

Original article:

Study the association of hs C-Reactive protein (HS CRP) level rise in patients of acute ischemic stroke

¹Dr. Jagannath S Dhadwad* , ²Dr Sumit Khupse

¹Associate Professor, Medicine Department, Dr. DY Patil Medical College, Hospital and Research Centre, Pimpri, Pune411018

²Resident, Medicine Department, Dr. DY Patil Medical College, Hospital and Research Centre, Pimpri, Pune411018
Corresponding author*

Abstract:

Introduction: Globally stroke becomes important common cause of mortalities after coronary artery disease (CAD). It is the leading condition of chronic adult disability. Overall risk of stroke in a lifetime over the age of 55 is one in five for women and one in six for men. More than eighty percent of all strokes cases occur in developing nations.

Material and methods: This was Prospective Observational Study carried out at Dr. D.Y. Patil Medical College and hospital and Research Centre, Pimpri Pune. Subject diagnosed first time with stroke in the medicine OPD or Ward of a tertiary care hospital in the city of Pune were included in this study. The sample size was estimated based on MRD data for last year admission rate for acute ischemic stroke in hospital.

Results: Among various risk factors found in study subjects only hypertension found significantly high level of Hs-CRP ($p < 0.05$).

Conclusion: Cerebral ischemia could provoke an acute response monitored by significant increase in levels of hs-CRP in AIS patients especially during early days of stroke.

Keywords: C-Reactive protein , Hypertension

Introduction:

Globally stroke becomes important common cause of mortalities after coronary artery disease (CAD). It is the leading condition of chronic adult disability. Overall risk of stroke in a lifetime over the age of 55 is one in five for women and one in six for men. More than eighty percent of all strokes cases occur in developing nations.¹ Worldwide there is increase in stroke cases due to lack of awareness and lack of prevention programmes and services which broadens the stroke prevention gap.² According WHO 2009 report in India prevalence is 90 to 222 per lakh population and 6,398,000 DALYs (Disability Adjusted Life Years)³

The process of stroke can be divided as embolic, lipohyalinic occlusion of the small arteries, or thrombosis over atherostenotic plaques. Strokes costs over \$ 70 billion yearly and have a disastrous effect on the quality of life on significant number of individuals and caregivers.⁴ The leading risk factors for stroke are hypertension, diabetes, smoking and hypercholesterolemia.⁵ Whereas other risks include alcohol consumption, illicit drug use and age above 55 years of age.⁶

The inflammatory marker like C-Reactive Protein Inter-cellular adhesion molecules-1, lipoprotein associated phospholipase A2, Homocysteine; Renin angiotensin system; Tissue factor; Fibrinogen;

Lipoprotein (a); Small dense LDL (Low Density Lipoprotein) have been proposed as new risk factors for stroke.⁷

CRP is acute phase protein described as the very sensitive marker of inflammation and tissue destruction⁸ and helps in binding of complement to foreign and destructed cells and which affects humoral response to disease. It is believed to play an important role in innate immunity, and hence measuring and charting of the CRP values can be helpful in determining disease processes or the effectiveness of treatment.⁹In acute ischemic stroke, CRP levels are correlated with infarct size and neurological deficits and has likely establishing the prognostic value for poor outcomes.¹⁰

The newer study focused on High sensitivity C-Reactive protein levels in relation to the ultimate functional outcome in ischemic stroke cases and to correlate the hs-CRP levels with various risk factors.

Material and methods:

This was Prospective Observational Study carried out at Dr. D.Y. Patil Medical College and hospital and Research Centre, Pimpri Pune. Subject diagnosed first time with stroke in the medicine OPD or Ward of a tertiary care hospital in the city of Pune were included in this study. The sample size was estimated based on MRD data for last year admission rate for acute ischemic stroke in hospital. On an average 20-25 cases of first ischemic stroke were admitted. For 2 years study duration considering same rate of admission total 50 subjects were included in study. Participants were selected using Purposive sampling technique.

Inclusion Criteria:

Patients who were presented in the 48 hours of the onset of the stroke for first time and who gave

informed consent for participation in the study were included.

