



SERUM C REACTIVE PROTEIN IN ACUTE ISCHEMIC STROKE WITH SPECIAL REFERENCE TO ITS PROGNOSTIC SIGNIFICANCE-A HOSPITAL BASED CASE-CONTROL STUDY

General Medicine

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ABSTRACT

Introduction: A stroke, or cerebrovascular accident, is defined as an abrupt onset of neurologic deficit that is attributable to focal vascular cause. Within the scope of the definition are included cerebral infarction which is responsible for about 85% of all first ever in a life time stroke, primary hemorrhagic stroke accounting for about 15% and subarachnoid hemorrhage accounting for 5% of all strokes respectively. High C reactive protein is critically evaluated as risk factor in ischemic stroke. The mechanism by which C reactive protein increases cardiovascular risk are not fully understood. C reactive protein play important role in development of atherosclerosis starting from the stage of plaque formation till formation of occlusive thrombus over ruptured plaque. **Materials And Methods:** It is case control study done in tertiary care hospital, Assam for duration of one year. All cases presented with ischemic stroke (CT scan diagnosis) in different medicine ward of tertiary care hospital, were taken up for study after applying inclusion and exclusion criteria. Age, sex and other base line characteristics matched healthy control sample from community was taken. **Results:** In the present study the age of patients ranged from 18-89 years. The maximum number of ischaemic stroke cases occurred in 50-59 years age group (31.6%). The mean c- reactive protein level was much higher in ischaemic stroke (10.11 ± 5.66) patients than control group (4.28 ± 2.75). The p value is <0.001 , which is statistically significant. Serum CRP was higher in patients having smoking habit (12.57 ± 6.48) in comparison to ischemic stroke patients without smoking habit (8.83 ± 4.63), $p < 0.05$. Ischemic stroke patients with hypertension had higher mean serum c reactive protein (11.89 ± 6.38) level than patients without hypertension (8.40 ± 3.93). The p value is <0.05 . 65.3% patients with NIHSS score <7 had CRP level $>6\text{mg/dl}$ where as 93.10% and 100% patients with NIHSS score >7 and >14 had CRP level $>6\text{mg/dl}$. CRP level was significantly higher (p value <0.05) in those patients who expired than those patients who survived. **Conclusion:** CRP level is significantly raised in ischaemic stroke patients in comparison to healthy individuals and can be considered as risk factor and an important marker to assess the severity as well as functional outcome of stroke patients.

KEYWORDS

Ischemic stroke, C-Reactive Protein (CRP).

INTRODUCTION

Cerebrovascular disease include some of the most common and devastating disorders, ischemic stroke and hemorrhagic stroke. Stroke is the second leading cause of death worldwide with 6.2 million dying from stroke in 2015.

A stroke, or cerebrovascular accident, is defined as an abrupt onset of neurologic deficit that is attributable to focal vascular cause. Thus, definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. If cessation of flow lasts more than few minutes, infarction or death of brain tissue results. When blood flow is quickly restored, brain tissue can recover fully and patients symptoms are only transient. This is called transient ischemic attack. The definition of TIA requires that all neurological signs and symptoms resolve within 24 hours without evidence of brain infarction on imaging. Stroke has occurred if the neurological signs and symptoms last for >24 hours or brain infarction is demonstrated. If low cerebral blood flow persists for longer duration, then infarction in border zones between the major cerebral artery distribution may develop. Focal ischemia or infarction, is usually caused by thrombosis of cerebral vessels itself or emboli from a proximal arterial source or the heart (1).

Within the scope of the definition are included cerebral infarction which is responsible for about 85% of all first ever in a life time stroke, primary hemorrhagic stroke accounting for about 15% and subarachnoid hemorrhage accounting for 5% of all strokes respectively. The incidence of various types of strokes are assessed by CT scan and is found similar all over the world except ICH, the incidence of which is reported to be more in Japan.

With the advancement of newer and newer diagnostic facilities the treatment of stroke has also improved considerably. But the importance of detection and correction of risk factors in the prevention of ischemic stroke is now recognized universally as the most important step in the management of stroke.

