

C-Reactive Protein Profile Among Acute Stroke Patients

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ABSTRACT:

BACKGROUND:

C-reactive protein (CRP) is an inflammation marker, which has been implicated in stroke severity, response to stroke, or a mixture of both.

OBJECTIVE:

This study has been conducted in order to clarify early CRP essay in relation to the type of acute stroke (ischemic and hemorrhagic), onset duration, severity, stroke disability and carotid stenosis.

METHODS:

A cross sectional randomized study included 50 patients with stroke (23 male and 27 females: mean age 54.7 + 10.3 years). They were classified into having ischemic or hemorrhagic strokes, deficit in less or more than 12hrs (within 24 hrs), large or small size infarction, severe or non-severe disability and severe or non-severe carotid stenosis.

RESULTS:

There is more significant association of C-reactive protein with the ischemic (82.4%) than the hemorrhagic types (56.3%). There is significant association of CRP positivity in relation to the late onset duration of the deficit (> 12 hrs: 85.2%) in comparison to the early onset (\leq 12hrs: 60.9%). C-reactive protein level showed statistically significant association with the size of infarction (CRP is positive in 91.3% of the large size versus 63.6% of the small size). There is significant association of CRP level in relation to carotid stenosis (68.8% in severe stenosis versus 31.2% in non-severe ones). The short-term disability was significantly associated with CRP level (CRP is positive in 83.8% with severe disability versus 57.8% with the non-severe one).

CONCLUSION:

High CRP level at the admission of the acute stroke patient is more associated with the ischemic type, the late onset, the large size infarction, severe disability and severe carotid stenosis.

KEY WORDS: CRP, stroke type, severity of infarction, carotid stenosis.

INTRODUCTION:

Stroke is the 3rd common cause of death in the world and the 2nd in the USA.^(1,2) It is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause⁽¹⁾ with a clinical and paraclinical evidence of stroke by means of brain imaging.^(3,4) It is well known that stroke is either ischemic (80%-85%) or hemorrhagic (5%-10%)⁽¹⁻⁵⁾. There is growing evidence that CRP, a member of the pentraxin protein family (molecular weight 120 KD), is a peripheral marker of inflammation and generalized atherosclerosis.⁽⁶⁻⁸⁾ The relationship between inflammation and atherosclerosis makes CRP a potential marker for prognosis for vascular events for stroke, and a potential predictor of

future vascular events. Several studies demonstrated that an elevated CRP level is an independent prognostic factor in patients with ischemic heart diseases (acute coronary syndrome and unstable angina),⁽⁹⁻¹¹⁾ peripheral vascular diseases⁽¹²⁾ and strokes.⁽¹³⁻¹⁵⁾ It was mentioned that the CRP level in patients with neurologic deficit was not significantly different among different stroke types including ischemic and hemorrhagic varieties.⁽¹⁶⁾ On the one hand, the recent trial has shown that the use of Rosuvastatin in patients with high CRP had a significant impact in reducing the CRP level and lowering future vascular events,⁽¹⁷⁾ on the other hand, Croso et al. study showed the role of CRP as a prognostic factor after stroke,⁽¹⁸⁾ however, the Rotterdam study showed that although high CRP was associated with the risk of future stroke, it is not useful for individual stroke prediction.⁽¹⁹⁾ Whereas, Framingham study showed that high CRP was associated with a greater risk for ischemic stroke or TIA.⁽²⁰⁾ Di Napoli et al concluded that there was insufficient evidence for justifying the routine use of CRP for either primary or secondary risk stratification for

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Cerebrovascular diseases alone,⁽²¹⁾ while many authors found an association between high CRP and stroke presentation, outcomes of future vascular events⁽²²⁻²⁸⁾ and the carotid stenosis severity.^(29,30) Because of these controversies; more studies are needed in order to clarify the exact role of CRP in Cerebrovascular diseases. This cross sectional randomized study is conducted to assess early CRP assay in relation to type of acute stroke, duration from onset, severity, disability and carotid stenosis within 24 of stroke onset.

MATERIAL AND METHODS:

This cross sectional randomized study is conducted at Annajaf city, which is 160 km south west to the capital Baghdad in the period from January 2012 to December 2012. The ethics are approved by Kufa Medical College; the investigation was carried out according to Helsinki guide lines. The study included 50 cases with age range of 30-68 years with the mean of 54.7 ± 10.3 year; all attended the emergency unit of the Middle Euphrates neurology center with acute stroke; 23 were males and 27 were females. The following groups of patients have been excluded from the study: patients with clinical evidence of nosocomial infection; renal, hepatic and malignant diseases; those undergone surgery or sustained major trauma in the previous month; patients with presence of concomitant CVD including peripheral vascular diseases and ischemic heart diseases; and patients whose clinical and radiological findings were not consistent with stroke. We classified our patients into several groups including: patients with ischemic or hemorrhagic stroke, duration to the onset within 24 hours (patient presented within 12 hour and more 12 hours), patients with large or small size ischemic strokes, patients with severe or non-severe disability, and patients with severe or non-severe carotid stenosis.

