Role Of High Sensitivity C-Reactive Protein (Hs Crp) As A Marker Of Ischemic Stroke

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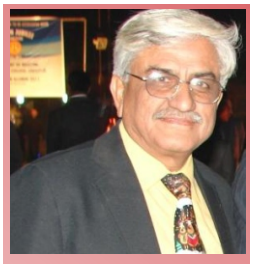
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Abstract

Background: High Sensitivity C-reactive protein (hs-CRP) is an indicator of underlying systemic inflammation and a novel plasma marker for atherothrombotic disease. The use of hs-CRP in clinical practice is rapidly expanding, particularly in the areas of cardio & cerebrovascular risk stratification and management which are major health concerns in India.

Aims: 1.To study the association of hs-CRP levels in patients of acute ischemic and haemorrhagic stroke.2. To study the Correlation of hs-CRP levels and severity of stroke.

Settings and Design: Prospective, single arm observational, validation study.

Methods and Material: 52 patients aged >25, CT/MRI Brain established cases of 1st Cerebrovascular (CVA) , within 24 hours of onset were included. hs CRP levels were gauged by Nephelometry. Severity was assessed by Glasgow coma scale (GCS) and correlated with hs-CRP levels. Patients with comorbidities causing raised CRP levels were excluded

Results: There was male predominant presentation of Stroke with sex ratio of 1.89:1 .Age of presentation was in 5th to 7th decades of life, mean age of 58 years. Out of total 52 patients, 40 (76.93%) were of ischemic stroke (IS) and 12 (23.07%) were of haemorrhagic stroke (HS). Commonest presentation was left hemiparesis both stroke types. hs CRP levels were significantly higher in IS as compared to HS (p value <0.005). hs CRP levels >0.4mg/dl were suggestive of IS with 90.00 % sensitivity and 91.67 % specificity ($p < 0.0001$). Higher hs CRP levels were associated with poor GCS in IS patients but same was not the case with HS.

Conclusions: hs-CRP levels were significantly higher in IS patients as compared with that of HS. hs-CRP showed a positive correlation with the severity of IS. Thus in patients of acute stroke a low cost, simple investigation, hs CRP, can be highly sensitive independent biomarker for predicting IS and its severity.

Key-words: Hs CRP, Ischemic stroke, prognostic marker.

THESIS SUMMARY

Introduction

Cerebrovascular diseases include some of the most common and devastating disorders like ischemic or hemorrhagic stroke, cerebrovascular anomalies such as intracranial aneurysms and arterio venous malformations (AVMs).

A Stroke is rapidly developing clinical symptoms and /or signs of focal and at times global loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. Most cerebrovascular diseases are manifest by the abrupt onset of a focal neurologic deficit, as if the patient was "Struck by the hand of God."

When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient: this is called a transient ischemic attack (TIA).

Developing countries like India are facing a double burden of communicable as well as non-communicable diseases. Stroke is one of the leading causes of death and disability in India. The estimated age adjusted prevalence rate of stroke range, 84-262/100,000 in rural and

334-424/100,000 in urban areas [1].

Two thirds of these individuals live in low-and middle income countries such as India. About 80per cent of all first ever-in-life time strokes are ischemic, 10 per centre due to primary intracerebral haemorrhage, and in remainder there is uncertainty.

It is the second commonest cause of death and fourth leading cause of disability worldwide. Low and middle-income countries account for 85.5% of total stroke deaths worldwide and the number of disability-adjusted life years in these countries was approximately seven times that in high-income countries [2].

Of all the causes of cerebrovascular disease, ischemic cause (atherothrombosis) is by far most important. This phenomenon involves large and medium size vessels that can lead to ischemic cardiac, brain damage or infarction. Following this, an inflammatory process might be initiated, and result in existence of inflammatory cells of innate immunity and production of acute phase proteins such as C-reactive protein in a first few hours of stroke [3].

However treatment of underlying disease process and preventing its complications presents an enormous challenge and opportunity simultaneously. There appears to be one inflammatory marker which has a superior ability to predict inflammation and is now considered as a golden marker for inflammation. This golden marker is High Sensitivity C-Reactive Protein (hs CRP).

