Original Article

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C-Reactive Protein Level in Admission and the Outcome of Stroke Survivors

A. Ahmadi Ahangar (MD)[1], P. Saadat (MD)*[1], S.T. Taheri Otaghsara (MSc)[2], S. Alijanpour (MSc)[3]

1.Mobility Impairment Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran

2.Rouhani Hospital, Babol University of Medical Sciences, Babol, I.R.Iran

3.Education, Research and Planning Unite, Pre-Hospital Emergency Organization and Emergency Medical Service Center, Babol University of Medical Science, Babol, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Elevated CRP level is independently associated with the excessive risk of ischemic stroke. However, there is currently no consensus on the use of CRP in detecting and tracking the progression of cerebrovascular diseases. The aim of this study was to determine the relationship between CRP and outcome in stroke patients.

METHODS: This was an analytical cross-sectional study. Patients admitted with diagnosis of ischemic stroke were enrolled. Demographic, and clinical characteristics, medical history, drug abuse and tobacco use and severity of stroke (National Institute of Health Stroke Scale) were completed in checklist.

FINDINGS: Of the total 214 patients, the serum CRP levels in 122 cases (57%) were positive. The mortality during the first week of hospitalization included 17 cases (8%). The differences in CRP serum level with underlying disease such as Diabetes Mellitus (82 cases (51%) of positive CRP vs. 77 cases (49%) of negative CRP, p= 0.007) and Hypertension (59 cases (50.4%) of positive CRP vs. 58 cases (49.6%) of negative CRP, p=0.03) were statistically significant. In addition, high CRP was seen in 10 thrombotic (91%) and 4 embolic (67%) of stroke expire patients (p= 0.034). The difference in CRP serum level in mortality cases was statistically significant (14 cases (82%) of positive CRP vs. 3 cases (18%) of negative CRP, p= 0.032).

CONCLUSION: The positive CRP serum level at the admission was accompanied by more severity of disability in stroke survivor. Checking serum level of CRP in admission is suggested for predicting disability and mortality rate during the first week of post-stroke hospitalization.

KEY WORDS: *C-Reactive Protein, Stroke, Prognosis, Patient Outcome Assessment, Patient Admission, Iran.*

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***Corresponding Author: P. Saadat (MD)**
Address: Mobility Impairment Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran
Tel: +98 11 32190557
E-mail: : sepanta1968@yahoo.com

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Introduction

Stroke is the second leading cause of death worldwide and imposes enormous financial costs on society (1). The types, distribution, and the contribution of stroke risk factors vary across populations(2). Many studies have been carried out to determine markers that can be used to determine the prognosis for different types of ischemic stroke (3).

In stroke, inflammation plays an important role in the pathophysiology of atherosclerosis and ischemic stroke (4). C-reactive protein (CRP), a marker of inflammation, can promote atherosclerosis and predict cardiovascular events (5). In many studies, the level of CRP in ischemic strokes had increased in comparison to the basal concentration and this can be indicative of the intensity of the inflammatory response in acute phase (6). Monitoring plasma hs-CRP levels and cutting down the elevated plasma hs-CRP levels will be beneficial in screening and treatment decisions for the prognosis of acute ischemic stroke (7). Despite numerous reports and studies, there is currently no consensus on the use of CRP in detecting and tracking the progression of cerebrovascular diseases (8).

Given these issues, measurement of CRP levels in acute phase of stroke and the possibility of using serum CRP levels in investigating the severity and prognosis of stroke was done in the present study. The aim of this study is to determine the relationship between CRP and outcome in stroke patients

Methods

This was an analytical study which has been conducted from April 2016 till the end of March 2017 to investigate the association between serum C-reactive levels in the first 24 hours after the onset of ischemic stroke subtypes, intensity, prognosis and outcome during hospitalization in the acute phase. The proposal of the current study was approved by the Research Council and the Ethics Committee of the Medical Researches of Babol University of Medical Sciences (IR.MUBABOL.HRI.REC.1392.1812).

