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Research Article

SERUM hsCRP IN HEMORRHAGIC AND ISCHAEMIC STROKE: A DIAGNOSTIC MARKER?

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A B S T R A C T

Ischemic stroke is the most common type of stroke and accounts for about 80%–85% of stroke cases last few decades. hsCRP is considered a marker of low-grade vascular inflammation, which contributes to the development and rupture of atheromatous plaque. hsCRP level when measured prior to the onset of clinical diseases may be an independent predictor of the first ischemic stroke. The present case control study was conducted in Gauhati Medical College & Hospital, Guwahati, Assam from February 2016 to February 2017. The case and control groups consisted of 50 patients diagnosed with cerebrovascular accident with duration of onset within 72 hours and age and sex-matched 50 healthy individuals respectively. Estimation of Serum hsCRP was done using Vitros 5600 Autoanalyzer. The values obtained were statistically analysed. In the Unpaired t test between control and case groups, the two-tailed P value for serum hsCRP was <0.0001 (extremely significant). The mean hsCRP was significantly higher (p=0.035) in haemorrhage cases than in infarct cases.Thus, we can conclude that hsCRP level is increased in both ischaemic and haemorrhagic stroke. Furthermore, it was seen that hsCRP was more increased in hemorrhagic stroke rather than in stroke due to infarct. Therefore, it can be suggested that hsCRP might be used in differentiating between the two types of stroke.

INTRODUCTION

A Stroke, or Cerebrovascular Accident (CVA), is defined by this abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature.[1] Annually 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled.[2] India ranks second worldwide behind China, in terms of deaths from stroke, with 771,067 deaths occurring in 2002. The total DALYs lost per 1000 population in India ranges from 10-14 in different areas of the country.[2] Several factors are known to increase the liability to stroke. The most important of these are hypertension, atrial fibrillation, diabetes mellitus, cigarette smoking, and hyperlipidemia. Others, such as systemic diseases associated with a hypercoagulable state and the use of birth control pills, also contribute, but only in special circumstances.[3] After age, hypertension is the second most powerful, modifiable stroke risk factor. Risk of stroke rises proportionately with increasing blood pressure.

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A consensus has emerged that inflammation plays a decisive role in the patho-physiology of acute cerebrovascular accidents. Stroke triggers an inflammatory reaction that causes injury to the brain and progresses for several days. Data is accumulating which demonstrate that inflammation plays an important role in the development of secondary brain damage following stroke, and is associated with increased infarct size, neuronal loss and impaired clinical outcome. Ischemia is accompanied by increased free radical generation, which induces expression of inflammatory cytokines and chemokines. Cytokines up regulate the expression of adhesion molecules on endothelial cells, leukocytes and platelets, and mediate the interaction between endothelial cells and leukocytes, leading to infiltration of leukocytes into the brain parenchyma. Inflammatory cells contribute to brain damage by producing free radicals and other inflammatory related products that are toxic and lead to blood brain barrier dysfunction, edema and cell death.[4] It has been suggested that plasma CRP, as a measure of low grade inflammation can predict increased risks of coronary heart disease. CRP has consistently been observed to be elevated in the circulation of patients after acute ischemic stroke, even when factors known to be associated with raised CRP concentrations viz. Infection and atherosclerosis are taken into account.[5]

Before measurement of this novel vascular risk indicator is introduced into routine clinical practice, it is important to examine critically the predictive role of CRP, especially the

'highly sensitive' variety (hsCRP), in stroke risk. Ischemic stroke is the most common type of stroke and accounts for about 80%-85% of stroke cases last few decades (Geng). hsCRP is considered a marker of low-grade vascular inflammation, which contributes to the development and rupture of atheromatous plaque. hsCRP level when measured prior to the onset of clinical diseases may be an independent predictor of the first ischemic stork Whereas the predictive and prognostic role of hsCRP has been well documented and researched in the field of atherogenesis and coronary vascular disease, both in India and elsewhere, there is a definite dearth of such research in the field of acute cerebrovascular accidents. With this view and encouraged by the probability of finding a definite and stronger correlation between the risk of cerebrovascular accidents and serum levels of hsCRP than between cerebrovascular accidents and other traditional markers, the present study was undertaken.

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry, the Department of Medicine, the Department of Cardiology and the Department of Neurology of Gauhati Medical College & Hospital, Guwahati. This work was sanctioned by the Institutional Ethics Committee, Gauhati Medical College and was carried out from February, 2016 to February, 2017. The target subjects were divided into 2 groups. The case group contained patients diagnosed with cerebrovascular accident (brain stroke) with duration of onset within 72 hours diagnosed on the basis of history, clinical evaluation and evidences of brain stroke on CT scan brain. And the Control group (Healthy Controls) contained age and sex-matched controls drawn from healthy population.

