ORIGINAL RESEARCH PAPER

Volume-7 | Issue-6 | June-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HIGH SENSITIVITY C-REACTIVE PROTEIN IN ISCHEMIC STROKE: EXPERIENCE FROM A TERTIARY CARE CENTRE FROM INDIA

General Medicine

Sehrawat Amit* MD General Medicine, DNB Medical Oncology Resident, Department of Medical Oncology, Dhraramshila Narayana Superspeciality Hospital, New Delhi-110096 (India) *Corresponding Author

Gupta Ritu MD General Medicine, Associated Professor, Department of General Medicine, N.S.C.B. Medical College, Jabalpur (MP) 482003 (India)

ABSTRACT

Context: 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 disease management which are major health concerns in India.

Aims: To study the association of hs-CRP levels in patients of acute ischemic and haemorrhagic stroke and its correlation with severity of stroke.

Settings and Design: Prospective single arm observational study.

Methods and Material: 52 patients aged >25, within first 24 hours of the onset of 1st Cerebrovascular (CVA) event were included. Nephelometry was used to obtain hs CRP levels; stroke severity was assessed by Glasgow coma scale (GCS).

Results: There was male predominant presentation of stroke with sex ratio of 1.89:1. Mean age was 58 years. Among 52 patients, 40 (76.93%) were of ischemic stroke and 12 (23.07%) were of haemorrhagic stroke. Most common presentation was left hemiparesis. hs CRP levels were significantly higher in ischemic stroke. Conclusions: hs-CRP levels were significantly higher in ischemic stroke vs haemorrhagic stroke. It showed a positive correlation with the severity of Ischemic Stroke.

KEYWORDS

Hs CRP, Ischemic Stroke, Prognostic Marker

INTRODUCTION

Cerebrovascular accidents (CVA) include some of the most common and devastating disorders like ischemic stroke (IS) or hemorrhagic stroke (HS), 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].

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 CVA, ischemic cause (atherothrombosis) is by far most important this is followed by an inflammatory process and result in 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 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. After acute stroke an increase level of CRP measured at discharge predicts unfavourable outcome and recurrence [4].

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 IS in first 24 hours and to differentiate it from HS.

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.

Subjects and Methods:

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

Method Data Collection:

This was single arm observation study of patients with first ever episode of Acute Stroke. The diagnosis was established by CT/MRI Brain and along with routine haematology and biochemistry, hs CRP levels were assessed by Nephelometry.

Inclusion Criteria:

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

Exclusion Criteria:

1. Patients with febrile illness, connective tissue disorders, ischemic heart disease, Diabetes Mellitus, pregnancy, hyperlipidaemia, chronic smokers.
2. 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.

Methodology:

Venous blood sampling was done and samples were collected in air-tight barcoded gel tube. Samples were transported in Chiller Boxes (Polystyrene Boxes) with intact leak proof packaging having guidelines laid down by WHO- IATA maintaining the cold chain.

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

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.

RESULTS:

Mean age of presentation was 58 years, 55 years in males and 64 years in females. Majority of the patients were 45 to 65 years, 65.38% (N=34) males and 34.62% (n=18) females, with male to female ratio of 1.89:1 76.93% (n=40) were having IS and 23.07% (n=12) HS. In ischemic CVA group 65% (n=26) were male and 35%(n=14) female, whereas in HS group 67 %(n=8) were male and 33%(n=4) were female [Figure 1].

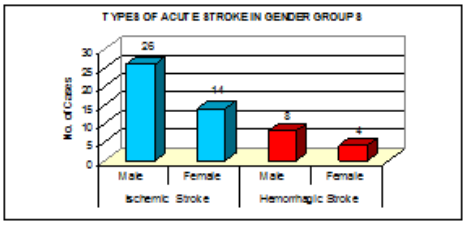

Figure 1: Gender and type of stroke.

