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Prognostic Influence the Levels of C-Reactive Proteins in the Outcome of Stroke of Atherothrombotic Etiology-A Prospective Study in Acute Ischemic Stroke Patients

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Abstract: It is well known fact that CRP measurements may be helpful in grading patients into high risk and low risk category for predicting future cardiovascular and neurovascular events. The current research focused the evaluation and the predictive value of hs-CRP (high sensitivity C – Reactive Protein) in relation to the ultimate functional outcome in first ever ischemic stroke after 4 weeks and to correlate the hs-CRP levels with various risk factors. A total number of 50 subjects were as included in the study. hs-CRP vs followings like hypertension, diabetics, GOS Score and GOS Groups were studied. hs-CRP levels vs hypertension was found to be statistically significant but both diabetics and non-diabetics results were statistically non significant. The CRP profile in hs-CRP vs GOS Score and hs-CRP vs GOS Group followed as per the quantia CRP US Glasgow Outcome Scale (GOS). Knowledge of the prognostic influence of the levels of CRP in the outcome of stroke of atherothrombotic etiology helps the clinician to offer realistic expectations to the families of stroke victims.

Key words: CRP measurements · GOS · Hypertension · Diabetics · GOS Score and GOS Groups

INTRODUCTION

There is growing evidence that C-reactive protein (CRP), a peripheral marker of inflammation, is also a marker of generalized atherosclerosis [1]. In recent years, there has been increasing evidence which shows strong links between inflammation and the pathogenesis of atherothrombotic stroke. Acute phase proteins have been implicated to play roles both during acute and chronic inflammatory processes in different diseases including ischemic stroke [2]. The onset of cerebral ischemia triggers a cascade of pro-inflammatory molecular and cellular events [3]. Clinical studies suggest that the strength of this acute response is important in early and late clinical outcomes, early clinical worsening and extent of brain damage.

Variables that are predictors of adverse stroke outcome include erythrocyte sedimentation rate and levels of CRP, interleukin-6, tumour necrosis factor-α and intercellular adhesion molecule-1. Current data indicate that inflammation serves to fuel atherosclerosis and can act as the link between atherosclerosis and atherothrombosis [4]. Inflammatory factors play an important role in the pathogenesis of ischemic stroke. The levels of acute phase proteins such as a fibrinogen, CRP, ferritin increase after acute ischemic stroke. These findings support a possible role of an inflammatory stimulus in the acute ischemic stroke. The WHO has recently set international reference standard for the use of highly sensitive CRP assays [12]. This has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events.

The predictors of stroke outcome are (a) Demographic factors like age, gender, race / ethnicity; (b) Cerebrovascular risk factors include the previous stroke and atrial fibrillation; (c) Clinical findings are level of consciousness and gaze deviation, blood Pressure and temperature; and finally (d) the laboratory findings includes Glycine and glutamate, S-100,neuron-specific enolase and serum glucose [13]. High Sensitivity CRP (hs-CRP) assays became available, allowing assessment of serum concentrations at the lower end of its distribution.

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In the subsequent years, hs-CRP levels far beneath the cut-off value, indicative of an immediate-phase response, predicted the risk of cardiovascular, cerebrovascular disease, diabetes mellitus and cognitive impairment. CRP the first acute-phase protein to be described and is an exquisitely sensitive systemic marker of inflammation and tissue damage [5]. It is thought to assist in complement binding to foreign and damaged cells and affect the humoral response to disease. It is believed to play an important role in innate immunity, as an early defense system against infection and thus measuring and charting CRP values can prove useful in determining disease processes or the effectiveness of treatment [6]. The current research focused the evaluation and the predictive value of hs-CRP (high sensitivity C – Reactive Protein) in relation to the ultimate functional outcome in first ever ischemic stroke after 4 weeks and to correlate the hs-CRP levels with various risk factors.

