

Association between High sensitivity CRP and Ischaemic stroke - A case control study

REHAN ANWAR¹, SYED SHAHEER HAIDER², SHAZIA ANWAR³

ABSTRACT

Background: Stroke also referred to as cerebrovascular accident (CVA) occurs when reduced blood flow to the brain results in cell death.

Aim: To determine the association between high sensitivity C - reactive protein and ischemic stroke patients.

Study design: Case-control study

Settings: Department of Medicine, Allama Iqbal Memorial Teaching Hospital Sialkot.

Duration: 06 months i.e. 1st January, 2018 to 30th June, 2018

Methods: Ischemic stroke presenting to outdoor, indoor and emergency department of Allama Iqbal Memorial Teaching Hospital Sialkot was offered to be enrolled in the study. Blood samples were withdrawn from cases at the time of presentation in emergency for baseline laboratory examination. Serum Hs CRP levels was measured. Data was collected in a predesigned proforma containing background information like age, sex and Hs CRP level along with history of current smoking and presence of dyslipidemia to allow for effect modification.

Results: Mean age (years) in the study was 58.53±13.01 whereas mean serum high sensitivity CRP was 4.67±2.92. There were 33(33%) male and 67(67%) female patients who were included in the study whereas raised hsCRP among both the groups was 30(60%) and 4(8%) respectively which showed that there is an association between high sensitivity C-reactive protein and ischemic stroke patients was statistically significant (p-value 0.000).

Conclusion: There is an association between high sensitivity C - reactive protein and ischemic stroke.

Keywords: Stroke, Ischemic stroke, hemorrhagic stroke, serum hs CRP, C-reactive protein

INTRODUCTION

Stroke occurs when reduced blood supply to the brain results in cell death. I World Health Organization defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" There are two main types of stroke: due to lack of blood flow, known as ischemic and due to bleeding, known as hemorrhagic causing part of the brain affected to not function properly. Signs and symptoms of a stroke may vary from loss of vision, movement or sensation, feeling of world spinning, or problems understanding or speaking.

Approximately 3.4 million people had hemorrhagic stroke and 6.9 million people had an ischemic stroke in 2013. About 33 million people who previously had a stroke in 2010, were still alive. After atherosclerotic CAD the second most frequent cause of death in 2013 was Stroke, responsible for 6.4 million deaths .¹About 3.3 million deaths resulted from ischemic stroke while 3.2 million deaths resulted from hemorrhagic stroke.

Inflammation plays a pivotal role in the development of atherosclerosis and in turn development of ischemic stroke.² C-reactive protein (CRP), is considered a biomarker of inflammation, which is an acute-phase reactant produced by hepatocytes. High sensitivity CRP (hs-CRP) reliably checks minor inflammation.³ Measurement of hs-CRP assays is widely used clinically, especially in cardiovascular disease (CVD) risk assessment A high hs-CRP is considered as a risk factor for ischemic or total stroke⁴.

CRP increases rapidly within two hours of onset of inflammation to 50,000-fold, and peaks at 48 hours. CRP is a screen for inflammation and its level correlated with the rate of production and severity of the triggering cause. In a previous study published in 2013, hsCRP was raised in 61.9% of cases and 6.6% of controls.⁵ The results of this study will help physicians to identify patients at higher risk for ischemic stroke hence better management and prevention.

The objective of the study was to determine the association between high sensitivity C-Reactive Protein and ischemic stroke.

OPERATIONAL DEFINITIONS:

Ischemic Stroke: It will be labelled if there is neurological deficit with a hypodense lesion in the brain parenchyma on CT scan brain plain, reported by HOD Radiology Department. (experience of more than 15 yrs in radiology)

Raised Serum hsCRP: It will be defined as serum hsCRP more than 3.0 mg/L determined by laboratory. (technician having experience of more than 20 yrs)

Hypothesis: Raised high sensitivity C- reactive protein (hsCRP) is associated with ischemic stroke.

