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A Study on High Sensitivity Crp as a Short Term Prognostic Factor in Acute Ischemic Stroke

Appandraj. S^{1*}, Sivagamasundari. V² and N. Jeeva³

¹Associate Professor, Department of Medicine, Melmaruvathur Adiparasakthi Institute of Medical Sciences & Research, Melmaruvathur Tamil Nadu – 603 319

²Senior Resident, Department of paediatrics, Melmaruvathur Adiparasakthi Institute of Medical Sciences & Research, Melmaruvathur Tamil Nadu – 603 319

³Professor of Therapeutics, Thanjavur Medical College, Thanjavur -613001

*Corresponding Author E-mail:

ABSTRACT

INTRODUCTION: Stroke by definition is a syndrome of rapidly developing clinical signs of focal disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than vascular origin. Recent research has shown that an inflammatory reaction is triggered within the hour in the brain tissue injured by an ischemic stroke and continues in the days following the appearance of symptoms and that this reaction contributes to neuronal damage. Increased CRP levels are accepted as a sensitive but non-specific marker of the acute inflammatory conditions. **Aim of the study:** To study the hs CRP level in acute ischemic stroke and its association with short term prognosis. **MATERIALS AND METHODS:** Totally 52 patients admitted within 48 hours of onset of first ischemic stroke were included in the study. The detailed history regarding the risk factors like diabetes, coronary artery disease, hypertension, hyperlipidaemia, smoking, and alcohol use were elicited from the patient. Standard approved protocol was used for all patients to measure the hs-CRP level. Analysis was done by Nephelometric method utilizing latex particles coated with CRP monoclonal antibodies. **CONCLUSION:** The hs -CRP level is increased in all patients after acute ischemic stroke. The hs- CRP level strongly correlates with short term outcome in patients after first ever ischemic stroke.

Key words: Acute Ischemic Stroke, hs-CRP, Diabetes, coronary artery disease.

INTRODUCTION

Acute ischemic stroke develops as a result of sudden interruption in the focal cerebral blood flow. The cause of the stroke is an embolic or thrombotic occlusion in 70-80% of patients with severe symptoms. Recent research has shown that an inflammatory reaction is triggered within the hour in the brain tissue injured by an ischemic stroke and continues in the days following the appearance of symptoms and that this reaction contributes to neuronal damage. Increased CRP levels are accepted as a sensitive but nonspecific marker of the acute inflammatory conditions. Laboratory and experimental findings have shown that atherosclerosis is a reflection of a chronic inflammatory process in addition to lipid deposition. Inflammatory mechanisms have been known to play a role in all stages of atherosclerosis, from initiation to development. It has been reported that it is possible to use the increase in the concentration of acute phase reactants and especially the high sensitivity C- Reactive proteins (hs -CRP) to help predict future cardiovascular mortality. Various prospective studies have found initial CRP levels to be higher in persons who develop stroke, IHD (ischemic heart disease), peripheral artery disease.

Epidemiology: Each year stroke affects 15,000,000 people worldwide, two thirds of who die or are left permanently disabled. In 1990 more than 38,000,000 disability adjusted life years were lost worldwide

due to stroke; this disease burden is projected to increase to 61,000,000 disability adjusted life years by 2020. Based on retrospective analyses of subjects admitted in urban hospitals in India it was found that stroke constitutes nearly 2% of all hospital cases and 20% of neurological admissions.

Pathophysiology of Ischemic Stroke: A fall in cerebral blood flow to zero causes death of brain tissue within 4-10 min CBF <16 to 18 ml/100gm tissue per min cause infarction within an hour. Values <20 ml/100gm tissue per min cause ischemia without infarction unless prolonged for several hours or days. There is a loss of neuronal electrical function which is reversible stage. When blood flow decreases to 10 ml/100gm/min then aerobic mitochondrial metabolism fails and anaerobic metabolism leads to lactic acidosis. As a sequel to this, sodium and water enter the cell and potassium leaks out of the cell due to failure of energy dependant intracellular homeostasis leading to irreversible cell death. Based on these facts, concept of ischemic penumbra was formulated. It is an area of brain that has reached the reversible stage of electrical failure, but has not yet passed into irreversible stage. Thrombolytic agents are used in this time window to salvage the ischemic penumbra zone.

