C–reactive Protein and Early Mortality in Acute Ischemic Stroke

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ABSTRACT

Background

There is growing evidence that inflammation plays an important role in atherogenesis. Several studies have shown that C-reactive protein (CRP), an inflammatory marker, is associated with stroke severity and outcome. But limited studies are there which show the relationship of CRP with early mortality i.e within seven days.

Objective

To study the association of CRP within 24 hours after acute ischemic stroke onset with severity during admission, types of ischemic stroke and outcome.

Methods

This cross sectional study was done including 100 consecutive cases of acute ischemic stroke admitted to Neurology center of College of Medical Sciences, Bharatpur (Chitwan), Nepal. The cases were classified as per TOAST classification and severity at admission assessed using National Institutes of Health Stroke Scale. C-reative protein (CRP) level was estimated by latex particle agglutination test.

Result

Thirteen percent patients expired by 7th day. In the expired group, CRP was positive in 15.3 percent, 15.3 percent and 61.5 percent in patients with lacunar, cardioembolic and large artery atherosclerotic infarction respectively (p 0.19). CRP was positive in all 7 patients (53.8%) who had expired with severe NIHS scale (p 0.004).

Conclusion

High CRP level is associated with stroke severity at admission and is an independent predictor of early seven day mortality after ischemic stroke

KEY WORDS

atherosclerosis, C-reactive protein, cardioembolic. ischemic stroke, lacunar

INTRODUCTION

Experimental and clinical evidence accumulated since 1990 have shown that inflammation plays a key role in atherogenesis.[1] The most studied biomarkers of inflammation C-reactive protein (CRP) is an acute phase reactant protein which is produced predominantly by hepatocytes under the influence of cytokines i.e. interleukin (IL)-6 and tumor necrosis factor-alpha. It is markedly up regulated in atheromatous plaques where it promote LDL cholesterol uptake by macrophages, a key step in atherogenesis.[2] CRP levels in high normal range have been shown to be a reliable measure of underlying systemic inflammation and predictor of future cardiovascular events in prospective cohort studies.[3-5] As in coronary artery disease, there is increasing evidence that inflammatory process is being involved in cerebral ischemia as well and an elevated CRP levels may predict future ischemic stroke.[6-9] In metaanalysis of studies of long term follow up, Preindropil Protection Against Recurrent Stroke (PROGRESS) clinical trial and "Benzfibrate Infarction Prevention (BIP) Study" the figures for recurrent event was 1.7, 1.34 and more than two fold increased risk in highest versus lowest tertile group respectively.[10-12] In addition, raised CRP levels may reflect the clinical course of the condition extent of brain infarction and an adverse prognosis.[13-16] In all these studies focus was on mortality at one month and thereafter. No such data is available from Nepal. With this background,

Table 1. Prevalence of CRP with the risk factors of stroke.

Risk Factors		No Cases (%)	CRP positive No of cases	Percentage
Smoking	yes	66	41	62.1%
	no	34	22	
Alcohol	yes	43	27	62.8%
	no	57	36	
HTN	yes	72	46	63.8%
	no	28	17	
DM	yes	19	11	57.9%
	no	81	52	
CAD	yes	15	9	60%
	no	85	57	
Dyslipidemia	yes	53	42	79.2%
	no	47	15	
Total		100	63*	63%

*CRP was positive in cases where risk factors were more than one.

the present study was undertaken to study the relation of CRP with severity and mortality in ischemic stroke.

METHODS

The present study was a cross sectional study which included 100 consecutive cases of first time ischemic stroke, admitted to Neurology Center of College of Medical Sciences (COMS), Bharatpur (Chitwan), during the period from November 2007 to April 2009. Written consent was taken from their relatives. All cases of hemorrhagic stroke, subarachnoid hemorrhage, TIA (Transient Ischemic Attack), brain tumor, and those having major systemic disorders and malignancy were excluded. Care was taken to exclude other causes associated with raised CRP. TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification was used to classify the etiology of stroke as lacunar, cardioembolic and large artery atherosclerosis.[17] Severity of stroke was categorized as mild (NIHS score less than 4), moderate (NIHS score 4 to 15) and severe (NIHS score >15) according to National Institute of Health Stroke (NIHS) Scale.[18] The risk factors were identified in each case. None of the patients were thrombolysed. All the cases were treated according to the American Stroke Association's (ASA) guidelines.[19] No neuroprotective drugs or vasodilators were used. All patients were put on deep vein thrombosis prophylaxis. The sample for CRP was taken at the time of admission and analyzed by qualitative rapid latex slide tests, based on the immunologic reaction between CRP as an antigen and latex particles coated with monospecific anti-human CRP.[20] The data was analyzed using SPSS version 16. p value was determined using Chi square test.

RESULTS

Relationship of CRP positivity to risk factors of stroke is shown in Table-1 and to stroke severity, type of the stroke and mortality in Table 2. In the present study CRP was positive in 79.2% in patients with dyslipidemia, 63.8% in patients with hypertension, 62.8% in alcohol consumers, 62.1% in smokers, 60% in patients with coronary artery disease and 57.9% in diabetic. CRP test was positive in 63% of cases studied and in 93% of cases who expired by seven days (p 0.01). In the discharged group, CRP was positive in 29.8% in patients with lacunar, 13.8% in patients with cardioembolic and 14.9% in patients with large artery atherosclerotic infarction. In the expired group, CRP was positive in 15.3%, 15.3% and 61.5% in patients with lacunar, cardioembolic and large artery atherosclerotic infarction respectively (p 0.19). The number of patients who expired having severe NIHS scale was 7/13 (53.8%) and CRP positive in all the cases (p 0.004).