The exclusion criteria were patients with intracranial haemorrhage (traumatic), intracranial infection mimicking stroke, intracranial tumour, history of recent clinical infection, major renal, hepatic, and cancerous disease, surgery or major trauma or invasive operations (e.g. angiography) within the last 3-6 months, signs and clinical evidence of acquired in-hospital infection. Previous infections were ruled out with an exhaustive medical history focusing on sign and symptoms of potential clinical infection during the last 4 weeks before stroke. Estimation of Serum hsCRP and CRP was done using Vitros 5600 Autoanalyzer. The blood pressure was measured using a Mercury Sphygmomanometer and a stethoscope by palpatory and auscultatory methods. After the biochemical estimations, the results obtained were statistically analyzed and compared between different groups of the study. Statistical analysis was performed using GraphPad InStat version 3.00 for Windows, GraphPad Software, San Diego California USA. All the statistical graphs were prepared using Microsoft Excel 2007.

RESULTS

In the normal control groups, comprising of 50 individuals, the mean age of the subjects was 58 years with a median of 58 years and with a standard deviation (σ) of ± 13.21 years. In both the case and control groups, 16 were females and 34 were males. Out of the 50 cases, 13 cases were haemorrhagic stroke whereas 37 cases were ischaemic stroke and out of the 50 cases, 27(54%) patients had a history of smoking. In the Unpaired t test for systolic BP between normal and case groups, the two-tailed P value is <0.0001 (extremely significant), t = 24.814 with 98 degrees of freedom, the mean being 112.84 mmHg and 159.72mmHg for the control and case group respectively.. In the Unpaired t test for diastolic BP between normal and case groups, the two-tailed P value is <0.0001 (extremely significant), t=15.954 with 98 degrees of freedom, the mean being 73.88 mmHg and 90.24mmHg for the control and case group respectively. The mean RBS in the control and case groups were 83.64±17.67 and 101.1±13.33 respectively, p value being <0.0001 considered extremely significant. The CRP levels in the control and case groups were 5 mg/L and 36.8 mg/L ± 10.6 respectively. The problem arises from the fact that the lower reportable range of CRP is 5 mg/L. Any value below this is still reported as 5 mg/L. So the whole range of 50 normal subjects had a CRP value of 5 mg/L. The serum hsCRP in the control and case groups were 4.4 ± 10.14 mg/L and 37.53 ± 16.19 mg/L respectively and the p value was <0.0001 considered extremely significant. Serum hsCRP in the hemorrhagic and ischaemic groups were 47.15±7.87mg/L and 39.86 ±11.15 mg/L respectively, p value being 0.0350 considered significant.

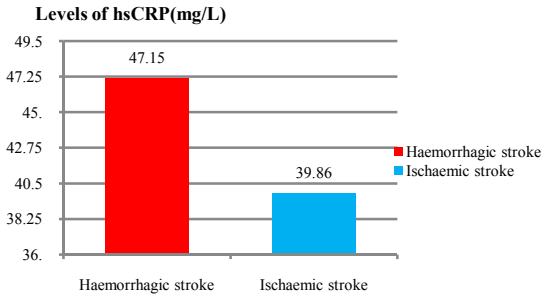

Figure 1 Showing hsCRP levels in hemorrhagic and ischaemic stroke

DISCUSSION

Men have a higher incidence of stroke as evident from the present study. This may be ascribed to a number of factors. Firstly, the reason might be the positive effects of estrogen on the cerebral circulation[6], in case of females. A second factor might be blood pressure. A study by Reckelhoff[7] has shown that blood pressure values are higher in men than women of similar ages.

In the present study, the average blood pressure of the patients was 160/90 mm Hg, which was extremely significantly high as compared to that in normal age and sex-matched controls (p<0.0001). This signifies that the frequency of hypertension is higher in stroke patients than in controls.

The existence of hypertension as a risk factor for development of stroke has been stressed upon by many researchers. Hadjiev *et al*[8] have found a high incidence of hypertension in stroke patients (65.8%, p = 0.0293) in a study comprising 500 volunteers followed up for 2 years. Similarly, Hart *et al*[9] in their 20 years follow up study of men and women in Scotland have reported an extremely significant association (p<0.0001) between hypertension and stroke risk. These findings tally with those of the present study.

Hypertension is a central risk factor for cerebrovascular events. Basic data suggest that increasing levels of blood pressure may stimulate a proinflammatory response and that endothelial inflammation may also herald the changes in arterial wall that characterize the hypertensive state. Hypertension, at least in the case of intracerebral haemorrhage, may lead to spontaneous rupture of a small

penetrating artery deep in the brain. The small arteries seem most prone to hypertension-induced vascular injury. The haemorrhage may be small or a large clot may form and compress adjacent tissue, causing herniation and death. Blood may dissect into the ventricular space, which substantially increases morbidity. Hypertension also accentuates the progression of atherosclerosis that has an inflammatory component which plays an integral role in the pathogenesis of stroke[10].