C - reactive protein (CRP) is an acute phase reactant synthesized majorly in liver. It is described as systemic marker of inflammation and is a predictor of morbidity and mortality independent of LDL cholesterol level. hs CRP is now the forerunner in the hunt for inflammatory markers and is subject to intensive research in numerous studies worldwide. CRP is easily and inexpensively measured and standardized. Because CRP levels are stable over long period of time, and demonstrate no circadian variation. This makes measuring CRP more convenient. The recent emphasis in cardiovascular medicine on "high sensitivity" or "highly sensitive" CRP, abbreviated as so called hs-CRP, is not a different analyse from "conventional" CRP. The "high sensitivity" refers simply to the lower detection limit of essay procedure being used.6

After acute stroke an increase level of CRP measured at discharge predicts unfavourable outcome and recurrence [4].CRP fulfils most of the requirements of a new risk and prognostic predictor.

The present study attempts to investigate role of high sensitivity C-reactive protein as a biomarker in acute ischemic stroke. Also, to study hs CRP levels as a serological marker in the evaluation of severity of acute ischemic stroke in first 24 hours and to differentiate it from haemorrhagic stroke.

Primary aim was to analyse hs CRP as a biomarker to differentiate Ischemic Stroke from haemorrhagic Stroke. Other secondary objectives were to study the clinical features of an acute stroke patient, hs CRP levels as a serological marker for evaluation of severity of acute ischemic stroke, ESR and hs CRP levels correlation.

AIMS:

1.To study the association of hs-CRP levels in patients of acute ischemic and haemorrhagic stroke.

2. To study the Correlation of hs-CRP levels and severity of stroke.

Methods And Material

Study was carried out on 52 indoor patients admitted in Department of Medicine, NSCB Medical College and Hospital, Jabalpur, from September 2011 to October 2012.

Method Of Collection Of Data

Case Selection

This was single arm observation study of patients with first ever episode of Acute Stroke. Stroke was defined according to WHO definition i.e. 'the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin. Detailed history and clinical examination was done, the diagnosis was established by CT/MRI Brain and along with routine haematology and biochemistry hs CRP levels were assessed.

Inclusion Criteria for patient inclusion were:

1. All patients aged >25 years with first ever CT/MRI proven Acute Stroke admitted within 24 hours of symptoms onset.

Exclusion Criteria included:

1. Patients with febrile illness.
2. Patients of Connective Tissue Disorders.
3. Patients of Ischemic Heart Disease.
4. Patients of Diabetes Mellitus.
5. Pregnant females.
6. Patients with Hyperlipidemia.
7. Chronic Smokers.
8. Diagnosed Cases of Hypertension, patients presenting with acute reactionary rise of blood pressure but normotensive during further stay in hospital were included in the study.

Protocol Of The Study

For every selected case, a detailed history was recorded including history regarding exclusion criteria following which a detailed clinical examination was performed. Glasgow Coma Score (GCS) of all patients was assessed on presentation in the hospital.

Venous Blood Sampling was done and samples were collected in air-tight Bar-coded Gel Tube, containing Patient's identity details, fed online by Thyrocare Service Providers. After collection, samples were centrifuged, refrigerated (at 5-6 degree C) until transported to the Centralized Processing Laboratory (CPL). Then it was ensured that all samples were transported in Chiller Boxes (Polystyrene Boxes) with intact leak proof packaging having guidelines laid down by WHO- IATA maintaining the cold chain throughout.

Once it was received at the laboratory it was thoroughly checked for sample acceptance criteria like clotting, temperature at receipt, haemolysis, leakage, wrong vial, wrong barcode etc.

These analyser (SysmexSF-3000 Nephelometer) was calibrated and samples were processed.

Results

Statistical analyses were performed using STATA 12 for Windows. Categorical data are presented as frequency counts) and compared using the chi-square or Fisher's exact statistic as appropriate. Continuous data are presented as means (± standard deviation) and compared using the t-test or analysis of variance as appropriate.

Mean age of presentation was 58 years, 55 years in males and 64 years in females. Majority of the patients were in the age group of 45 to 65 years. There were total of 34 (65.38%) males and 18 (34.62%) females, with male to female ratio of 1.89:1.