The size of the sample population (around 250 patients) has been chosen according to the sample size determination formula and based on the rate of stroke occurring in this area, which are 50 per 100,000 people (9). Ayatollah Rouhani Hospital (Babol) is the main center of admissions for stokes patients in the city of Babol and the surrounding villages. Stroke was diagnosed by a neurologist, based on the patient's history, neurological examination and neuroimaging studies which were performed for all stroke patients. Inclusion criteria of current study were all patients admitted to Ayatollah Rouhani hospitals with diagnosis of ischemic stroke with informed consent, and were enrolled in the study. Patients with transient ischemic attack (TIA), metabolic, systemic, traumatic, space occupying lesions with hemi paresis or any focal neurological symptoms or signs, or stroke mimickers (seizure, migraine) were excluded. Those who had renal or hepatic failure, gout and the ones treated with corticosteroid were also excluded. Demographic data and history of hypertension, diabetes, cardiovascular disease, hyperlipidemia, TIA and drug and tobacco use were collected based on a checklist. The amount of serum CRP levels was also recorded. Diagnosis of stroke and its types was made according to the criteria of the study by Yew et al. (10).

Stroke in this study was divided into ischemic and hemorrhagic types. Hemorrhagic strokes were excluded. The ischemic type was divided into thrombotic and embolic subtypes. Embolic ischemic patients of our study included both artery-to-artery embolism and cardio embolisms. At least one brain imaging (C.T. or M.R.I. scan) was performed for all patients and definitive diagnosis of stroke cases was confirmed by the neurologist responsible to do the project.

Severity of stroke was determined on the basis of NIH Stroke Scale (NIHSS) criteria: score $\leq$ 8 mild stroke; 9 – 15, moderate stroke; and $\geq$ 16 severe stroke (1). At the time of this study, it was not possible to perform intravenous thrombolytic therapy or any interventional procedures at the mentioned center, although these facilities are now available.

Serum CRP levels were measured using Latex Particle Agglutination Test. In this method, anti-CRP-sensitized latex particles adjacent to the CRP present in the serum sample produce agglutination (11). In this study, CRP values greater than 5 mg/dl of serum were taken as positive and lower amounts were considered normal (negative). The higher rates were reported as qualitative as +1, +2, +3, +4 according to the agglutination status.

The data were analyzed quantitatively and qualitatively using the SPSS (version 23). Chi-square test was used to determine the difference between serum CRP and prognosis of ischemic stroke, and other variables influencing the stroke were analyzed using Fisher's Exact Test. Odds ratio (OR) was measured due

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to association between the exposure and outcome. P-values less than 0.05 were considered significant.

Results

246 patients with diagnosis of ischemic stroke were admitted to the Ayatollah Rohani Hospital in Babol, among whom 214 cases were considered eligible for the study. Table 1 shows the frequency of different types of ischemic stroke and gender and age of patients. Patients with a history of ischemic heart disease were statistically significant with a significance level of 0.02 and a confidence interval of (1.038-1.859) had approximately 1.5 times more chance of having ischemic stroke than others. This is more likely for embolic compared to thrombotic ischemic stroke.

The levels of CRP in serum was seen to be more than 5 mg/dL (positive) in 122 patients who account for 57% of cases of ischemic stroke. Out of 122 cases of CRP-positive patients, 64 cases (52%) were female and the remaining 58 cases (48%) were male (p=0.21). Of the cases of ischemic stroke with serum CRP positive levels, 76 patients (62%) had a thrombotic ischemic stroke and the remaining 46 cases (38%) had embolic stroke (p=0.002). CRP positive patients had twice more chance of suffering an ischemic stroke of the thrombotic type (in the presence of a variable of age); this association is significant (p=0.01) with a confidence interval of (1.140-3.429). Moreover, in the presence of gender variable, individuals with positive CRP with a significance level of (p=0.01) and a confidence interval of (1.144-3.445) are approximately twice more likely to suffer from ischemic stroke of the thrombotic than embolic type.

As shown in table 2, the differences in CRP serum level in underlying disease such as D.M (82 cases (51%) of positive CRP vs. 77 cases (49%) of negative CRP, p=0.007) and HTN (59 cases (50.4%) of positive CRP vs. 58 (49.6%) of negative CRP, p=0.03) were statistically significant. Ischemic stroke patients with more sever stroke at the time of admission in hospital were significantly 5 times more likely to have positive CRP levels than patients with milder stroke at the time of admission (p=0.027). The positive serum CRP levels at the time of admission of ischemic stroke patients increased the likelihood of severity upon discharge time (p<0.001). Subjects with positive CRP levels upon admission were significantly approximately twice as likely to be placed in severe stages after the first week of admission (p=0.032) (Table 2). The mortality during the first week of hospitalization was 17 cases (8%). In addition, 8 cases (47%) were male and 9 cases (53%) were female and most of these patients (11 cases (64.7%)) were thrombotic and 6 cases (35.3%) were embolic subtypes. Furthermore, high CRP was seen in 10 thrombotic (91%) and 4 embolic (67%) of stroke expire patients (p=0.034). The difference in CRP serum level in mortality cases was statistically significant (14 cases (82%) of positive CRP vs. 3 cases (18%) of negative CRP) (p=0.032)