Risk factors for stroke may be non modifiable and modifiable. The non

modifiable risk factors are age, sex and family history. Modifiable risk factors are diet with elevated lipid levels, hypertension, cigarette smoking, diabetes, obesity, oral contraceptives, alcohol sedentary living etc. the growing list of new and emerging risk factor include hyperfibrinogenemia, hyperhomocystinemia, high C – reactive protein, elevated lipoprotein(a), insulin resistance, inflammation and infectious agents (2). High C reactive protein is critically evaluated as risk factor in ischemic stroke. It is called C reactive protein as it reacts with somatic C polysaccharide present in the capsule of pneumococcal bacteria. This protein is found in the serum of normal individuals and it is found to appear only in acute phase and could no longer be detected after the acute crisis is over, so its is designated as acute phase protein. It was observed that sera from patient with various other infections, inflammation, malignancies and tissue destruction were also found to precipitate C- polysaccharide (3)(4).

The mechanism by which C reactive protein increases cardiovascular risk are not fully understood. C reactive protein play important role in development of atherosclerosis starting from the stage of plaque formation till formation of occlusive thrombus over ruptured plaque.

AIMS AND OBJECTIVES

To evaluate the clinical manifestations of ischemic stroke.

To evaluate the various risk factors of ischemic stroke.

To find out the association of serum CRP level and Ischemic stroke.

MATERIALS AND METHODS

This study was a prospective case control study conducted in department of medicine, Gauhati Medical College and Hospital, Guwahati, a tertiary care hospital, Assam for duration of one year.

Inclusion criteria:

All cases presented with ischemic stroke (CT scan diagnosis) in different medicine ward of tertiary care hospital, were included for study.

Age more than 18 years.

Duration of stroke <72 hours.

Exclusion criteria:

Haemorrhagic stroke (CT scan diagnosis)

Patient having rheumatic valvular heart disease.

Those patients suffering from:

Angina, Myocardial infarction

Infection: Meningitis, urinary tract infection, pneumonia
 Inflammation: acute appendicitis, acute pancreatitis.
 Connective tissue disease: Rheumatoid arthritis, SLE
 Malignancy

After surgery, severe burn patients.

Detailed history and thorough clinical examination was performed in all these patients soon after admission.

Control: age, sex and other base line characteristics matched healthy control sample from community was taken

Assessment of stroke severity:

It was done at the time of admission to hospital by using national institute of health stroke scale(NIHSS).

Assessment of stroke outcome:

Assessment of short-term outcome was done by Modified Rankin scale(mRS) after 7 days from the admission.

Diagnostic methods used:

CT scan Brain: CT scan brain was done in radiology department, tertiary care hospital. CT scan brain was performed in an axial axis with a 15-20° angulation of gantry to the canthomeatal line. In most cases complete studies of brain could be done in 2-3min.

Measurement of C reactive protein:

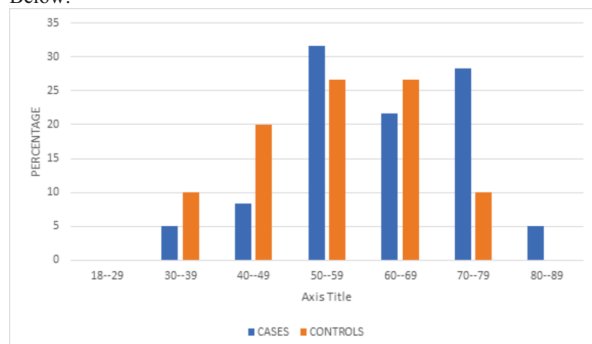
The RCRP metho is based on particle enhanced turbidimetric immunoassay technique.(PETIA)

STATISTICAL ANALYSIS

The data recorded on predesigned and pretested proforma was tabulated and the master chart was prepared. The Hardy-Weinberg equilibrium was performed using chi-square test by comparing the observed to the expected genotype frequencies. The Statistical analysis of data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 21.0. Chicago, SPSS Inc.) and Microsoft Excel 2010. Results on continuous measurements are presented as Mean $\pm$ Standard Deviation, Post Hoc Analysis was done to find out the significance between the 2 individual groups. Discrete data were expressed as number (%) and were analyzed using Chi Square Test and Fischer's Exact Test (where the cell counts were ≤ 5 or 0). For all analysis, the statistical significance was fixed at 5% level (p value < 0.05).

