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ORIGINAL ARTICLES

Association of High Sensitivity C-reactive Protein in Acute Ischemic Stroke

ISLAM S[1], HAMID R[2], HAQUE MA[3]

Abstract:

Objectives: *Stroke causes 9% of all deaths around the world and it remains the second common cause of death. Around 85% cases, the cause of stroke proved to be ischemic in which atherosclerosis is the pathogenic mechanism. Recent studies have shown that high sensitivity CRP(hsCRP) is a risk factor for ischemic stroke.* ***Aims:*** *To evaluate the association of hsCRP with acute ischemic stroke in Bangladeshi patients.* ***Methods:*** *This case control study was carried out from June 2011 to November 2011 in the department of Neurology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka in all the OPD and admitted stroke patients meeting the inclusion criteria. Serum hsCRP level was assessed in all stroke patients and controls.* ***Results:*** *Mean value of hsCRP among cases was 4.01(SD±2.61) mg/L and among controls was 1.65(SD±1.41)mg/L which was highly significant (p value <0.001). Mean hsCRP value in lacunar infarcts [3.12(SD±2.73)] was lower than nonlacunar large infarct [4.46(SD±2.50)], but the difference was not statistically significant.* ***Conclusion:*** *hsCRP was elevated in the acute phase of ischemic stroke and may be used as a prognostic marker in stroke patients.*

Key words: *High sensitivity, C-Reactive Protein (hsCRP), acute ischemic stroke*

Introduction:

Cerebrovascular stroke is the commonest neurological disorder of adult life is a leading cause of death and disability worldwide[1].It causes 9% of all deaths around the world and after ischemic heart disease it remains the second common cause of death[2]. Around 85% cases, the cause of stroke proved to be ischemic in which atherosclerosis is the pathogenic mechanism due to thrombosis in situ or emboli from extra-cranial sources[3]. Inflammation plays a key role in atherosclerosis, in which immune mechanism interact with metabolic risk factors to initiate, propagate and activate lesions in the arterial tree[4].C-reactive protein (CRP), historically known as an acute phase reactant since 1930, becomes raised in response to various infections, inflammation, immunologic stimuli, necrotic processes, malignancy and tissue injury[5].Physiologic and pathologic variables known to affect CRP results include race, age, sex,lifestyle (exercise, smoking, obesity, alcohol, high protein diet, hormone therapy)[5], diabetes mellitus, obstructive sleep apnea, hypertension and metabolic syndrome[6].In 2003, the centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) recommended plasma CRP measurement as an adjunct to the use of established risk factors for assessing the risk of coronary heart disease(CHD) in persons with a calculated 10-year CVD risk of 10% to 20%[7].They also recommended that the adult population should be stratified in 3 tertiles, at different CV risk: low risk (CRP concentration <1.0 mg/L), average risk

1. Dr. Susmita Islam, Junior Consultant (Medicine), Bangabandhu sheikh Mujib Medical College Hospital, Faridpur, Bangladesh
2. Dr. Rayhan Hamid, Assistant Professor, Department of Physical Medicine &Rehabilitation, NITOR, Dhaka, Bangladesh
3. Dr. Md.Amirul Haque,Professor,Department of Neurology, Bangladesh Specialized Hospital, Dhaka, Bangladesh

(1.0 to 3.0 mg/L) & high risk (>3.0 mg/L). Later in 2003, the CRP Pooling Project Special Report was published as an extension of the AHA/CDC recommendations in respect to cerebrovascular disease[3]. Recent evidence has clearly demonstrated that those with baseline CRP concentrations or more specifically, high-sensitivity C-reactive protein (hsCRP), in the highest tertile are at two to four times the risk of future cardiac death compared with those with hsCRP in the lowest tertile at all levels of low-density lipoprotein (LDL)-cholesterol, metabolic syndrome and Framingham Risk Score[8].