Exclusion Criteria:

1. Subarachnoid haemorrhage, subdural haemorrhage and intracerebral haemorrhage were excluded with the help of the CT scan.
2. Patients having repeated history of stroke
3. Patients having evidence of active infections and neoplastic conditions at the time of study were excluded.
4. Patients having rheumatic heart diseases and collagen vascular diseases
6. Patients having prior history of the transient ischemic attacks or reversible ischemic neurological deficits

Total number of 50 individuals who presented with acute ischemic stroke enrolled for study. Detailed history and clinical examination findings were recorded on case sheet (Proforma)

Computerised Tomography/Magnetic Resonance Imaging of brain performed in 24 to 72 hours for all patients.

Blood samples drawn in 24 to 72 hrs following stroke. Fibrinogen levels, hs-CRP levels, white blood cell counts, lipid profile and Erythrocyte Sedimentation Rate was calculated.

Patients reviewed after four weeks following the time of the onset of stroke and compared using Glasgow Outcome Scale. High sensitivity-C-Reactive Proteins levels were compared with functional recovery of the patients after four weeks with the help of the Glasgow Outcome Scale. Patients with score of 4 and 5 were included in the good outcomes and patients with score of 1, 2, 3 were included in the poorer outcomes category.

Results:**Table 1: hs-CRP findings among study subjects**

hs CRP	Frequency	Percent
High	35	70.0
Normal	15	30.0
Total	50	100.0

Table 2: MRI Brain findings among study subjects

MRI Brain	Frequency	Percent
Anterior perfusion stroke	44	88.0
Posterior perfusion stroke	6	12.0
Total	50	100.0

Table 3: 28days follow up outcome [Glasgow Outcome Scale (GOS)] among study subjects

Outcome (Functional status)	Frequency	Percent
Poor	31	62.0
Good	19	38.0
Total	50	100.0

Table 4 : Age wise hs-CRP finding among study subjects

Age group	hs CRP		Total
	Normal	High	
≤50yrs	1(16.7%)	5(83.3%)	6
51-60yrs	6(28.6%)	15 (71.4%)	21
61-70yrs	6(40.0%)	9(60.0%)	15
>70yrs	2(25.0%)	6(75.0%)	8
Total	15	35	50

Table 5 : Gender wise hs-CRP finding among study subjects

Gender	hs CRP		Total
	Normal	High	
Female	6(30.0%)	14(70.0%)	20
Male	9(30.0%)	21(70.0%)	30
Total	15	35	50

Table 6: Relation of 28days follow up outcome [Glasgow Outcome Scale (GOS)] with hs-CRP among study subjects

Outcome (Functional status)	hs CRP		Total	P value
	Normal	High		
Good	15(78.9%)	4(21.1%)	19	0.0001
Poor	0	31(100.0%)	31	
Total	15	35	50	

Table 7 : Relation of 28days follow up outcome [Glasgow Outcome Scale (GOS)] with ESR among study subjects

Outcome	ESR		Total	P value
	Normal	High		
Good	13(68.4%)	6(31.6%)	19	0.0001
Poor	3(9.7%)	28(91.3%)	31	
Total	15	35	50	

Table 8 : Mean value of age, RSB and hs-CRP among 28days follow up outcome [Glasgow Outcome Scale (GOS)] group.

Variables	Outcome	Mean \pm Std Deviation	Std. Error Mean	P value
Age	Good (n=19)	60.32 \pm 8.02	1.840	0.721
	Poor (n=31)	61.29 \pm 10.02	1.800	
RBS	Good (n=19)	178.95 \pm 56.3	12.916	0.252
	Poor (n=31)	160.61 \pm 52.94	9.509	
hs CRP	Good (n=19)	9.37 \pm 1.09	0.25	0.0001
	Poor (n=31)	14.05 \pm 1.65	0.29	

Table shows mean hs-CRP among poor outcome group was 14.05 ± 1.65 and 9.37 ± 1.09 among good outcome group. There was significantly high value for CRP among poor outcome group ($P < 0.05$) but there was no much difference for mean value of age and Random Blood Sugar (RBS) for good and poor outcome groups ($P > 0.05$).

Table 9 : Relation of risk factors with hs-CRP

Risk factors	hs-CRP		P value
	Normal	High	
Obesity	4(40.0%)	6(60.0%)	0.341
Smoking	5(50.0%)	5(50.0%)	0.125
Alcohol	6(54.5%)	5(45.5%)	0.054
Diabetes	6(37.5%)	10(62.5%)	0.318
Hypertension	2(6.5%)	29(93.5%)	0.001
LDL	4(26.3%)	11(73.7%)	0.507

Among various risk factors found in study subjects only hypertension found significantly high level of Hs-CRP ($p < 0.05$).