MATERIALS AND METHODS

This study is single centred prospective study carried out in department of medicine of thanjavur medical college during the period of February 2006- August 2007. Total number of subjects included in the study was around 52 patients. The detailed history regarding the risk factors like diabetes, coronary artery disease, hypertension, hyperlipidaemia, smoking, and alcohol use were elicited from the patient. Standard approved protocol was used for all patients. Inclusion criteria Age group of patients was around 41-85 First acute ischemic stroke were included only ischemic stroke patients confirmed by CT brain were included Patients who got admitted within 48 hrs of stroke onset were included. **Exclusion criteria:** Other than ischemic stroke were excluded. Patients admitted after 48 hrs.of stroke onset were excluded. Patients with lymphoma, lupus, rheumatoid arthritis, osteomyelitis, malignancy, and other connective tissue diseases were excluded recentinfection, trauma or surgery within a month. Patients with valvular heart disease, atrial fibrillation, Acute myocardial infarction,thyroid disease, renal disturbance, previous history of stroke, TIA, RIND were excluded from the study.

Clinical Examination: All patients were examined for hypertension, obesity, carotid artery thrill and bruit. A detailed cardiovascular and CNS examination were performed and the findings were recorded. ECG and Chest X Ray PA view were taken to rule out AF and valvular heart disease as well as acute MI. BP at the time of admission were recorded and BMI were calculated. Patients with BMI>30 were labelled as obese.

Biochemical Assay For hs-CRP TEST: Serum or heparinised or EDTAplasma. Off volume: 0.5 – 1.0 ml. Stored: refrigerate for maximum 8 days. May be frozen at -25°c or lower if samples are frozen within 24 hrs after collection. Repeated freeze thaw cycles to be avoided. Nephelometric method utilizing latex particles coated with CRP monoclonal antibodies. Instrument used in the analysis were BN-100 from Dade Behring, USA.

Assessing Functional Outcome: On seventh day patients clinical and functional status were assessed using Glasgow Outcome Scale.

1. Death

2 .Persistent vegetative states- Patient exhibit no obvious cortical function.

3 Severe Disability-(Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both)

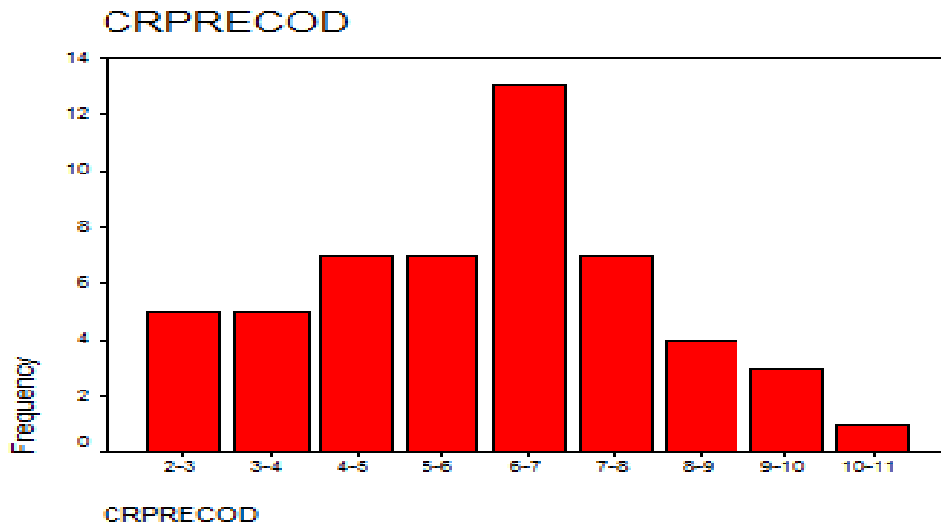
4.Moderate Disability-(Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.