Out of total 52 patients, 40 (76.93%) were of ischemic stroke and 12 (23.07%) were of haemorrhagic stroke. In ischemic CVA group 26(65%) were male and 14 (35%) female, whereas in haemorrhagic CVA group 8(67 %) were male and 4 (33%) were female . Majority (60%) of ischemic Stroke patients was in the age group of 46-65 years, but in haemorrhagic stroke 7 (58 %) patients belonged to 36-55 age groups. 31% (16) patient had right hemiparesis, 22 (42.3%) left hemiparesis, 6 (11.5%) quadriparesis, 19 (36.5%) had speech disturbances .8 patients had various other manifestations on presentation (monoparesis, headache, seizure activity etc.) Left Hemiparesis was commonest presentation in both haemorrhagic (50%) and ischemic stroke (40%).

Mean Age and Blood Pressure was higher in hemorrhagic Stroke. Mean Hb., Total Cholesterol, HDL,LDL,

Mean ESR levels were higher in ischemic stroke patients (34.95mm 1st hour) as compared to hemorrhagic stroke (29.9195mm 1st hour). But this came out to be statistically insignificant with p value of >0.05 [Figure 4]. 21 (40%) patients presented with GC Score of 13-15, 15 (29%) with 9-12 and 16 (31%) with GCS of 3-8.Patients in the age group of 46-65 had maximum no.(54%) of stroke in the study group, and they presented with better GCS than their younger and elder corresponding groups.60% of age 36-45 and 63 % of age 66-75 had GCS in the range of 3-8.

Patients with ischemic Stroke had mean hs CRP of 0.738 mg/dl with SD of ±0.2747885 as compared to hemorrhagic Stroke patients who had mean hs CRP levels 0.326 with SD of ±0.107647. With t value of 5.0416 and p value of < 0.0001 there was very high statistical significance in the difference of mean value of hs CRP in two Stroke groups .

Mean hs CRP in all cases was 0.643 mg/dl , 0.327 in haemorrhagic stroke and 0.738 in ischemic stroke. Mean hs CRP levels in every GCS severity category were higher in Ischemic Stroke as compared to haemorrhagic stroke. {p value was< 0.0001 in poor GCS (3-8), p < o.o5 in GCS 9-12 and p> 0.05 in GCS 13-15.}

ANOVA analysis results for relation of severity of stroke by GCS and hs CRP levels. In ischemic Stroke GCS groups revealed that there was strong correlation in severity of stroke and increasing hs CRP levels. But same was not applicable to the haemorrhagic stroke with form factor 0.37 and p >0.05.

Discussion

Stroke is a devastating global health problem with rising incidence in developing countries like India. Stroke is now often referred to as a "brain attack" to denote the fact that it is caused by a lack of blood supply to the brain, very much like a "heart attack" is caused by a lack of blood supply to the heart. The term brain attack also conveys a more urgent call for immediate action and emergency treatment by the general public.

C-reactive protein was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C polysaccharide of pneumococcus.[5] The mid-1990s, immunoassays for C-reactive protein (hs-CRP), with greater sensitivity than those previously in routine use, revealed that increased CRP values, even within the range previously considered normal, strongly predict future coronary events. These findings triggered widespread interest, especially, remarkably, in the US, where the clinical use of CRP measurement had been largely ignored for about 30 years.

In addition, the Framingham Heart Study as provided evidence that hsC-Reactive Protein independently predicts thrombotic events in the cerebral circulation. Finally, within the Framingham Heart Study, data has also been presented that demonstrates the ability of hsC-Reactive Protein to predict stroke risk independent of the Framingham co-variates. After adjustment for age, smoking, blood pressure, diabetes and total cholesterol and HDL, LDL-cholesterol, the risk of future stroke in the Framingham heart study increased 25% in men (p = 0.036) and 29% in women (p = 0.0087) for each increasing quartile of hsC-Reactive Protein.

Thus, measures of inflammation such as hsC-Reactive Protein seem to provide independent and complementary information on risk beyond that achievable by direct measures of atherosclerotic burden [6].