Discussion:

This was a prospective observational study involving 50 cases of first attack of acute ischemic stroke and admitted to medicine ward within 24hrs of attack and assessed for the functional outcome using Glasgow Outcome Scale (GOS) at end of 28 days (4 weeks) after discharge from wards.

In our research, proportion of men and women with elevated levels of hsCRP was higher (70%) compared to low levels of the hsCRP (30%). Devaraj et al.¹¹ and Wakugawa et al.¹² noticed that high hsCRP level was non dependent risk factors for anticipated ischemic stroke only in men but not in women. Endogenous estrogen is believed to protect the formation of atherosclerosis, and also has anti-inflammatory effect in women.^{13,14} However, Muir et al. not found any type of relation between gender and elevated C-Reactive Protein ($>10\text{mg/L}$) levels in acute ischemic stroke individuals.¹¹⁴ studies have shown a five times increase in the risk of any

vascular incident in women having highest CRP levels.^{15,16} Hence, increased CRP level may be responsible for damage to men as well as women. Our study findings has no significant difference in increased levels of hs-CRP among male and female ($p > 0.05$)

We noticed that high serum hsCRP levels was significantly associated with older age group in our patients; identical to other studies. Rost et al. noticed increased levels of CRP as a significant predictor of future risks of ischemic strokes in the elder individuals.¹⁷ Large prospective studies in healthy subjects have proven prognostic importance of CRP in the elder individuals.^{18,19}

It was demonstrated that stroke activates an acute phase responses. Elevated values in of CRP and fibrinogen is noticed in nearly 25 percent of individuals with ischaemic cerebro-vascular accidents.¹⁹ In our study we confirmed 70% had

elevated levels of hs-CRP (>3mm) at the admission time.

According to the Framingham Risk Score, C-Reactive Protein as the more valuable risk factor for coronary artery diseases than are LDL cholesterol levels¹⁷. Reaserchers established the relation between C-Reactive Proteins levels and the short term prognosis in acute ischaemic cerebrovascular accidents¹². It was found that high levels of C-Reactive Proteins is non dependent prognostic component which forecasts presence and percentage of carotid stenosis.^{12,13}

Hence, its presumed that elevated C-Reactive Protein level is a risk for the carotid stenosis in individuals who have normal LDL levels without a known thrombotic risk.¹²

We also found that hs-CRP was higher among normal LDL individuals and LDL was unimportant for outcome evaluation. Factors which includes poor Prognosis include fever, elevated levels of C-Reactive Proteins, fibrinogen concentrations.²⁰ Clinical data depicts risk of death is more in persons having higher CRP levels in the first 72 hours after acute ischemic stroke.

Sahan M et al²¹ in their study noticed that the comparison of average CRP values in individuals who died in the study period with those people who survived demonstrated significant relation between prognosis and levels of C-Reactive Proteins ($p = 0.029$). It was interesting to note that CRP is related with more cerebrovascular disease mortality as well as the cardiovascular disease mortality. Hence, C-

Reactive Protein is an important component in establishing prognosis whether the ischemic stroke is the cardioembolic or athero-thrombotic. Also in addition, it should be taken into consideration that such patients have more mortality rate due to cardiac disease. Alike fibrinogen levels, CRP polymorphism are essential in establishing cardiovascular risk and an relation between the CRP genotype and ischemic strokes.^{13,14,15}

In this study, Low Density Lipoproteins had no statistical notable correlation with high sensitivity-C-Reactive Proteins levels. This is in disparity with study conducted by previous researcher^{12,16,17} as we have not included the complete lipid profile of patients and the no of samples were also less findings of our study not correlating with literature.

Clinical significance of relation between C-Reactive Proteins and functional outcomes of strokes is unclear. Presently, its presumed that there is not much evidences as to recommend C-Reactive Proteins levels in the assesing the stroke risk in primary prevention. Nevertheless, in secondary prevention of stroke, increased C-Reactive Proteins included to present prognostic markers, although it remain to be determine whether specific therapy can be produced from this.¹⁹ and we also agree on the same.

Conclusion:

Cerebral ischemia could provoke an acute response monitored by significant increase in levels of hs-CRP in AIS patients especially during early days of stroke.

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