The size of infarction was assessed by using Alberta Stroke program Early CT Score (ASPECTS)⁽³⁾ with volumetric assessment by 2 expert board certified radiologist at middle Euphoarates neuroscience center in order to assess the size of infarction,⁽³⁰⁾ if the score was <7, the infarction size was considered small, and if score >7, it was large. All these scores were assessed by using computed tomography (Philips Brilliance 64TM; Philips Medical Systems, Eindhoven, the Netherlands) and magnetic resonance image 1.3 T MRI scanner (Achieva, Philips Medical Systems, Best, The Netherlands). The degree of carotid stenosis was determined by Philips SD800 ultrasound scanner (Philips

Ultrasound International, USA) of carotid artery trunk, bulb and internal carotid artery in both sides, and in all of the patients the stenosis was severe if it was $\geq 70\%$, and non-severe, if <70%. The stroke disability can be assessed by the modified Rankin score (mRS),⁽³¹⁾ which consists 6 points and categorized as non-severe when it is ≤ 3 and severe when it is > 3 .

Blood samples were drawn (two milliliters) from the patients and sent to laboratory for CRP analysis, which was measured semi quantitatively by CRP- latex slide agglutination (CRP-Latex Kit: SPINREACT, SAU Ctra. Santa Coloma, Spain). The CRP obtained by this method was positive if its level in the blood was ≥ 6 mg/dl; and negative, if the level was < 6 mg/dl. In the statistical analysis, chi-square test was applied for categorical variables and Fischer Exact probability test was when chi square cannot apply (small numbers) at the level of significance ($\alpha = 0.05$) using SPSS software (SPSS release 19, company, city), in addition to the descriptive statistics.

RESULTS:

Epidemiological data

The age ranges, gender and percentage of the patients enrolled in the study are shown in table 1, which showing the CRP positive and negative within each age group as well as their gender, there was no significant relation to age and gender (p value > 0.05).

C-reactive protein in relation to stroke type

Among the 50 patients included in this study, thirty four patients (shown in table 2) had the ischemic type (68%); 28 patients were CRP positive (82.4%), and six patients were CRP negative (17.6%). Thirty two percent of the patients (16 patients out of 50) had the hemorrhagic type of stroke, among them nine patients were CRP positive (56.3%) and seven CRP negative (43.7%). There is significant association of higher CRP level with ischemic type of stroke (P -value was 0.049).

C reactive protein in relation to onset duration

According to the onset of events; twenty seven patients (of the total 50) had duration > 12 hrs, among them 23 were CRP positive (85.2%), whereas 4 patients were CRP negative (14.8%). Twenty three patients had duration of ≤ 12 hrs (out of 50), among them fourteen patients were CRP positive (60.9%), while nine patients were CRP negative (39.1%). There is significant association of higher CRP level with duration to the onset of stroke deficit (P -value was 0.049) as shown in table 3.

C- reactive protein in relation to size of infarction

Among those with large infarction (23 patients), twenty one were CRP positive (91.3%), while only two were CRP negative (8.7%). Among those with small infarction (11 patients), seven were CRP positive (63.6%) and four were CRP negative (36.4%). There is significant association of higher CRP level in relation to size of stroke (P-value was 0.049) as shown in table 4.

C-reactive protein in relation to disability

Among the 50 patients included in this study, thirty one had severe and nineteen had non-severe disability. Among those with severe disability only 26 (83.8%) were CRP positive and five were CRP negative; accordingly, 11 (57.8 %) were CRP positive and 8 (42.2%) were CRP

negative, respectively, in the non-severe disabled patients. There is significant association of higher CRP level with sever disability (P-value was 0.049) as shown in table 5.

C-reactive protein in relation to degree of carotid stenosis

Regarding carotid stenosis in ischemic stroke, 18 patients (out of 34 one) had severe stenosis. Out of them, 17 were CRP positive (94.4%) and only one patient was CRP negative (5.6%). In non-severe stenosis (16 patients), eleven (68.8%) showed positive reaction to CRP and the rest were with negative one (5 patients: 31.2%). There is significant association of higher CRP level with sever severe stenosis (P-value P-value = 0.049) as shown in table6.

Table 1: Age and gender distribution of study group and their relation to CRP.

Variables	CRP +ve (N/%)	CRP -ve (N/%)	Total	P value
Age (yr)mean 54.7±10.3				
30-39				P value > 0.05
40-49	2 (5.4%)	3 (23.1%)	5	
50-59	6 (16.2%)	2 (15.3%)	8	
60-69	8 (21.6%)	3 (23.1%)	11	
Total	21 (56.7%)	5 (38.4%)	26	
	37	13	50	
Sex				
Male	16 (69.5%)	7 (30.5%)	23	P value > 0.05
Female	20 (74.1%)	7 (25.9%)	27	
Total	36	14	50	

Table 2: Relation between stroke type and CRP.

Stroke subtype	CRP +ve	CRP -ve	Total
Ischemic	28 (82.4%)	6 (17.6%)	34
Hemorrhagic	9 (56.3%)	7 (43.7%)	16
Total	37	13	50

P value=0.049

Table 3: Relation between onset of deficit and CRP.