It has been consistently observed that higher concentrations of CRP are associated with larger brain infarct and worst neurologic outcome[6]. Analysis by etiologic subtype according to TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria showed associations for all subtypes during the acute stage[9]. At the follow-up, there was a strong association between CRP and large-vessel disease, whereas no significant association was detected for small-vessel lacunar stroke, cardio embolic stroke or cryptogenic stroke[9].

CRP fulfils most of the requirements of a new risk and prognostic predictor, but several issues await further confirmation and clarification before this marker can be included in the routine evaluation of stroke patients and subjects at risk for cerebrovascular disease. The purpose of this study is to evaluate the association between hsCRP with acute ischemic stroke.

Materials and method:

This case control study was conducted in the department of Neurology in collaboration with the department of Immunology in BIRDEM General Hospital, Dhaka from June 2011 to November 2011.All the patients with stroke attending the outpatient department and also admitted into Neurology Department were included in the study. Patient of >30 years of age presented with acute ischemic stroke (<4 weeks of duration) proved clinically and by neuroimaging (CT/MRI of brain) were defined as case and apparently healthy and age and sex matched with the case were control. Patient with stroke from any cause other than cerebral infarction, ongoing or recent (within 1 month) infectious disease, history of chronic inflammatory disease, cancer, myocardial infarction (MI) within 3 months, previous stroke within 3 months, recent (within 1 month) trauma or surgical operation, recovery of the neurological deficit less than 24 hours, inability to demonstrate a consistent brain ischemia at CT or MRI were excluded from the study. The study was approved by the Ethical Committee of BIRDEM Hospital and informed consent was taken from all individual participants. After taking detailed history and doing physical examination a total of 57 patients were included for neuroimaging (CT scan/ MRI of brain) study. Among them 17 patients were excluded due to the evidence of stroke other than infarction. Ultimately a total of 30 patients were included in the study group from the remaining 40 patients. Among the 10 discarded patients 3 of the female patients had urinary tract infection, 2 had very high ESR (~80 mm in 1st hour), 3 had ECG evidence of recent inferior MI and remaining 2 had hsCRP level > 10mg/L. All of them were routinely investigated for hsCRP, complete blood count, urine R/E, serum creatinine, fasting blood sugar, serum lipid profile, ECG and chest X-ray P/A view. A total of 30 age and sex matched and apparently healthy non-stroke persons were taken as controls. Ischemic stroke patients were divided on the basis of TOAST[10] criteria (lacunar syndrome and imaging evidence of subcortical and brainstem infarcts <1.5 cm) into two broad groups - lacunar and non-lacunar stroke groups. According to the CRP pooling project special report[11]hsCRP values are categorized into low(<1mg/L), average (1-3mg/L) and high (>3mg/L) tertile risk groups. All the obtained data were recorded in a pre-structured case record form. Data analysis was done by Computer based software; statistical package for social sciences (SPSS) version 22 was used to analyze collected data. Appropriate analysis, such as Unpaired Student's 't' test, Chi-square test were carried out. P value<0.05 was taken as level of significance.

Results:

Among 30 patients 23 patients (76.7%) were male and 7 patients (23.3%) were female. Majority

(73.3% in cases and 63.3% in controls) of study subjects were sedentary in occupation(Table- I).

In case group 13(43.3%) were smokers compared to 9(30%) among control group (p value>0.10^{ns}). Hypertension were almost similarly prevalent among case [9(30%)] and control [13(36.7%)]. Diabetes was significantly (p value <0.05*) distributed among cases[10(33.3%)], only 2 controls had DM. Ischemic heart disease were present among 7 (23.3%) cases and among 3 (10%) controls (p value>0.10^{ns}). (Table -II)

Among cases almost all [28(93.3%)] had hsCRP values between average to high risk whereas most of the controls [27(90%)] had values between low to average risk (Table-III). Mean value of hsCRP in cases was 4.01 (SD±2.61) mg/L compared to 1.65 (SD± 1.41) in controls which was highly significant (p value<0.001) (Table-IV).

Mean hsCRP value in lacunar infarcts [3.12(SD±2.73)] was lower than nonlacunar large infarct [4.46(SD±2.50)], but the difference was not statistically significant (Table-V).