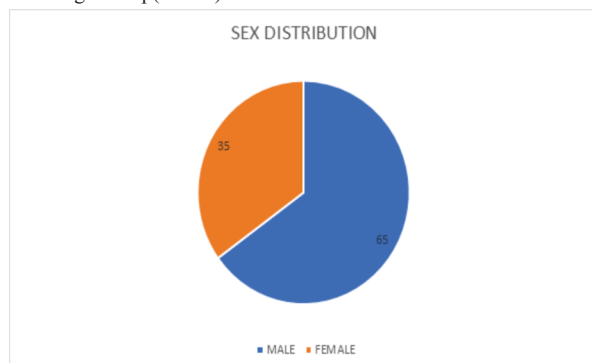
RESULTS

Results And Observations Obtained From This Study Are Shown Below:



Age Distribution Of Cases And Controls (figure 1.0):

In The Present Study The Age Of Patients Ranged From 18-89 Years. The Maximum Number Of Ischaemic Stroke Cases Occurred In 50-59 Years Age Group (31.6%).



Sex Distribution Of Cases (figure 1.1):

In Our Study, It Is Evident That Male Patients Are Predominant, With The Male To Female Ratio Being 1.85:1.

Smoking Habit Of Cases And Controls (table 1.0):

SMOKING HABIT	CASES		CONTROLS	
	NUMBER	%	NUMBER	%
SMOKER	22	36.6	10	33.33
NON SMOKER	38	63.33	20	66.66
TOTAL	60	100	30	100

In Our Study, It Was Found That 36.6% Of The Cases Were Smoker.

Alcoholic Habit Of Cases And Control (table 1.1):

ALCOHOL HABIT	CASES		CONTROLS	
	NUMBER	%	NUMBER	%
ALCOHOLIC	20	33.33	8	26.66
NONALCOHOLIC	40	66.66	22	73.33
TOTAL	60	100	30	100

In The Present Study 33.33% Of Patients Were Alcoholic.

Regional Variation Of Cases And Control (table 1.3):

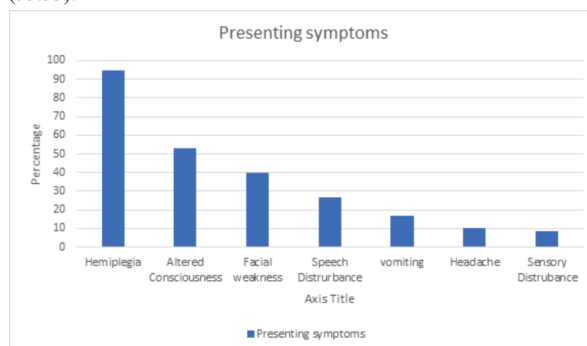
REGION	CASES		CONTROLS	
	NUMBER	%	NUMBER	%
RURAL	32	53.33	18	60
URBAN	28	46.66	12	40
TOTAL	60	100	30	100

In Our Study 53.3% Of Ischaemic Stroke Patients Were From Rural Area And 46.6% Of Patients From Urban Area.

Traditional Risk Factors Of Stroke In Cases (table 1.4):

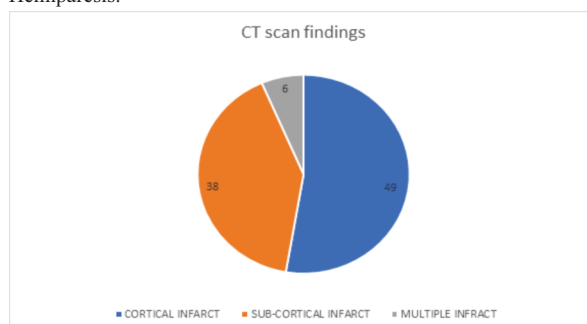
RISK FACTOR	NUMBER OF CASES	PERCENTAGE
Hypertension	32	53.33
Smoking	22	36.66
Alcoholism	20	33.33
Serum cholesterol >200 mg%	18	30
Serum TAG >150mg%	29	48.33
Serum LDL >130mg%	12	20
Past h/o TIA or stroke	8	13.33
Diabetes mellitus	10	16.66
obesity	18	30

Most Common Traditional Risk Factor Observed Was Hypertension (53.33%).



Presenting Symptoms Of Cases (figure 1.3):

In Our Study The Commonest Presenting Symptom Was Hemiplegia/Hemiparesis.



Ct Scan Findings In Cases (figure 1.4):

Ct Scan Shows Most Cortical Lesions Were In The Parietal Region And Most Sub-cortical Lesions Were In Basal Ganglia, Thalamus And Internal Capsule.

