Serum C-Reactive Protein Level as a Biomarker for Differentiation of Ischemic from Hemorrhagic Stroke

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Abstract- Cerebrovascular accidents rank first in the frequency and importance among all neurological disease. Although a number of studies had shown increased level of the high sensitive C-reactive protein (hs-CRP) in patients with ischemic stroke, the association of increased hs-CRP with various type of stroke especially the assessment hs-CRP level in ischemic and hemorrhagic stroke have not been investigated. In the present study, we assessed the concentration of hs-CRP in patients with documented ischemic and hemorrhagic stroke in the first 24 hours of the onset of symptoms. Thirty-two patients with Ischemic and hemorrhagic stroke were evaluated at neurology department of Poursina Hospital. The presence of baseline vascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking, was determined. The blood samples were then collected and routine hematology and biochemistry tests were done. hs-CRP levels were determined using a highly sensitive immunonephelometric method. In this cross sectional study, the age of patient varied from 45–85 years (Mean 70.9 ± 9.4). Serum level of hs-CRP in Ischemic patients were 18.92 ± 11.28 and in hemorrhagic group was 2.65 ± 1.7. This relationship was statistically significant (P<0.0001). It might be concluded that hs-CRP might be considered as a usefully adjunct method for the initial diagnosis of the type of stroke.

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Keywords: Cerebrovascuar accidents; High sensitive C-reactive protein (hs-CRP); Ischemic stroke; Hemorrhagic stroke

Introduction

Stroke is considered as a life threatening cause in neurological patients. It is one of the leading causes of morbidity and mortality worldwide (1). This neurological deficit appears over a few hours, persists for more than 24 hours, and is presumed to be due to an impairment of the blood supply to one part of brain.

Of all the causes of cerebrovascular disease, atherothrombosis is by far most important (2). This phenomenon involves large and medium size vessels that can lead to ischemic cardiac, brain damage or infarction. Following, an inflammatory process might be initiated, and result in existence of inflammatory cells of innate immunity and production of acute phase proteins such as C-reactive protein in a first few hours of stroke(3).

C-reactive protein (CRP) is a glycoprotein produced by the liver, which is normally absent from the blood. The presence of acute inflammation with tissue destruction within the body stimulates its production. The CRP typically rises within 6 hours of the start of inflammation, allowing the inflammation to be confirmed. There are two types of CRP, which could be measured. The standard CRP is used to assess how active inflammation is in such chronic problems as arthritis; to assess for a new infection; and to monitor response to treatment of these conditions. The other type of CRP is high-sensitivity CRP (hs-CRP). This substance is considered a marker of low-grade vascular inflammation, which is a key factor in the development and rupture of atheromatous plaque (2,4).

Recent data suggest that CRP is an inflammatory marker for coronary artery disease and as well as potent & strongest predictor in cardio vascular disease in men and women (5, 6). Although in a few study has been used increased level of CRP for determining ischemic stroke, we found no comparative study on serum level of

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CRP between hemorrhagic and Ischemic stroke. Therefore, we evaluated the ability of hs-CRP levels as a biomarker to predict cerebrovascular events in hospitalized patients.

Materials and Methods

Study population

In this cross sectional study, patients who referred to Poursina Hospital, Rasht between March 2007 and April 2008 were selected regarding to computerized tomography scanning report and matched by age, sex and risk factor of stroke such as hypertension, diabetes, hyperlipidemia. The total studied sample consisted of 32 examines divided into different groups as follows: patients with Ischemic stroke and patients with hemorrhagic stroke.

Subjects with previous history of myocardial infarction, inflammatory disease such as RA, drug consumption such as steroids, oral contraceptive & Angiotensin-converting Enzyme Inhibitors, liver and renal disorder were excluded. Participants with recent inflammatory conditions, such as major trauma, surgery, or obvious acute infectious disease, were not included in the present study.

The presence of baseline vascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking, was determined. Hypertension was defined as blood pressure ≥140/90 mmHg; or current antihypertensive therapy. Diabetes mellitus was defined as a history of a random blood glucose level≥127mg/dL or current anti-diabetic therapy. Dyslipidemia was defined as a total cholesterol level≥200mg/dL or current cholesterol-lowering therapy. Our institutional ethics committee approved the study, and all of the participants provided their written informed consent.

Blood samples and hs-CRP measurement

Blood samples were collected from an antecubital vein. The samples were collected into vacuum tubes containing EDTA. After sampling, tubes were centrifuged at 1500×*g* for 10 min immediately. Aliquots of serum were stored at −20 ◦C, and routine hematology and biochemistry tests were done within a few hours after blood sampling. hs-CRP levels were determined using a highly sensitive immunonephelometric method (RT 1000,Germany) by laboratory personnel who were blinded to group status of the study participants.