Significant difference (p value <0.05) in hsCRP value between case and control were observed in all age group except > 70 years of age. Females in both case [4.65(SD ±2.62)] and control

Table-I

Demographics of study subjects

Parameters	Case (n=30)		Control (n=30)		P value	Odds ratio	95% CI
	No.	(%)	No.	(%)			
Sex				>0.50^{ns}	1.000	0.302	3.308
Male	23	(76.7)	23	(76.7)			
Female	7	(23.3)	7	(23.3)			
Occupation				>0.10^{n}	1.592	0.531	4.775
Sedentary	22	(73.3)	19	(63.3)			
Non sedentary	8	(26.7)	11	(36.7)			

Chi square test
ns = Not significant
*** = Significant

Table-II

Risk factors present among the study subjects

Parameters	Case (n=30)		Control (n=30)		P value	Odds ratio	95% CI
	No.	(%)	No.	(%)			
Smoking habit					>0.10^{ns}	1.784	0.616 5.169
Yes	13	(43.3)	9	30.0)			
No	17	(56.7)	21	(70.0)			
Hypertension					>0.50^{ns}	0.740	0.252 2.175
Yes	9	(30.0)	11	(36.7)			
No	21	(70.0)	19	(63.3)			
Diabetes Mellitus					<0.05*	7.000	1.381 35.478
Yes	10	(33.3)	2	(6.7)			
No	20	(66.7)	28	(93.3)			
Past history of stroke					<0.05*	2.250	1.670 3.032
Yes	6	(20.0)	0				
No	24	(80.0)	30	(100.0)			
Presence of IHD					>0.10^{ns}	2.739	0.635-11.823
Yes	7	(23.3)	3	(10.0)			
No	23	(76.7)	27	(90.0)			

Chi square test

Table-III

Level of hsCRP among study subjects

Parameters	Case (n=30)		Control (n=30)		P value
	No.	(%)	No.	%	
hsCRP (mg/L)					<0.001***
<1(low)	2	(6.7)	12	(40.0)	
1 3 (average)	12	(40.0)	15	(50.0)	
>3 (high)	16	(53.3)	3	(10.0)	

The tertile values of hsCRP are adapted from the CRP pooling project special report[11].

Table-IV

Comparison of hsCRP level between study groups

hsCRP (mg/L)	Case (n=30)	Control (n=30)	t value	df	P value
Mean±SD	4.01±2.61	1.65±1.41	4.362	58	<0.001***
Range	0.16 9.63	0.16 6.75			

Unpaired Student's 't' test

Table-V

Effect of aetiologic subtypes of cerebral infarction on hsCRP level

hs CRP (mg/L	Lacunar infarction (n=10)	Non-lacunar large infarction (n=20)	t value	df	P value
Range	0.81-9.63	0.16-9.36			
Mean±SD	3.12±2.73	4.46±2.50	-1.352	28	>0.10ns

Unpaired Student's 't' test

[2.26(SD±1.20)] has elevated mean hsCRP value than male case[3.82(SD±2.64)] and control [1.47(SD±1.44)] groups respectively although it was not significant. Mean hsCRP value in slightly higher between normal and overweight subjects in both case and control group. Similarly mean hsCRP values were slightly higher in smoker than nonsmokers in both case and control groups. Among hypertensive stroke patients mean hsCRP values were surprisingly lower than their normotensive counterparts. But hypertensive controls had slightly higher value than normotensive controls. Reverse was seen among diabetic case and controls. Those who had recurrent stroke had higher mean hsCRP value than who had a single attack of stroke. Interestingly ischemic heart disease (IHD) patients in both case and control groups had lower mean hsCRP value than subjects who did not had IHD. Those subjects who were taking CRP lowering agents (Aspirin or ACE-I/ARB or Statins) had relatively lower mean hsCRP value than who did not take in both case and control groups. None of the values in this analysis reach statistical significance (Table-VI)