Serum C-reactive Protein Level In Cases And Control(table 1.5):

GROUP	NUMBER OF CASES	MEAN CRP LEVEL mg/dl $\pm$ SD	P VALUE
CASE	60	10.11 $\pm$ 5.66	<0.001
CONTROL	30	4.28 $\pm$ 2.75	

The Mean C Reactive Protein Level Was Much Higher In Ischaemic Stroke Patients Than Control Group. The P Value Is <0.001, Which Is Statistically Significant.

Serum C Reactive Protein Level Of Ischaemic Stroke Patients In Relation(table 1.6):

SMOKING HABIT	NUMBER OF CASES	MEAN C REACTIVE PROTEIN LEVEL mg/dl	P value
SMOKER	22	12.57 $\pm$ 6.48	0.012
NON SMOKER	38	8.83 $\pm$ 4.63	

In The Present Study Ischaemic Stroke Patients With Smoking Habit Had Higher Mean Serum Reactive Protein Level Than Patients Without Smoking Habit. P Value Is 0.012, Which Is Statistically Significant.

Serum C Reactive Protein Level Of Ischaemic Stroke Patients In Relation To Hypertension(table 1.7):

BLOOD PRESSURE	NUMBER OF CASES	MEAN C REACTIVE PROTEIN LEVEL mg/dl	P value
HYPERTENSIVE	32	11.89 $\pm$ 6.38	0.015
NON-HYPERTENSIVE	28	8.40 $\pm$ 3.93	

Relation Of Stroke Severity(nihss) With Crp Level(table 1.8):

ADMISSION NIHSS	No. of pt. with CRP $\geq$ 6mg/dl	No. of patients with CRP<6mg/dl	Total	Percentage (Pt. with CRP $\geq$ 6mg/dl)	P value
<7	17	9	26	65.38	0.016
7-13	27	2	29	93.10	
$\geq$ 14	5	0	5	100	

Relation Of Crp With Stroke Outcome Assessed By Modified Rankin Scale(mrs)(table 1.9):

mRS score after 7 days from admission.	No. of pt. with CRP $\geq$ 6mg/dl	No. of patients with CRP<6mg/dl	Total	Percentage (Pt. with CRP $\geq$ 6mg/dl)	P value
0-1	15	10	25	60	0.004
3	12	1	13	92.30	
3-6	21	1	22	95.45	

Above Table Shows That Higher Crp Level Is Associated With Poor Short Term Functional Outcome Of Stroke.

Showing Relation Of Crp Level With Expired Patinets Within 1 Week From Admission And Survive Patinets(table 1.10):

GROUP	NO. OF CASES	MEAN CRP LEVEL Mg/dl $\pm$ SD	P value
EXPIRED	3	18.33 $\pm$ 7.76	0.008
SURVIVORS	57	9.68 $\pm$ 5.27	

Above table shows that CRP level was significantly higher (p value <0.05) in those patients who expired than those patients who survived.

DISCUSSION

As shown in figure 1.0 the age distribution of cases and controls were comparable. Among the cases 53.33% were hypertensive, 36.6% were smoker, 33.33% were alcoholic and 53.33% were from rural area. Among control 33.33% were smoker, 26.66% were alcoholic and 60% were from rural area.

The study was conducted on 60 patients of ischemic stroke in tertiary care hospital, assam for duration of one year with 30 no. of healthy control.

The most common presenting symptom was hemiplegia(95%). Similar observations were also made by jolly et al(9), LA Gauri et al(10). Altered consciousness was present in 53.33% of cases in this study. LA Gauri et al reported that 46% patients had altered sensorium. 81.6% cases had cortical infarction and 63.3% cases had subcortical

infarction. Yumihio, Tanizaki et al documented 56% of cases of lacunar infarction in their study(11).

In our study mean serum CRP level in ischaemic stroke cases were 10.11mg/dl with standard deviation of $\pm$ 5.66 and in control group mean CRP level was 4.28mg/dl with standard deviation of $\pm$ 2.75. the p value is <0.001, which is statistically significant. Keith W et al studied serum CRP level in ischemic stroke patients and found significant association between cases and control group(7). Di Napoli M et al and Tamam Y et al also had similar results where they concluded that high CRP is independent risk factor for cardiovascular events in stroke patients(3)(8).

Serum CRP was higher in patients having smoking habit(12.57 $\pm$ 6.48) in comparison to ischemic stroke patients without smoking habit(8.83 $\pm$ 4.63), p<0.05. in Framingham study observed that patients with smoking habit had higher mean CRP level; than non smoker(12).