60% of IS patients were of 46-65 years, in HS 58 % (n=7) were of 36-55 years. 31% (n=16) patient had right hemiparesis, 22 (n=42.3%) left hemiparesis, 11.5%(n=6) quadriparesis, 36.5%(n=19)had speech disturbances . [Figure2].

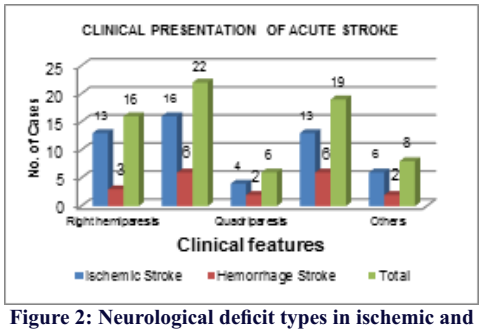

Figure 2: Neurological deficit types in ischemic and haemorrhagic stroke.

Mean age and blood pressure was higher in HS. Mean Hb, Total Cholesterol, HDL,LDL, VLDL were higher in IS patients but statistically insignificant, p-value >0.05 [Table 1].

Table1: Clinical and biochemical parameters in acute stroke patients.

Parameter	CVA	Cases	Mean	Std. Deviation	p value
Age(in years)	B*	12	59.58	17.906	>0.05
	I*	40	57.25	11.827	
BP Systolic (mmHg)	B	12	132.33	9.099	>0.05
	I	40	126.73	11.927	
BP Diastolic (mmHg)	B	12	84.33	6.372	>0.05
	I	40	78.70	8.624	
Hb.(gm/dl)	B	12	10.6167	1.67105	>0.05
	I	40	11.1175	1.96533	
T.CHL.(mgl/dl)	B	12	167.0583	32.46600	>0.05
	I	40	170.1950	31.08786	
HDL(mg/dl)	B	12	43.1292	8.78048	>0.05
	I	40	43.9398	11.27975	
LDL(mg/dl)	B	12	94.6525	24.52653	>0.05
	I	40	101.2088	27.78724	
VLDL(mg/dl)	B	12	16.0483	2.03854	>0.05
	I	40	17.9932	5.04781	
ESR(mm/hr)	B	12	29.92	12.471	>0.05
	I	40	34.95	16.898	
hs-CRP(mg/dl)	B	12	.3267	.10765	<0.0001
	I	40	.7380	.27479	

B*= Hemorrhagic Stroke , I* = Ischemic Stroke

Table 2: hs CRP* levels in acute stroke

Type of stroke	No. of Cases	hs CRP levels		P value
		Mean(mg/dl)	Std. Deviation	p<0.0001
Ischemic	40	0.738	±.2747885	
Hemorrhagic	12	0.326	±.107647	

Mean ESR levels were higher in IS patients (34.95mm 1st hour) as compared to HS (29.9195mm 1st hour), p value of >0.05. 40% (n=21) patients presented with GCS of 13-15, 29% (n=15) with 9-12 and 31%(n=16) with GCS of 3-8.Patients in the age group of 46-65 presented with better GCS.

Patients with IS had mean hs CRP of 0.738 mg/dl with SD of ±0.2747885 as compared to HS patients who had mean hs CRP levels 0.326 with SD of ±0.107647,with p value of < 0.0001 it was statistical significant. [Table2, Figure 3].

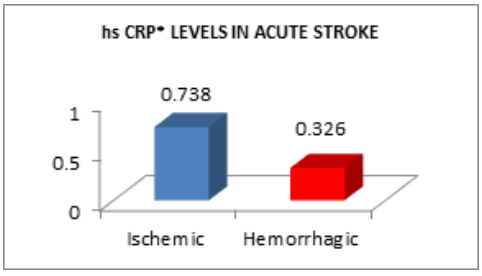

Figure 3: hs-CRP levels (in mg/dl) and type of stroke.

Mean hs CRP in all cases was 0.643 mg/dl, 0.327 in HS and 0.738 in IS. Mean hs CRP levels in every GCS severity category were higher in IS. (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 IS 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 [Figure 4].

