs-CRP as a diagnostic indicator of acute ischemic stroke, it requires further studies with large sample size.
2. The clear prediction of future correlation between hs-CRP levels and acute ischemic stroke requires a longer follow-up.
3. Serial hs-CRP could be a better prognostic predictor than isolated sample of hs-CRP estimation, which was not done in this study.

**CONCLUSIONS**

1. In the present study, mean hs-CRP levels were significantly higher in patients with ischemic stroke when compared to controls.
2. Increased risk of morbidity and mortality was observed in cases with elevated hs-CRP levels within 72 h of ischemic stroke.
3. Hence, elevated hs-CRP levels can be considered as a poor prognostic indicator.

**REFERENCES**

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