Table-VI

Effect of age,sex and risk factors on hsCRP level

Age/ hsCRP (mg/L)	Case (Mean±SD)	Control (Mean±SD)	t value	df	P value
41 50 years	4.55±2.86 (n=9)	1.79±2.02 (n=9)	2.371	16	<0.05*
51 60 years	3.52±2.48 (n=11)	1.67±1.35 (n=11)	2.172	20	<0.05*
61 70 years	4.10±2.86 (n=7)	1.45±0.75 (n=7)	2.366	12	<0.05*
71 80 years	4.00±2.85 (n=3)	1.65±1.13 (n=3)	1.332	4	>0.10ns
Sex/ hsCRP (mg/L)	Case (Mean±SD)	Control (Mean±SD)	t value	df	P value
Male	3.82±2.64 (n=23)	1.47±1.44 (n=23)	3.762	44	<0.001***
Female	4.65±2.62 (n=7)	2.26±1.20 (n=7)	2.193	12	<0.05*
P value	>0.10n s	>0.10ns			
Risk factors/ hsCRP (mg/L)	Case (Mean±SD)	Control (Mean±SD)	t value	df	P value
BMI(kg/m^2)					
Normal (<24.99)	3.92±2.61 (n=26)	1.37±0.90 (n=22)	4.369	46	<0.001***
Overweight (25.00 29.99)	4.62±2.96 (n=4)	2.42±2.21 (n=8)	1.462	10	>0.10ns
P value	>0.50ns	>0.05ns			
Smoking habit					
Present	4.58±2.80 (n=13)	1.29±1.17 (n=9)	3.313	20	<0.01**
Absent	3.59±2.46 (n=17)	1.81±1.50 (n=21)	2.748	36	<0.01**
P value	>0.10ns	>0.10ns			
Hypertension					
Present	3.22±2.62 (n=9)	2.04±1.74 (n=11)	1.201	18	>0.10ns
Absent	4.36±2.59 (n=21)	1.43±1.17 (n=19)	4.525	38	<0.001***
P value	>0.10ns	>0.10ns			
Diabetes mellitus					
Present	4.36±2.27 (n=10)	1.48±0.81 (n=2)	1.715	10	>0.10ns
Absent	3.85±2.81 (n=20)	1.66±1.45 (n=28)	3.514	46	<0.001***
P value	>0.50ns	>0.50ns			
Past history of stroke					
Present	4.41±3.05 (n=6)	0			
Absent	3.91±2.55 (n=24)	1.65±1.41 (n=30)	4.138	52	<0.001***
P value	>0.50ns				
Presence of IHD					
Present 3.18±1.69	0.94±0.52 (n=7)	2.184 (n=3)	8	>0.50ns	
Absent	4.27±2.81 (n=23)	1.73±1.46 (n=27)	4.090	48	<0.001***
P value	>0.10ns	>0.10ns			
History of CRP lowering drugs					
Present	3.13±1.54 (n=6)	1.26±0.82 (n=5)	2.428	9	<0.05*
Absent	4.24±2.80 (n=24)	1.73±1.50 (n=25)	3.931	47	<0.001***
P value	>0.10ns	>0.50ns			

Unpaired Student's 't' test

Discussion:

Several prospective studies found a significant independent association between CRP and the risk of stroke[12]. A meta-analysis of studies with long-term follow-up showed that the risk for stroke in healthy individuals with the highest quartile of CRP concentrations increased nearly 1.7-fold compared with those with the lowest quartile.[13]. In a nested case-control study among patients after a cerebrovascular event included in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) clinical trial, odds ratios for a recurrent event associated with the top versus bottom tertile were 1.39 for CRP[14].

In our study 77.6% of cases were male and male to female ratio was 2.7:1, which coincide with the other study done in Bangladesh[15].The high percentage of male in this study probably reflect the neglected state of our womenfolk who less frequently seek health care support. In this study hypertension were present only in 30%(9) of cases which was far less than the findings of the studies done previously in Bangladesh[15,16]. But it coincides with recently published Heart disease and stroke statistic: 2008 update by AHA which showed that 35.3% of non lacunar stroke patients has hypertension[17]. Probable explanation in our context was selection bias and or small number of study subjects.In this study 43.3%(13) were smoker, which is lower than a previous study (59.84%) done by Ullah et al., in 2002[18]. Diabetes mellitus was present in 33.3% (10) of cases, which corroborate with another finding of Ullah et al., who in 1993 found diabetes among 30% of their stroke patients[19]. Most (73.3%) of the stroke patients were sedentary which validated the fact that regular exercise prevents ischemic stroke[17].