Onset of deficit	CRP +ve	CRP -ve	Total
>12 hrs	23 (85.2%)	4 (14.8%)	27
≤12 hrs	14 (60.9%)	9 (39.1%)	23
Total	37	13	50

P value=0.05

Table 4: Relation between infarction size and CRP.

Infarction size	CRP +ve	CRP -ve	Total
Large	21 (91.3%)	2 (8.7%)	23
Small	7 (63.6%)	4 (36.4%)	11
Total	28	6	34

P value=0.047

Table 5: Relation between disability and CRP.

Stroke disability	CRP +ve	CRP -ve	Total
Severe	26 (83.8%)	5 (16.2%)	31
Non-severe	11 (57.8%)	8 (42.2%)	19
Total	37	13	50

P value=0.042

Table 6: Relation between carotid stenosis and CRP.

Carotid stenosis	CRP +ve	CRP -ve	Total
Sever	17 (94.4%)	1 (5.6%)	18
Non-sever	11 (68.8%)	5 (31.2%)	16
Total	28	6	34

P value=0.049

DISCUSSION:

The clinical implication of CRP assay is to find out any relationship of this marker to the stroke. The main limitation in this study is small sample as the stroke is common problem but complete patient survey within 24 hour including brain CT scan, measurement of CRP level, with other parameters of inclusion and exclusion criteria makes many of presented stroke cases to emergency unit out of this study. We enrolled 50 patients who completed their surveys with an epidemiological data (shown in table 1) consistent with other investigators.^(1, 3, 32)

The data also show that there was high association between the C-reactive protein level and the type of stroke (ischemic stroke versus hemorrhagic one) as shown in table 2, this may be related to atherosclerosis as a cause of the ischemic stroke, since atherosclerosis increases the C-reactive protein level by inflammatory mechanism as mentioned by Di Napoli.^(33,34) Moreover, hemorrhagic stroke can cause rapid increase in the C-reactive protein that evolves within few hours of the symptoms onset due to acute cerebral injury³³. On the other hand, the C-reactive protein level showed statistically significant association with the size of infarct, particularly the large ones (table 3). This can be explained by a distinct possibility that the elevated the CRP maybe caused direct response to the cerebral tissue injury volume,⁽³⁵⁾ but as an inflammatory marker, it is also possible that the high CRP resulted from other factors such as the underlying processes that caused the severe stroke.⁽⁸⁾

The C-reactive protein level within 24 hours of onset shows high statistically significant association (85.2%) to the late onset of the deficit (within 24 hour but > 12 hrs), while the early onset (≤ 12hrs) shows less significant association (60.9%) as shown in table 3. Few investigations

have been done about these factors enrolling small number of patients.⁽³⁶⁻³⁹⁾

A group in this study were used to assess the relationship between CRP and the stroke disability, the results show that the short-term disability was significantly associated with CRP positivity even after adjusting for other parameters such as age, sex and stroke severity, this is consistent with the findings of others who reported an association between high CRP and poor disability.⁽⁴⁰⁾ In clinical practice, we may consider high CRP as a "red flag" marker of high morbidity, but the therapeutic implications of this finding remain uncertain.

On the other hand, evaluating the carotid artery stenosis shows that CRP level was a statistically significant factor and may be a useful adjunct to accurate global vascular risk assessment, which is consistent with the findings of Mullenix et al in 2007,⁽⁴¹⁾ who confirmed the existence of a temporal relationship with the elevated CRP levels and the carotid artery stenosis. This may provide additional diagnostic index for evaluating the outcome of the patients with subclinical carotid artery stenosis identified by duplex examination.

In order to clarify the above results and the remaining unexplained discrepancies, we wonder whether high CRP level is a cause or a result of a more severe stroke deficit and/or stroke complications, Muir et al proposed three hypotheses regarding the relationship between the CRP level and stroke. He revealed that the CRP level may reflect the severity of stroke, instability of atherosclerotic plaque and /or its increase as a result of complications secondary to the stroke occurring at the time of the blood sample collection.⁽¹⁵⁾ He concluded that CRP assay in acute stroke patient at the admission could be more associated with ischemic stroke type, while later measurement could be

associated with large size of infarction, poor morbidity and severe carotid stenosis. The clinical implications of these findings are unclear at present and whether CRP is a marker of stroke severity, or a response to stroke, or a mixture of both remains unclear.

In this study, important limitations should be considered about the CRP, which was measured only at one time point (within 24 of the admission), which can be influenced by many factors including infections stress, timing of measurement and laboratory error. In addition, the CRP level measurement following the acute phase of stroke is confounded by many factors including the index of stroke severity, co-existing infections, and complications of stroke such as deep vein thrombosis. A serial measurement of CRP was not planned in this study. A large size sample is necessity for detecting the effects and associations of CRP with acute strokes, but substantial heterogeneity in stroke is so complex that the sample size problem is expected.

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C-REACTIVE PROTEIN

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