In this study ischemic stroke patients with hypertension had higher mean serum c reactive protein(11.89 $\pm$ 6.38) level than patients without hypertension(8.40 $\pm$ 3.93). The p value is <0.05, which is statistically significant. Similar study done by in Framingham study showed the relationship between serum c reactive protein level and hypertension(12).

Among 60 patients, 3 patients expired within one week after hospital admission. These expired patients had higher mean serum CRP level(18.33 $\pm$ 7.76) than patients who survived(9.68 $\pm$ 5.27), with significant p value 0.008. Mohan R et al reported that greater extent of elevation in serum c reactive protein level had higher in hospital mortality(4).

65.3% patients with NIHSS score <7 had CRP level >6mg/dl where as 93.10% and 100% patients with NIHSS score $\geq$ 7 and $\geq$ 14 had CRP level >6mg/dl. Similarly Titto T. Idicula, Jan Brogger et al found high CRP level associated with high NIHSS score in their study(the Burgen Stroke study 2008)(6).

In our study the short term function outcome of ischemic stroke was poorer in patients who had higher CRP level shown by 92.30% of patients with > modified Rankin scale score(after 7 days from admission) had CRP level >6mg/dl compared to 60% of patients with <3 modified Rankin scale score who had CRP level >6mg/dl. Similarly Titto T Idicula, functional outcome shown by high modified Rankin scale score in their study(6).

Thus increase CRP level is found to be an independent risk factor for ischemic stroke and is associated with increased severity and poor short term functional outcome in this study.

CONCLUSION

Present study concludes that c reactive protein level is significantly raised in ischaemic stroke patients in comparison to healthy individuals and can be considered as risk factor and an important marker to assess the severity as well as functional outcome of stroke patients. Thus C-reactive protein measurement should be encouraged to assess the overall risk profiles of individuals as well as to see the prognosis of ischemic stroke and to monitor tailoring of the preventive interventions. However, further studies are needed involving larger number of ischaemic stroke patients and with longer duration of follow up to confirm this observation.

REFERENCES

- Wade S. Smith, S.Claiborne Johnston JCH. Ischemic Stroke. In: Jamenson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's principles of internal medicine. 20th ed. New York: McGraw-Hill Education; 2018. p. 3079-91.
- Cojocaru IM, Druta A et al: Study of some inflammation in atherothrombotic pathogenesis of acute ischaemic stroke. Carol Davila university of Medicine pharmacy: clinic of neurology, Colentina Clin Hospital, Romania: Rom J Inter Med.2002;40(1-4):103-16.
- Di Napoli, Donatonic weber D et al: Evaluation of CRP measurement for assessing the risk and prognosis in ischaemic stroke, Stroke 2005 Jan;36(6): 1316-29.
- Mohan R, Vij A et al: Role of C reactive protein in thrombotic stroke. JAPI, 2003, vol.51.p.1280.
- SC Mahapatra et al: C reactive protein in thrombotic stroke. JAPI,2004; Vol.52.p.1512
- Titto T. Idicula, Jan Brogger, Halvor Naess, Ulrike Waje-Andersson and Lars Thomson, Admission C reactive protein after acute Ischemic stroke is associated with stroke severity and mortality. Th Burgen Stroke study BMC neurology 2009;9:18
- Keith W. Muir, Christopher J. weir et al, outcome of Ischemic stroke, stroke, 1999;30:981-985
- Taman Y, Apok I et al: Assessment of acute ischaemic stroke: Dicle University Faculty of Medicine; Dep. Of Neurology, Turkey, Tohoku J. Ex Med.2004 Jan;206(2),91-8.
- Jolly SS, Singh N, Rai B, Singh G; A Study of cerebrovascular disease in Punjab; Ind. Med. Gaz 1970; Dee Vol 10:57.

10. L.A Gauri, D.K Kochar et al: Clinical profile of stroke in Bikaner, JAPI, Vol 149, Jan.2001.
11. Yumihiro T, kiyohara Y, Kato I et al incidence and risk factor for subtypes of cerebral infraction in a general population, Stroke.2000;31:2616-2622.
12. Yamini S, Emelia J, Benjamin et al; Relation of smoking status to panel of inflammatory markers: The Framingham offspring, Vol 201, issue 1, 2008 Nov, 217-224.