In the present study, the average Serum CRP level in patients was 36.80 ± 10.6 mg/L. The mechanisms by which CRP may be associated with stroke remain uncertain. CRP may be an 'epiphenomenon', or marker of the inflammation that is present in atherosclerosis but not directly responsible for it. Alternatively, growing evidence suggests that CRP may play a direct or causative role in atherosclerosis.[11,12]

In apparently healthy persons, blood CRP levels are below 5 mg/L. For conventional CRP assays, test values are typically considered to be clinically significant at levels above 10 mg/L. With these assays, the level CRP was detectable only during significant inflammation in most individuals. This limits the use of conventional CRP as a predictive marker in stroke. However, hsCRP assays have allowed studies to be performed on individuals who are apparently healthy. Several reports now indicate that hsCRP concentrations are elevated in individuals who are at high-risk of developing coronary artery and cerebrovascular events. Indeed, the elevated hsCRP may be found years before first detection of the vascular problems.[13] So hsCRP scores over conventional CRP as a predictive marker in stroke.

Elkind *et al*[14] in their study of levels of acute phase reactants in stroke have found that levels of hsCRP were significantly higher in stroke patients than in stroke-free patients ($p<0.05$). Moreover, there was no evidence of a time trend in levels of hsCRP during 28 days of follow-up of stroke patients. It thus appears that if levels of hsCRP increase at the time of stroke, they remain elevated for at least one month. This finding is also corroborated by Soliman *et al*[15] who observed in their study that there was a highly significant increase in serum hsCRP level in the first 48 hours after stroke onset. Similar observations of elevated hsCRP levels have also been reported by Talreja Mishra *et al*[16] in their study, who found a highly significant increase in level of hsCRP ($p<0.001$) in 40 patients with stroke than in normal age and sex-matched subjects. In a prospective case-referent study Andersson *et al*[17] demonstrated that hsCRP, divided into three groups, i.e. <1, 1-3 and >3 mg/L, is significantly associated with the risk of first-ever stroke. This finding is significant because this establishes the first ever reference range for hsCRP in relation to cerebrovascular risk assessment and it is the same as that for cardiovascular risk assessment.

Stroke is a heterogeneous multifactorial disorder. Acute stroke is thought to be caused largely by inflammation-mediated destabilization and rupture of atherosclerotic lesions. It is known that inflammation plays an important role in the pathogenesis of atherosclerosis. Inflammatory response injury is considered to be related to the initiation, growth, and complications of the atherosclerotic plaque, and elevation of the hsCRP level according to the progression of atherosclerosis has been considered to be a consequence of inflammation in the arterial wall. Recently, it was also reported that hsCRP itself, as a mediator of inflammation, may cause progression of arterial wall damage[18].

Serum hsCRP in the hemorrhagic and ischaemic groups were 47.15 ±7.87mg/L and 39.86 ±11.15 mg/L respectively, p value being 0.0350 considered significant. These findings corroborates with findings of Choudhury *et al*[19] that hsCRP is strongly associated with acute ischaemic stroke and is an independent predictor as well. As per Jayabhaskar *et al*[20], hsCRP is raised in both ischemic and hemorrhagic stroke. The rise in hsCRP is less in small lesions compared to that of large lesions and the levels are high in diseased than in survivor group. In larger lesions, hsCRP levels are more compared to the smaller lesions and the levels correlate with the size of the lesion. This is supported by the study of Youn CS, *et al*[21] who states that raised hsCRP levels correlate with the volume of the affected tissue in stroke. PinkyTalreja Mishra *et al*[16] also concluded that increased levels of hsCRP correlate with large infarct and large bleeds and severe neurological deficits[20]. As per Jayachandra *et al*[22], hsCRP levels are increased in cases of stroke – ischemic as well as hemorrhagic, but more in hemorrhagic stroke suggesting more severe inflammatory response. Furthermore, the increased levels correlated with larger volume bleed and infarct size, severe neurological deficit, and worse outcome.

CONCLUSION

From this study we conclude that hsCRP level is increased in cases of stroke – ischaemic as well as haemorrhagic, suggesting an inflammatory response in acute stroke. Furthermore, the hsCRP levels were more in haemorrhagic cases than in ischaemic stroke. As we had a small sample size, a larger study is needed to endorse our observations, and to analyse further about association between hsCRP level and haemorrhagic stroke occurrence. A larger study needs also focus on whether hsCRP level needs to be included as a health screening protocol.

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