MATERIALS AND METHODS

The study protocol was approved by institutional ethics committee of AarupadaiVeedu Medical College, Pondicherry. The research was a descriptive, prospective carried out on the proven cases of stroke patients admitted in AarupadaiVeedu Medical College Hospital, Pondicherry from September 2011 to September 2012.

The protocol was explained to the patients and an informed consent was obtained from the participants. The following were the inclusion criteria; all patients who presented within 48 hrs of onset of stroke and admitted in ICU of AarupadaiVeedu Medical College Hospital. The exclusion criteria were patients with, subdural haemorrhage, subarachnoid haemorrhage and intracerebral haemorrhage (resulted from CT scan), above 70 years of age, known active infection and neoplastic conditions, rheumatic heart disease and collagen vascular disease, actively smoking at the time of study and previous history of transient ischemic attack or reversible ischemic neurological deficit were excluded.

Study Method: From September 2011 to September 2012 50 patients who were diagnosed with acute ischemic stroke were enrolled into the study. That the stroke was an ischemic and confirmed by CT scan. As soon as the patients were admitted within 48 hrs of onset of stroke, serum samples were taken for hs-CRP estimation. And further the age, time of sample (hs-CRP) collection & time interval of (hs-CRP) collection, cholesterol levels, a correlation between the hs-CRP **vs** Age group; sex, smoking condition and alcohol consumption were also noted. The results were compared with hs-CRP vs Hypertension; hs-CRP vs Diabetics; hs-CRP vs GOS Score and hs-CRP vs GOS group. The standard guidelines for the treatment of acute ischemic stroke were followed. None of the patients received any thrombolytic treatment. They were treated only with anti-edema measures and anti-platelets such as aspirin alone and with good nursing care and physiotherapy. The patients were reviewed after 4 weeks after onset of stroke and were stratified using the Glasgow Outcome Scale (GOS) (7). The data's were statistically done by Chi- Square test using Windows-based SPSS statistical package (Version 19.0).

Measurement of hs-CRP: The Quantia CRP-US (from Tulip Diagnostics Pvt. Ltd) was used for the measurement of hs-CRP by turbidimetric immunoassay, for ultrasensitive determination in human serum based on the principle of agglutination reaction. The reagent was designed to measure CRP concentrations in the range of 0.015-1.0 mg/dl in a linear form. The human serum specimen was mixed with quantia CRP US latex reagent and activation buffer and allowed to react. Presence of CRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured at wavelength between 505-578 nm. The increase in turbidity corresponds to the concentration of CRP in the test specimen. The quantia CRP VS GLASGOW OUTCOME SCALE (GOS) specifies followings were the scoring techniques.

Score	Condition
•	Indicates death
•	A vegetative state (the patient is unable to interact with the environment)
•	Severe disability (the patient is unable to live independently but can follow commands)
•	Moderate disability (the patient is capable of living independently but unable to return to work or school)
•	Mild or no disability (the patient is able to return to work or school)

The favorable outcome was defined as a score of 4 or 5 and unfavorable outcome as a score of 1, 2, or 3.

RESULTS AND DISCUSSION

CRP has a direct relationship with other cardiovascular risk factors, like smoking, alcohol consumption, hypertension, diabetes and cholesterol. Thus CRP levels are the marker for preclinical cardiovascular disease.CRP profile in hypertensives showed that 60% were hypertensives 10% of CRP < 10.1 mg/L and 50% has ≥ 10.1 mg/L. Out of the 20 non-hypertensives the CRP levels were 20% of CRP < 10.1 mg/L and 20% have CRP ≥ 10.1 mg/L (Table 1). Relation of hs-CRP levels and hypertension was found to be statistically significant with the various studies conducted using hs-CRP as a prognostic indicator of acute ischemic stroke. Our research agrees with previous studies indicating a statistically significant correlation between high BP and hs-CRP [8, 9].