MATERIAL AND METHODS

This case control study was conducted in the Department of Medicine, Allama Iqbal Memorial Teaching Hospital Sialkot during a period of six months 1st January, 2018 to 30th June, 2018. Non probability consecutive sampling technique was used. With the help of WHO sample size calculator, following are the calculations;

Level of significance = 5%

Power of test = 80 %

Anticipated population proportion = 61.9%⁵

¹Assistant Professor of Medicine, Kh. M S Medical College, Sialkot

²MO, BHU Abdullahpur Kollar SKP

³PGR Medicine, Lahore General Hospital

Correspondence to Dr. Rehan Anwar,
Email: drrehan85_hfh@hotmail.com

Anticipated population proportion = 6.6 %⁵

Sample Size = n = 50 patients in each group (i.e. total 100 patients)

Inclusion criteria:

1. Age 40 – 80 years
2. Both Gender
3. Patients with first acute ischemic stroke according to operational definition (determined by history and CT scan reported by HOD Radiology Department)
4. Controls were patients from wards admitted for other diseases matched by age (within ± 5 years) and gender

Exclusion criteria: For cases and controls

1. Recent surgery or trauma determined by history
2. Any liver disease determined by abnormal alanine aminotransferase and ultrasonography (coarse echotexture, hepatomegaly or fatty infiltration)
3. Patient with autoimmune disease ruled out with help of antinuclear antibody.
4. History fever/ septicemia
5. Patients with chronic kidney disease (creatinine >1.4 mg/dl)
6. Patients with history of previous stroke
7. Controls with history of Cardiac disease

Data collection procedure: Ischemic stroke presenting to outdoor, indoor and emergency department of Allama Iqbal Memorial Teaching Hospital Sialkot was offered to be enrolled in the study. After explaining the purpose of study, informed consent was taken from patients. After matching for age and gender, controls were enrolled preferably the patients with other diseases admitted in wards. CT scan of brain was performed and diagnosis confirmed. Blood samples were withdrawn from cases at the time of presentation in emergency. Serum Hs CRP levels were measured. Data was collected in a predesigned proforma containing background information like age, sex and Hs CRP level. History of current smoking and presence of dyslipidemia were also recorded to allow for effect modification.

Data analysis plan: Data was entered and analyze in SPSS version 21.0. Mean with standard deviation was calculated for quantitative variables like age and serum Hs CRP.

Frequency and percentages were calculated for qualitative variables like smoking, hypertension, diabetes mellitus, hyperlipidemia, gender, raised Hs CRP. Frequency of Hs CRP was compared in cases and control by using Chi-square test. Odds ratio were calculated. Effect modification like diabetes mellitus, hyperlipidemia, hypertension and smoking were controlled through stratification. P-value ≤.05 was taken as level of significance.

RESULTS

Data was entered and analyzed in SPSS version 21.0. Total 100 patients were included according to the inclusion criteria of the study. Patients were divided into two equal groups; cases were consisted of patients presented with ischemic stroke and control were the healthy population.

Mean age (years) in the study was 58.53±13.01 with ranges from 40 to 80 years. Mean serum high sensitivity CRP was 4.67±2.92. There were 33(33%) male and 67(67%) female patients who were included in the study according to the inclusion criteria. There were 34 (34.0) patients who had raised hsCRP in the study, as shown in Table1.

There were 16(16%) patients who have history of current smoking, as shown in Table. No 05. There were 47(47%) patients presented with dyslipidemia. There were 63(63%) patients who were found hypertensive. There were 79(79%) patients who were presented with diabetes mellitus. The objective of the study was to determine the association between high sensitivity C-reactive protein and ischemic stroke patients. In the study, raised hsCRP among both the groups was 30(60%) and 4(8%) respectively. Chi-square test was used to compare frequency of high sensitivity C-reactive protein among both the groups which was statistically significant (p-value 0.000), as shown in Table 2.

Effect modifier like age was stratified and compared with frequency raised hsCRP among both the groups. There were 18(60%) and 1(25%) patients who have raised hsCRP among both the groups having age 40 – 50 years whereas 12(60%) and 3(6.5%) patients have raised hsCRP level among both the groups, these patients have age 51 - 80 years which was statistically not significant (p-value 0.185), as shown in Table 3.