Table 2. Association of CRP with stroke severity, stroke etiology and stroke outcome.

Variable	No of cases	Discharged cases (n=87)		Expired cases (n=13)		X^2	p value
		CRP positive	CRP negative	CRP positive	CRP negative		
TOAST							
Lacunar	45	26 (29.8%)	17 (19.5%)	2 (15.3%)	0	3.32	0.19
Cardioembolic	19	12 (13,8%)	4 (4.6%)	2 (15.3%)	1 (7.7%)		
LAA	36	13 (14.9%)	15 (17.2%)	8 (61.5%)	0		
NIHSS							
<4	29	11 (12.6%)	18 (20.7%)	0	0	11.04	0.004
4-15	53	35 (40.2%)	12 (13.8%)	5 (38.4%)	1 (7.7%)		
>15	18	7 (8.0%)	4 (20.7%)	7 (53.8%)	0		
Mortality							
7-day	13	-	-	12 (92.3%)	1(7.7%)	5.5	0.01

*LAA-Large artery atherosclerosis..

DISCUSSION

Traditional methods for measuring serum CRP are available for use in patients with infectious and inflammatory disorders.[21] These assays typically have a detection limit that in the range of 3 to 5 mg/L, which is above the concentration observed in most apparently healthy individuals. High sensitivity methods for measurement of CRP (hs-CRP) detect concentrations down to 0.3 mg/L. The assays are necessary for cardiovascular risk stratification, which is based upon discrimination of CRP levels extending below 3 mg/L. This test is sensitized to detect CRP levels less 1 mg/dl (10micgm/ml). The latex slide test has the advantage of rapid performance, simple and cost effective in comparison to other tests for detection of CRP.[22]

In the present study a positive level of CRP was noted in 63 percent of cases studied. It was unrelated to the presence or absence of risk factors of obesity, smoking, alcohol abuse, hypertension, diabetes mellitus and coronary artery diseases. In "Benzfibrate Infarction Prevention (BIP) Study" which included 3122 cases of stable coronary heart disease (aged 45-74 years) and followed up for 6.2 years raised CRP levels was noted in high proportion of women and in those having risk factors for stroke. Only total and LDL cholesterol was not related to CRP levels. While the fasting blood glucose and triglycerides were directly related to CRP levels and an inverse relationship was noted with HDL cholesterol.[12] However, in contrast to our studies where only 15 percent patient has coronary artery disease, all patients in BIP study had preexisting stable athero-thrombotic cardiac disease.

Several studies have reported a significant relationship with the type of stroke and its severity.[14-16] In this study CRP positive rate of 61.5 percent was found in patients having large artery atherosclerosis (p 0.19) but 92.2% was noted in patients having moderate and severe neurological deficits (p 0.004) which showed a significant relationship with severity at presentation.

Nepal is a developing country with low per capita income where patient has to bear the cost of treatment, hence in our hospital there is a trend to go on early discharge. Thus, only data of early mortality can be reliably studied. Also, early worsening is common in stroke cases necessitating corrective measures to avoid short and long term adverse events. Hence in this study early mortality at seven day was studied and CRP was positive in 92% of the expired cases (p 0.01). However, studies reporting early mortality are few and have not studied the impact raised CRP on mortality.[22-24] The studied quoted above had reported adverse impact of raised CRP on late mortality only.[14-16]

Di Napoli et al measured CRP levels in 193 patients of acute ischemic stroke at 24, 48 and 72 hours and at discharge and found that persistently elevated (> 1.5 mg/dl) or a increasing CRP values (crescendo pattern) at discharge predicted adverse prognosis and had strongest association with outcome at one year in a multivariate model.[15] This pattern represented either an ongoing inflammatory process or the extension of cerebral lesion. Similar to our study, in this study patient with raised CRP had significantly lower Canadian Neurological Score Scale score and had large infarcts and cortical involvement.

The 'Bergen stroke study'(2009) concluded that high admission CRP level, when measured after 24 hours after the ictus, is significantly associated with etiology, stroke severity functional outcome and with late mortality.[16] But unlike our study, the patients with high CRP value had a higher frequency of stroke of cardioembolic origin and early mortality was not studied.

Inspite of small number of cases studied within 18 months and non-availability of the test for detecting highly sensitive CRP levels (hsCRP), our findings supported the previous observations that an elevated CRP reflects the severity and the extent of brain infarct.and is related to early mortality.[9,14-16] CRP can thus be added to the list of predictor of prognosis in ischemic stroke as its levels are affected little by other factors than inflammation, its risk prediction is independent of other known cardiovascular risk factors, and highly sensitive reproducible assays are now available. A study over longer period and involving large number of patient with quantitative estimation of serum CRP levels following the guidelines of Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) is needed for detection of high risk values for prediction of ischemic stroke and for predicting mortality following stroke.[3]

CONCLUSION

High CRP level is associated with stroke severity at admission and is an independent predictor of early seven day mortality after ischemic stroke.

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