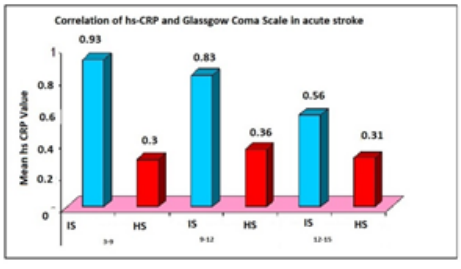

Figure 4: Correlation of hs-CRP and GCS in both types of stroke. (IS: Ischemic Stroke,HS: Haemorrhagic Stroke, hs CRP in mg/dl)

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'.

CRP 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 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.

In addition, the Framingham Heart Study as provided evidence that hs-CRP independently predicts thrombotic events in the cerebral circulation. Finally, within the Framingham Heart Study, data has also been presented that demonstrates the ability of hs-CRP 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 hs-CRP.

Thus, measures of inflammation such as hs-CRP 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 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. [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, but as lesions progress they become more cellular with more lipid retention, still later they exhibit phenomenon of hproliferation, formation of variable thickening of fibrous cap of atherosclerotic plaque. The initial trigger, which alters endothelial normal function, is still debatable.

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. 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, 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/dl During inflammation the plasma concentration of C-Reactive Protein can rise up to 10000 fold[10].

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.

Our study showed that hs CRP levels were significantly higher in IS as compared to HS. 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 GCS in IS patients but there was no association between GCS and hs CRP levels in HS.

In our study hs-CRP levels were significantly higher in IS. Also, levels of hs-CRP showed a positive correlation with the severity of IS.

CONCLUSIONS

In acute stroke patients, hs-CRP is a low cost, easily available, 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 IS

REFERENCES:

1. Pandian JD, Sudhan P. Stroke Epidemiology and Stroke Care Services in India. *Journal of Stroke*. 2013;15(3):128-134.
2. Taylor FC, Kumar S, Stroke in India Factsheet, South Asia Network for Chronic Disease, IIPH Hyderabad, Public Health Foundation of India. Apr 2012
3. Roudbary SA, Saadat F, Forghanparast K, Sohrabnejad R. Serum C-reactive protein level as a biomarker for differentiation of ischemic from hemorrhagic stroke. Acta Med Iran. 2011;49:149-52.
4. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. Stroke. 2001 ;32:917-24.
5. Ananthanarayan R, Paniker C (1978). Ananthanarayan and Paniker's Textbook of Microbiology (7th ed.). Himayatnagar, Hyderabad: Orient Longman. p. 218. ISBN 9788125028086.
6. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R Sr, O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. Circ Cardiovasc Qual Outcomes. 2008 ;1:92-7.
7. Williams KJ, Tabas I. The Response-to-Retention Hypothesis of Early Atherogenesis. Arteriosclerosis, thrombosis, and vascular biology. 1995;15:551-61.
8. Falk E. Pathogenesis of Atherosclerosis. J Am Coll Cardiol. 2006;47(8s1):C7-C12.
9. Osman R, L'Allier PL, Elgharib N, Tardif J-C. Critical Appraisal of C-Reactive Protein Throughout the Spectrum of Cardiovascular Disease. Vascular Health and Risk Management. 2006;2:221-37.
10. Glenn Reeves. 5 min read, C-reactive protein, Aust Prescr 2007;30:74-61
11. Qiu R, Gao Y, Hou D, Wang Y, Yu C, Wang W, *et al*. Association between hs-CRP Levels and the Outcomes of Patients with Small-Artery Occlusion. Front Aging Neurosci. 2016 Aug 9;8:191.
12. Chehaibi K, Trabelsi I, Mahdouani K, Slimane MN. Correlation of Oxidative Stress Parameters and Inflammatory Markers in Ischemic Stroke Patients. J Stroke Cerebrovasc Dis. 2016 ;25):2585-93