5. Good Recovery-Resumption of normal activities even though there may be minor neurological or psychological deficits.

RESULTS

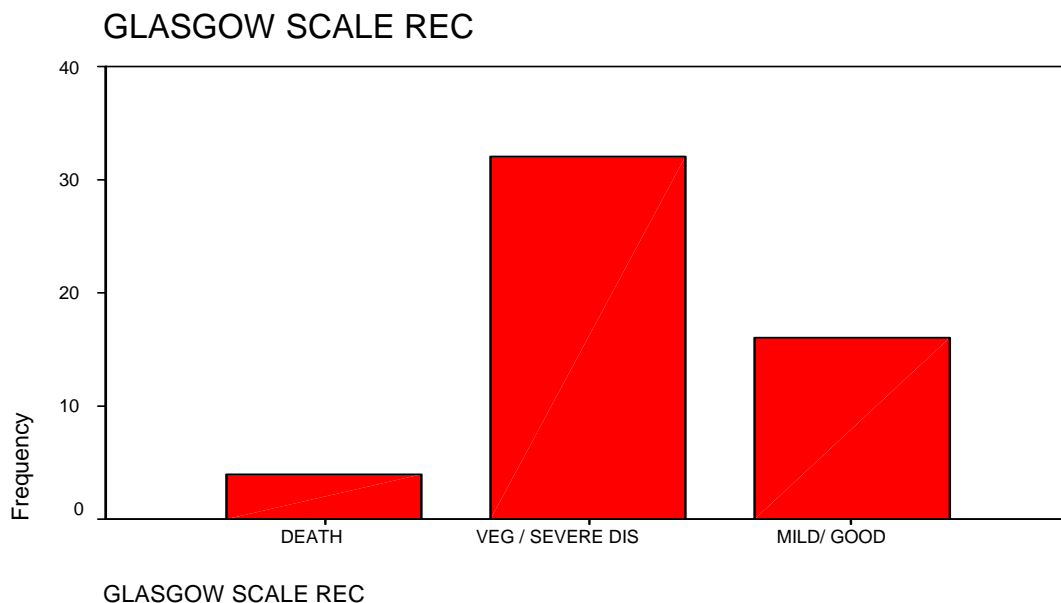
Patients of age > 40 yrs and < 85 yrs were included in this study. Total no of patients – 52 Mean ages of patients was around 60.3 yrs. Among the population 75 % of patients were males. And 25% were females. •57.7 % of this study group were smokers who smoke more than one packet per day. 15% of patients were alcoholics. 23% were diabetics in this study. 57.7% found to have high BP. Only 8% had previous history of CAHD. Only 10% were obese in this study. In this study only 22% had HDL > 45mg/dl. Mean TC/HDL 4.64 ± 0.6 .

Graph 1: Shows the Crp Distribution Patients

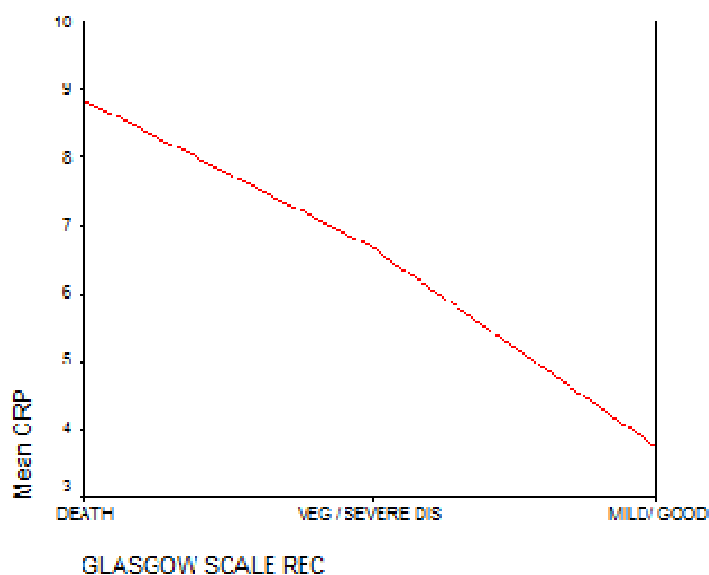


Legend:1 Mean hs- CRP of all patients were around 5.94 ± 1.97 . Maximum value – 10.1mg/l and Minimum value off – 2.1mg/lit shows >94 % of patients had hs CRP > 3mg/lit shows clearly that hs CRP levels are increased in stroke.