The CRP profile in both diabetics and non-diabetics results was statistically non significant;40% of diabetics, 8% has CRP values < 10.1 mg/L and 32% had CRP ≥ 10.1 mg/L. Out of the 30 non-diabetics (60%), 22% had CRP < 10.1 mg/L and 38% had CRP ≥ 10.1 mg/L (Table 2). Thus the correlation between hs-CRP levels and diabetes was not statistically significant and the results were in contrast to many of the previous studies. This may be because of the small sample size and also because of the fact that our study included only acute ischemic stroke patients; it was not done exclusively on diabetic with acute ischemic stroke patients [9, 10].

The correlation between hs-CRP levels measured within 48 hours of onset of stroke to that of the functional outcome of the patient at the end of 4 weeks (using GOS) was carried out. Patients with CRP levels < 10.1 mg/L has a condition either death or a vegetative state (the patient is unable to interact with the environment) when compared to patients with levels ≥ 10.1 mg/L has either severe disability, moderate disability or mild or no disability. Out of the 50 cases enrolled in the study, 70% were CRP values ≥ 10.1 mg/L and 30% has CRP < 10.1 mg/L (Table 3). Out of the 35 cases with CRP ≥ 10.1 mg/L, 4% had GOS score of 1, 26% cases had GOS score of 2, 34% cases had GOS score of 3. On the other hand, of the remaining 15 cases with CRP < 10.1 mg/L, none had a GOS score of 1, 2 or 3. 14% cases had a GOS score of 4 and 16% cases had a GOS score of 5 (Table 4). As 2 cases had very high hs-CRP levels they died.

The major differences between our study and others were we have focused only hs-CRP levels and no other acute phase reactants like fibrinogens, we assessed the outcome of patients with acute ischemic stroke at the end of four weeks and not at the end of one year, we measured the CRP levels only within 48hrs after the onset of ischemic stroke and not at the end of four weeks or at the time of discharge. All above by keeping in scientific view that the prognostic importance of the 48-hrs concentration of CRP may be partly related to the extent of ischemic necrosis and partly to the unknown individual determinants of the intensity of the acute phase reactants. CRP is a very vital indicator of the inflammatory states during the acute phase of an ischemic stroke [11].

Table 1: Relation of hs-CRP levels with Hypertension

	hs-CRP(mg/L)		
Hypertension	<10.1(0)	≥10.1(1)	Total
Yes(1)	5 (10%)	25 (50%)	30 (60%)
No(0)	10 (20%)	10 (20%)	20 (40%)
Total	15 (30%)	35 (70%)	50 (100%)

Table 2: Relation of diabetes with hs-CRP levels

	hs-CRP(mg/L)		
Diabetics	<10.1(0)	≥10.1(1)	Total
Yes(1)	4 (8%)	16 (32%)	20 (40%)
No(0)	11(22%)	19 (38%)	30 (60%)
Total	15 (30%)	35 (70%)	50 (100%)

Table 3: hs-CRP vs GOS Score

	hs-CRP(mg/L)		
GOS Score	<10.1(0)	≥10.1(1)	Total
1	0 (0%)	2 (4%)	2 (4%)
2	0 (0%)	13 (26%)	13 (26%)
3	0 (0%)	17 (34%)	17 (34%)
4	7 (14%)	3 (6%)	10 (20%)
5	8 (16%)	0 (0%)	8 (16%)
Total	15 (30%)	35 (70%)	50 (100%)

Table 4: hs-CRP vs GOS Graph

	hs-CRP(mg/L)		
GOS Group	<10.1(0)	=10.1(1)	Total
Favourable(F)	15 (30%)	2 (4%)	17 (34%)
Unfavourable(UF)	0 (0%)	33 (66%)	33(66%)
Total	15 (30%)	35 (70%)	50 (100%)

CONCLUSIONS

Knowledge of the prognostic influence of the levels of CRP in the outcome of stroke of atherothrombotic etiology helps the clinician to offer realistic expectations to the families of stroke victims. Thus CRP measurements may be helpful in grading patients into high risk and low risk category for predicting future cardiovascular and neurovascular events.

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