Atherosclerosis literally means hardening of arteries. Atherosclerosis is characterized by intimal lesions called atheromas (also called atheromatous or atherosclerotic plaques) that protrude into vessel lumens. Response-to-injury hypothesis the model views atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury. Lesion progression occurs through the interaction of modified lipoproteins, monocyte-derived macrophages, and T lymphocytes with the normal cellular constituents of the arterial wall [7].

It is a well-known fact that earlier lesions in atherosclerosis exhibit a feature of inflammation and immune reaction by the presence of monocytes, macrophages, foam cells and T-lymphocytes and the presence of VCAM, but as lesions progress they become more cellular with more lipid retention, still later they exhibit phenomenon of proliferation, myeloproliferation with formation of variable thickening of fibrous cap of atherosclerotic plaque. The primary pathology is seen in the endothelium with either structural disruptions or functional alteration. The initial trigger, which alters endothelial normal function, is still debatable. It may be LDL cholesterol or indirect influence of infections or constituents of Tobacco smoke, atmospheric

pollution or hypoxia or homocystein or mere shear stress or abnormal glucose metabolism or lipid metabolism.

Pro-inflammatory cytokines released by inflamed endothelium facilitate interaction of endothelial cells with circulating leucocytes and may then contribute to the development and progression of atherosclerosis [8].

Recent investigations of atherosclerosis have focused on inflammation, providing new insight into mechanisms of disease. Inflammatory cytokines involved in vascular inflammation stimulate the generation of endothelial adhesion molecules, proteases, and other mediators, which may enter the circulation in soluble form. These primary cytokines also induce production of the messenger cytokine interleukin-6, which stimulates the liver to increase production of acute-phase reactants such as C-reactive protein. In addition, platelets and adipose tissue can generate inflammatory mediators relevant to atherothrombosis. Inflammation is present during all stages of atherogenesis and is intimately linked with atherosclerotic plaque formation and rupture. With increasing recognition that inflammation plays a significant causal role in atherosclerosis, assessment of systemic inflammation has become important in overall risk stratification. While a number of circulating markers of inflammation correlate with IHD and CVA risk, C-reactive protein (CRP) has emerged as one of the simplest and most sensitive [9].

The median circulating concentration of C-Reactive Protein is 0.8 mg/l.Normal range may be as low as 0.07 mg/l and in apparently healthy individuals, 90% have less than 3 mg/l ,and 99% have less than 10 mg/l48 During inflammation the plasma concentration of C-Reactive Protein can rise upto 10000 fold[10].

The American Heart Association and US Centers for Disease Control and Prevention have defined hs CRP Level risk groups as follows (for cardiovascular risk):

Low risk	:	less than 1.0 mg/L
Average risk	:	1.0 to 3.0 mg/L
High risk	:	above 3.0 mg/L

High-sensitivity C-reactive protein (hs-CRP) is not only a marker of inflammation but also a prognostic factor for ischemic stroke. The objective of our study was to investigative the association between hs-CRP levels and immediate outcomes of patients with stroke. Various studies have revealed that Elevated hs-CRP in patients with ischemic stroke is an independent predictor of poor prognosis [11] as shown in this study. Studies also suggest that the antioxidant activity of plasma may be an important factor that provides protection from ischemic stroke [12]. hs CRP concentrations can be used as a clinical screening tool to identify individuals with higher risk of ischemic stroke.

This study showed that hs CRP levels were significantly higher in ischemic stroke as compared to haemorrhagic stroke. hs CRP levels >0.4mg/dl were suggestive of ischemic stroke with 90.00 % sensitivity and 91.67 % specificity. Higher hs CRP levels were associated with poor Glasgow Coma Score in ischemic stroke patients but there was no association between GCS and hs CRP levels in haemorrhagic stroke patients.

In our study hs-CRP levels were significantly higher in ischemic stroke patients as compared with that of haemorrhagic stroke. Also, levels of hs-CRP showed a positive correlation with the severity of Ischemic Stroke.

Thus in patients of acute stroke a low cost, simple investigation, hs CRP, can be highly sensitive independent biomarker for predicting ischemic stroke and its severity.

Furthermore, hs CRP measurement might be a useful tool for identifying high-risk patients in order to plan aggressive diagnostic protocols and preventive therapies like life style modifications and statins to reduce the incidence of ischemic stroke.

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