Graph 2: Glasgow Outcome Scale



Legend: 2 70 % of the patient had poor prognosis. 7.7 % mortality was noted in these patients, only 30 % had good recovery. Patients with score of 2 and 3 were unable to walk. Patients with score of 4 and 5 were able to walk.

Graph 3 :Hs Crp Level and Functional Outcome

Legend : 3 Mean hs- CRP of all 52 patients 5.94 ± 1.96 mg/l. Mean hs -CRP of all patients who died during study 8.85 ± 1.98 mg/l. Mean hs- CRP of all patients who were unable to walk (patients in GOS score of 2 and 3) is 6.68 ± 1.1 mg/l. Mean hs- CRP of patients who were able to walk (patients in GOS score of 4 and 5) is 3.73 ± 1.1 mg/l. Mean hs- CRP who had massive infarct is 8.7 ± 0.96 mg/l. Mean hs -CRP of patients who had lacunar infarct is 3.27 ± 0.93 mg/l. Applying chi square test for association between hs- CRP levels and Glasgow Outcome Scale (GOS), $p < 0.0005$ which is statistically significant.

DISCUSSION

Atherogenesis is itself an inflammatory process. When endothelium is physically challenged or becomes dysfunction, a cascade of events precipitated initiating a cycle of injury, immunological induction and amplification. Causes of endothelial dysfunction include shear stress related to hypertension, oxidized LDL, homocysteinemia, and smoking. Dysfunctional endothelium leads to increased permeability to lipoprotein and up regulation of leucocyte and endothelial adhesion molecules. In response to the presence of certain activating substances including oxidized LDL, monocyte chemo attractant protein (mcp-1), interleukin IL-8 and PDGF leukocytes migrate into the wall of the artery. Induced by oxidized LDL, mcp-1 promotes diapedesis of monocytes across the endothelium. Granulocyte macrophage colony-stimulating factor transforms monocytes into macrophages, which elaborate tumour necrosis factor- α (TNF- α), IL-1, proteolytic enzymes including matrix metalloproteinases and growth factors including PDGF, insulin like growth factor (IGF). Studies by Tahir Yoldas et al in 2007 clearly showed that levels of hs- CRP done on 2nd day after the ischemic stroke strongly associated with short term unfavorable prognosis. (9) The study also showed that patients with stroke have a higher circulating serum hs- CRP and Homocysteinemia levels. Kirstein Weinbeck et al in 2002 also gave similar results. (10) Experimental studies have shown that secretion of inflammatory mediators as a direct response to cerebral injury starts within 2 hours of focal ischemia and anti-inflammatory treatment have neuroprotective role. Muir et al (44), have shown CRP levels within 1st 72 hours following an acute ischemic stroke as an independent predictor for predicting survival. (11) Studies by Di Napoli (14) has shown that a large infarct and cortical involvement in patients had a highest hs-CRP values than normal at the time of presentation. This study also confirmed that prognosis in patients with increased hs- CRP level is worse (12). Our findings that patients who were able to walk had lower hs- CRP levels than the patients who were unable to walk, and also the patients who had death as end point, may be an indicator of the degree of inflammation.

CONCLUSION

The hs-CRP level is increased in all patients after acute ischemic stroke. The hs-CRP level strongly correlates with short term outcome in patients after first ever ischemic stroke. ($P < 0.0005$). The hs-CRP level is high in patients with massive infarct thus reflecting the severity of stroke. Commonly the hs-CRP level is increased in smokers, obesity, diabetes, hypertension and post-menopausal women due to increase in inflammatory response

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