Effect modifier like gender stratification was compared with frequency raised CRP level among both the groups. There were 08 (50.0) male and 22(64.7%) female patients having raised CRP levels which was statistically significant (p-value 0.001), as shown in Table4. There were 24(61.5%) and 3(12.5%) patients who are hypertensive among both the groups which was statistically significant (p-value 0.000), as shown in Table 5. There were 19(73.1%) and 3(14.3%) patients having dyslipidemia among both the groups respectively which was statistically significant (p-value 0.000), as shown in Table. No. 06. There were 03 (42.9) patients of ischemic stroke who have history of current smoking, which was statistically not significant (p-value 0.029), as shown in Table 7.

Table1: Frequency and percentage of Raised hsCRP

	Frequency	Percentage
Raised HsCRP		
Yes	34	34.0
No	66	66.0
Cases		
Yes	30	60.0
No	20	40
Control		
Yes	4	8.0
No	46	92.0

Table 2: Comparison of Raised hsCRP among both the groups

	Cases	Control
Raised HsCRP		
Yes	30(60%)	4(8%)
No	20(40%)	46(92%)
Total	50(100%)	50(100%)

P value=0.000, Odd ratio+17.25

Table 3: Effect modifier like Age stratification with Raised hsCRP in both the groups

Raised HsCRP	Cases	Control
40-50 years (P value=0.18, odd ratio=4.50)		
Yes	18(60%)	1(25%)
No	8(40%)	43(93.5%)
51-80 years (P value=0.000, Odd ratio=21.50)		
Yes	12(60%)	3(65%)
No	8(40%)	43(93.5%)
Total	245(100%)	245(100%)

Table 4: Effect modifier like Gender stratification with Raised hsCRP in both the groups

Raised HsCRP	Cases	Control
Male (P value=0.001, odd ratio=1.45)		
Yes	8(50%)	1(1.2%)
No	22(64.7%)	4(12.1%)
Female (P value=0.000, Odd ratio=1.10)		
Yes	8(50%)	17(100%)
No	12(35.3%)	28(87.9%)
Total	50(100%)	50(100%)

Table 5: Effect modifier like stratification of Hypertension with Raised hsCRP among both the groups

Raised HsCRP	Cases	Control
Hypertension Yes (P value=0.000, odd ratio=11.20)		
Yes	24(61.5%)	3(12.5%)
No	15(38.5%)	21(87.5%)
Hypertension No (P value=0.000, Odd ratio=30.0)		
Yes	6(54.5%)	1(3.8%)
No	5(45.5%)	25(96.2%)
Total	50(100%)	50(100%)

Table 6: Effect modifier like Dyslipidemia stratification with Raised hsCRP in both the groups

Raised HsCRP	Cases	Control
Dyslipidemia Yes		
Yes	19(73.1%)	3(14.3%)
No	7(26.9%)	18(85.7%)
Dyslipidemia No		
Yes	11(45.8%)	1(3.4%)
No	13(54.2%)	28(96.6%)
Total	50(100%)	50(100%)

Table 7: Effect modifier like Smoking with Raised hsCRP in both the groups

Raised HsCRP	Cases	Control
Smoking Yes (P value=0.029, Odd ratio=6.75)		
Yes	3(42.9%)	1(1%)
No	4(57.1%)	9(100%)
Smoking No (P value=0.000, Odd ratio=15.19)		
Yes	27(62.8%)	4(9.8%)
No	16(37.2%)	36(90.2%)
Total	50(100%)	50(100%)

DISCUSSION

High levels of CRP are associated with increased risk of acute stroke. Patients with elevated CRP levels within 72 hours of stroke have increased mortality rate. CRP is a biomarker for systemic inflammation. However, vascular inflammation is more linked to high-sensitivity CRP (hsCRP). The association between hsCRP and a high stroke severity remains unexplained. Possibility exists that elevated hsCRP may be a direct outcome of the extent of cerebral tissue injury.