Mean value of hsCRP among cases was 4.01(SD±2.61)mg/L and among controls was 1.65(SD±1.41)mg/L which was highly significant (p value <0.001). The value ranges from 0.16 to 9.63 mg/L among cases and from 0.16 to 6.75 among controls. These findings are consistent with several studies[20,21,22]. Keith et all. showed a higher proportion of patients with CRP above the mean had definite infarcts identified on CT scan (84% versus 66%;). In the low-CRP group, 35 of 132 patients died compared with 46 of 96 in the high-CRP group in the study period; this equated to a significant survival difference in survival between above and below mean log CRP groups (P=0.00009, log-rank test), with increased mortality in those with higher CRP concentrations[23].David et all. showed that ischemic stroke rates per 1000 person-years rose in a dose-dependent manner, from 4.1% for CRP levels in the bottom tertile to 5.9% in the middle tertile and 10.5% in the top tertile (P<0.001). Rates of ischemic stroke nearly doubled between those with CRP levels >10 mg/L and those with levels 3 to 10 mg/L, providing further support for the predictive value of CRP levels >10 mg/L[24].

We also compare the CRP level between lacunar and nonlacunar large stroke. Although not statistically significant, mean value in lacunar stroke [3.12(SD±2.73) mg/L] were lower than large atherovascular stroke [4.46(SD±2.50)mg/L]. The findings coincide with main conclusions of many studies that high concentrations of plasma CRP are associated with progression, and rupture of atherosclerotic plaques; and subsequent cerebrovascular events[6]. The mean hsCRP value of lacunar stroke is consistent with the findings of a recent study by Teruzzi et al[21].

We also sought to find out the effect of sex, BMI, smoking, hypertension, diabetes mellitus, recurrent stroke, ischemic heart disease and certain CRP lowering drugs on both case and control groups. Although none of the findings reach statistical significance, there were some interesting observations. Over weight persons in both cases [4.62(SD±2.96) mg/L] and controls [2.42(SD±2.21) mg/L] had higher values than normal cases [3.92(SD±2.61) mg/L] and controls [1.37 (SD±.090)mg/L] respectively. Smokers [4.58(SD±2.80)mg/L] with stroke had higher value than nonsmokers [3.59(SD±2.46)mg/L]. This is consistent with previous studies[5].

Diabetic stroke patients had higher mean values [4.36(SD±2.27)mg/L] than nondiabetic stroke patients [3.85(SD±2.81)mg/L] consistent with other studies[5,6]. Recurrent stroke patients had slightly higher mean value [4.41(SD±3.05)mg/L] than who

have only single attack[3.91(SD±2.55)mg/L] coincides with study done by Di Napoli et al [22]. In both case and control subjects with IHD mean hsCRP values were surprisingly lower. Possible explanations for these unusual discrepancies are that it may be due to selection bias or small number of study subjects or due to confounding variables.

Limitations of Study:

This was a relatively small study, so the study results should be cautiously extrapolated to larger perspective. As it was an observational study and not prospectively designed for a significant period of time, all the participants were assessed at a single point of time. So, the study was not powered to assess the efficacy of hsCRP as a prognostic marker for ischemic stroke.

Conclusion:

Our study found that serum hsCRP level was significantly elevated in the acute phase of ischemic stroke in either sex. But this elevation was not significantly affected by age, smoking habit, body weight, intake of certain medications and other co-morbidities; i.e. hypertension, diabetes mellitus, previous stroke and ischemic heart disease. Although not statistically significant hsCRP were more elevated in nonlacunar large stroke than lacunar stroke.

Conflict of Interest: None

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