Table 1. Ischemic stroke according to age, gender of patients and distribution of risk factors

Variable	Ischemic stroke		P-value
	Embolic N(%)	Thrombotic N(%)	
Hypertension	75(45)	88(55)	0.27
Diabetes	53(45)	64(55)	0.89
Hyperlipidemia	48(46)	56(54)	0.78
Ischemic Heart Disease	52(53)	46(47)	0.02
T.I.A.	39(52)	35(48)	0.11
Smoking	21(40)	31(60)	0.52
Age			
<65	29(46)	33(54)	0.76
>65	67(46)	85(56)	
Gender			
Female	50(43)	66(57)	0.58
Male	46(47)	52(53)	

Table 2. Severity and associated factors with C-reactive protein level in Babol Stroke patients

Variable	CRP		P-value
	Negative	Positive	
Ischemic Stroke			0.01
Thrombotic	42(36)	76(64)	
Embolic	50(52)	46(48)	
Severity at admission			
Mild	30(55)	24(45)	0.02
moderate	48(43)	64(57)	
Severe	14(30)	34(70)	
Severity at discharge			0.002
Mild	45(61)	28(39)	
moderate	33(41)	48(59)	
Severe	11(26)	32(74)	
Death	13(48)	14(52)	
Gender			
Male	40(41)	58(59)	0.7
Female	52(45)	64(55)	
Age			0.9
<45 year	5(62)	3(38)	
46-65 year	22(41)	32(59)	
>66 year	62(46)	80(56)	
Hypertension	77(49)	82(51)	0.007
Diabetes	58(49.6)	59(50.4)	0.03
Hyperlipidemia	50(48)	54(52)	0.14
Cardiovascular disease	48(49)	50(51)	0.10
T.I.A.	35(48)	39(52)	0.35
Smoking	24(47)	28(53)	0.59

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Discussion

The present study was conducted to determine the relationship between CRP and outcome in stroke patients. The results of the present study showed that the positive serum CRP levels were associated with the severity of ischemic stroke and poor prognosis. Napoli et al. found that that high levels of CRP in different stages after ischemic stroke is accompanied by poor prognosis (12), which is consistent with the results of the present study. The reason for the association of positive CRP level with a poor prognosis in stroke patients is probably more severe inflammatory events in cases of ischemic stroke and the worse prognosis of patients with more severe thrombotic events, which are associated with more inflammation.

In the study of Eikelboom et al., they reported that higher CRP was associated with higher severity of ischemic stroke, but its association with the types of ischemic stroke was lower (13). However, in our study, in patients with ischemic stroke with positive CRP levels, there have been a higher number of thrombotic cases.

In the study of Chei et al., the association between ischemic stroke and elevated (CRP) level has been confirmed(14). In the study of Iso et al., they reported that this association was significantly and positively correlated with ischemic heart disease and less intensely connected with stroke (15). In the study of Chei et al., high plasma CRP levels, independent of other risk factors for cardiovascular disease, can be significantly used as a predictor of the risk of TIA and ischemic stroke among the elderly (14). In the study of Xie et al. study, it was suggested that high sensitivity C-reactive protein may be used as a marker for intracranial and/or extra cranial artery occlusion (IEAO) (16).

Regarding the risk factors of stroke, hypertension and diabetes mellitus were significantly associated with positive (CRP) in patients during a stroke upon admission. The reason for the relation between positive (CRP) and HTN has been associated with the increase in blood pressure in the acute phase of the stroke (17). However, the association between the high blood pressure of the patient before the stroke and the CRP can also be considered (18). Confirming these reports in other studies could show a strong relationship between high blood pressure and high (CRP) in ischemic stroke.

The limitations of this study were the small population of the studied patients, measuring values of (CRP) either positive or negative, instead of measuring its quantity and the lack of long-term follow-up of patients after discharge. The strengths of this study were to evaluate the association of (CRP) level with subtypes of ischemic stroke and association of (CRP) level with ischemic stroke risk factors in the presence of age and sex variables.

High levels of CRP at the admission were associated with a higher incidence of thrombotic ischemic stroke and higher ischemic stroke severity, and hypertension diabetes mellitus were the risk factors that were significantly associated with cases of stroke patients with positive CRP during admission. High levels of CRP at the start of admission can also predict greater disability and higher mortality rate during the first week of post-stroke hospitalization. So, it's better to check serum level of CRP in admission time.

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