Infections and inflammation provide the essential pathophysiological basis for atherosclerosis. High sensitive C-reactive protein (hsCRP) is a sensitive marker of inflammation and tissue insult in the arterial wall. CRP, synthesized in the liver is a glycoprotein and plays a pivotal role in the development of atherosclerotic disease in cardiac and cerebral circulation.

Cerebrovascular ischemia has been associated with bronchial and periodontal infections.⁸⁴ High hsCRP being marker of infection and inflammation has been linked with acute stroke. Infections and inflammatory diseases being more common in Indo-Pak compared to western countries so we decided to investigate the relation of high hsCRP (>3 mg/L) levels in patients with ischemic stroke and its subtypes. A very limited number of studies are available from India and Pakistan on the association of hsCRP with ischemic stroke subtypes.

In our study, mean age (years) in the study was 58.53±13.01 with ranges from 40 to 80 years. Similarly, in a study by Chaudhuri et al,⁵ mean age in years was 61.2±14.2.

In a study conducted in 2013⁵, observed that mean serum high sensitivity CRP was 3.8±2.5. Whereas, in our study, mean serum high sensitivity CRP was 4.67±2.92. In our study, there were 34(34%) patients who have raised hsCRP. Likewise, in a study by Chaudhuri et al⁵ frequency and percentage of raised hsCRP was 130 (61.9). In our study, there were 16(16%) patients who have history of current smoking. Similarly, in a study conducted in 2013⁵, patients with history of current smoking was 89(42.3%).

CONCLUSION

The study concluded that there is an association between high sensitivity C - reactive protein and ischemic stroke patients. This study will help physicians to identify patients at higher risk for ischemic stroke with the help of biomarkers like hsCRP so that mortality and morbidity associated with stroke can be reduced.

REFERENCES

- Vos.T, Barbar.RM, Bell.B, Bertozzi-villa.A, Biryukov.S, Bolliger.I, et al, Global, regional and national incidence, prevalence and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013, a systematic analysis for the Global burden of disease study 2013. The Lancet 2015;386:743-800.
- Di Napoli M, Elkind MS, Godoy DA, Singh P, Papa F, Popa-Wagner A. Role of C-reactive protein in cerebrovascular disease: a critical review. Expert Rev Cardiovasc Ther. 2011; 9: 1565-84
- Cai C, Hua W, Ding LG, Wang J, Chen KP, Yang XW et al. High sensitivity C-reactive protein and cardiac resynchronization therapy in patients with advanced heart failure. Journal of Geriatric Cardiology. 2014;11: 296-302.
- Luna JM, Moon YP, Liu KM, Spitalnik S, Paik MC, Cheung K, et al. High-sensitivity C-reactive protein and interleukin-6-dominant inflammation and ischemic stroke risk: the northern Manhattan study. Stroke. 2014; 45: 979-87
- Chaudhuri JR, Mridula KR, Umamahesh M, Swathi A, Balaraju B, Bandaru VC. High sensitivity C-reactive protein levels in Acute Ischemic Stroke and subtypes: A study from a tertiary care center. Iranian journal of neurology. 2013;12(3):92.

6. Den Hertog HM, Van Rossum JA, Van der Worp HB, Van Gemert HMA, De Jonge R, Koudstaal PJ, et al. C-reactive protein in the very early phase of acute ischemic stroke: association with poor outcome and death. *J Neurol*. 2009;256(12):2003-8
7. Libby P. Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr*. 2006;83(2):456S-60S
8. Pftzner A, Forst T. High-sensitivity C-reactive protein as cardiovascular risk marker in patients with diabetes mellitus. *Diabetes Technol Ther*. 2006;8(1):28-36.
9. Wakugawa Y, Kiyohara Y, Tanizaki Y, Kubo M, Ninomiya T, Hata J, et al. C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. *Stroke*. 2006;37(1):27-32
10. Ishikawa J, Tamura Y, Hoshide S, Eguchi K, Ishikawa S, Shimada K, et al. Low-grade inflammation is a risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives: the Jichi Medical School ABPM Study, wave 1. *Stroke*. 2007;38(3):911-7.