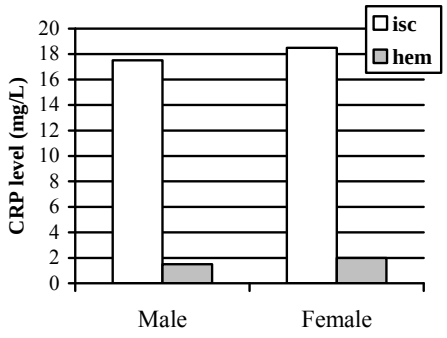

Figure 1. Concentration of hs-CRP in patients with Ischemic and hemorrhagic stroke according to their gender

Statistical analyses

The differences in serum level of hs-CRP were compared between two mentioned groups using the Student's *t* test. *P* values <0.05 were considered significant. The analyses were performed using the SPSS statistical package, version 11.5.

Results

In this study, 16 patients with Ischemic stroke (5 males & 11 females) and 16 patients with hemorrhagic stroke (9 males & 7 females) were included. The age of patient varied from 45–85 years (Mean 70.9 ± 9.4). According to One-Sample Kolmogorov-Smirnov Test, the normal distribution is indexed by only one parameter; the mean. This sample of hs-CRP averaged about 10.7906 mg/L in subjects with cerebrovascular accident that is meaning the normal distribution with a parameter.

Serum level of hs-CRP in Ischemic patients were 18.92±11.28 and in hemorrhagic group was 2.65 ± 1.70. This difference was statistically significant (*P* <0.0001).

The mean serum hs-CRP level in different gender groups with cerebrovascular accident was not significant statistically in this study. Fig. 1 depicted the concentration of hs-CRP in patients with Ischemic and hemorrhagic stroke according to their gender. Moreover, there was no significant association between the hs-CRP titer and strokes from any causes in the model adjusted by age and other classical vascular risk factors.

Discussion

The findings of this study reveal that types of stroke were related to elevated hs-CRP levels. Moreover, the

present study could not show a gender difference for the association between hs-CRP level and the stroke.

The most imperative risk factors for stroke and cardiovascular disease, like diabetes, and hypertension, smoking, are associated with higher hs-CRP levels (7,8). This relationship might clarify the associations between hs-CRP level and cerebrovascular infarction. Nevertheless, in view of the fact that above mentioned factors adjusted in this study, the traditional risk factors cannot completely explain the relationship between the hs-CRP level and cerebral vessel impairments.

Atherothrombosis of the cerebral vessels is considered a disorder of inflammation and acute phase reactant proteins produced in a first few hours (2). A large number of proteins are recognized as acute phase reactant such as fibrinogen, CRP, TNF and hapotglobulin. Instability of TNF and haptoglobulin in unfrozen condition restricted their use, as markers. The degree of inflammation that determined by elevated hs-CRP levels has been associated with an increased risk of vascular complications and predicts future events (9-11).At the initial stage of atherosclerosis some adhesion molecules are expressed (12-14). Additionally, recent studies have found high rates of cardiovascular (15) and cerebrovascular disease in subjects who had increased levels of soluble adhesion molecules previously (16, 17).

The results obtained in this study have been agreed by some researches (3, 18). Dinapoli (19) found that CRP concentration wasWorld Health Organization increased in first 24 hours following stroke and this increment had associated to size of infarct, so mounting CRP level in first 24 hours was synchronized to poor prognosis. Conversely, inflammatory process has theoretically no important role in pathogenesis of hemorrhagic stroke. Although, it means that in hemorrhagic stroke no quantifiable changed might be measured, in our study revealed a trivial increase in CRP level than its baseline.

Others are of the opinion that CRP as an indicator is less useful for the prediction of symptomatic brain infarction (20, 21). However, this study suggests that measurement of hs-CRP, as an acute phase reactant result from inflammation, may be useful as surrogate marker for detection and differentiation of Ischemic from hemorrhagic stroke.

Although we made an effort to check all the known reasons affects on hs-CRP level, some limitations should be noted. Subjects who had recent acute inflammatory conditions were not included. Nevertheless, it should be considered that some participants might have any chronic infections. In conclusion, hs-CRP level is increase in patients with Ischemic infarct dramatically but not in hemorrhagic stroke which might be considered as a usefully adjunct method for determining type of stroke in patients with cerebrovascular problems.

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