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Crescent Journal of Medical and Biological Sciences
Vol. 4, No. 4, October 2017, 173–176
eISSN 2148-9696

High Sensitive CRP in Behcet Disease With and Without Uveitis Compared With Idiopathic Uveitis: A Cross-Sectional Study

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Abstract

Objective: Uveitis is one of the important manifestations of Behcet disease (BD). High sensitive C-reactive protein (hs-CRP) is an acute phase reactant, which may increase in BD. There are controversies in different studies regarding the relation between hs-CRP and uveitis in BD. This study aimed to determine serum values of hs-CRP and its relationship with uveitis in BD.

Material and Methods: A total of 94 patients, divided into 3 groups (Behcet's uveitis (n=31), Behcet's without uveitis (n=37) and idiopathic uveitis (n=26), participated in the study. Serum levels of hs-CRP were compared among those groups.

Results: The mean serum hs-CRP level was 6.49±3.27 mg/L (BD with uveitis), 6.41±3.85 mg/L (BD without uveitis) and 6.97±3.9 mg/L (idiopathic uveitis. Tukey test was done among groups and there were no significant differences between them (P=0.69).

Conclusion: Our results revealed no significant difference among the 3 groups regarding the mean serum hs-CRP level. However, further studies are warranted in this regard.

Keywords: Behcet syndrome, High sensitive C-reactive protein, hs-CRP, Uveitis, Idiopathic uveitis

Introduction

Behcet disease (BD) is an autoimmune disease with unknown etiology; it is characterized by oral and genital aphthous and arthritis (swelling and joint pains), cutaneous lesions and ocular, gastrointestinal, and neurologic manifestations (1). BD is more common in the Middle East and Mediterranean region (2). The prevalence of BD in Iran is 80 out of 100 000 patients (3).

For detecting the activity of the disease, cytokines such as serum interleukin (IL)-6, IL-8, IL18 and IL-10, erythrocyte sedimentation rate (ESR), serum level of endocan and C-reactive protein (CRP) have been suggested (4-6).

Uveitis results in considerable morbidity including blindness in BD (7). Uveitis cases which are initially considered idiopathic may fulfill the criteria of BD after several years. To date, no specific test has been introduced for prediction of uveitis development in BD. Several studies have shown that certain acute phase reactants, other biomarkers or heat shock proteins (HSP) such as HSP65, HSP27, HSP69 and HSP 70 could be used to predict developing uveitis in BD (8-11).

High sensitive CRP (hs-CRP) is produced by the liver and considered as an acute phase reactant; it can be found in the serum within a few hours after tissue injury. Literature regarding the role of hs-CRP in BD is scarce. This is a hypothesis that, hs-CRP increases due to inflammation in uveitis. To date, few studies have evaluated the role of hs-CRP in uveitis (12, 13). This study aimed to investigate the serum values of hs-CRP in BD, its relationship with uveitis in comparison to idiopathic uveitis. Moreover, according to our previous study we briefly present here the correlation of hs-CRP and HSP-27, which was measured previously in those patients (9).

The rise in the incidence of BD has been reported to be associated with certain HLA, especially HLA-B51 (14). The risk for the manifestation of BD in HLA-B51 positive population varies according to the living environment. The level of HLA-B51 is higher in families which had a single incidence of the disease. The presence of HLA-B51 indicates a more severe disease activity (2). The other alleles of HLA can also increase the risk of the BD. In one study, the association of HLA with BD was reported to be less than 20% (14). If a member of the immediate family has got the BD, the risk for the disease in other members of the family increases. Children with BD parents, may develop the disease in an earlier age.

Material and Methods

In this cross-sectional study every consecutive patient fulfilling the international criteria for BD (15), referred

Received 23 September 2016, **Accepted** 14 March 2017, **Available online** 8 April 2017

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to the Rheumatic Diseases Research Center (RDRC) in north east of Iran was enrolled from 2010 to 2013. In total 68 BD patients and 26 patients with idiopathic uveitis entered the study.

The studied patients were divided into 3 groups: (A) Behcet disease with uveitis, (B) Behcet disease without uveitis, and (C) Idiopathic uveitis.

All participants were initially visited by a single ophthalmologist for confirming the presence of uveitis. Patients with a history of infection in the previous month, those who had used high dosage of glucocorticoids or were under treatment with cytotoxic drugs and BD patients with uveitis who had started treatment before sampling, were excluded from the study.

At study initiation baseline characteristics of the patients were recorded. Moreover, the following lab tests were performed in all patients to rule out secondary uveitis: rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies (P and C), HCV antibody, HTLV1, cytomegalovirus, HIV, Wright, 2ME, anti-toxoplasmosis, IgM HSV1, HLA B27, angiotensin converting enzyme (ACE), complete blood count, ESR, VDRL and chest and pelvic x-ray. Idiopathic uveitis was defined for patients with uveitis who had no etiology for at least 6 months and examined by 2 ophthalmologists to rule out characteristic ophthalmic features of secondary uveitis.

After obtaining a 5 cc venous blood sample from each individual, hs-CRP was measured by CRP high sensitivity ELISA (hs-CRP, IBL International GMBH), following the manufacturer's instructions.

HSP27 level was measured from them on the same serum and the result was reported in our previous article. We compared the level of HSP27 with hs-CRP and reported it here briefly.

The collected data were analyzed by SPSS version 11.5 (SPSS, IBM Corporation, New York). K-S Lilliefors test was applied for determining the normality distribution of the studied variables. We used student *t* test for parametric variables, chi-Square for categorical variables and Tukey test for further analyses. A P value < 0.05 was considered as statistically significant.

Results

Ninety-four patients consisting of 37 BD cases without uveitis, 31 BD cases with uveitis and 26 idiopathic uveitis with the mean age of 33.3 ± 10.6 years participated in this study. The mean age of Behcet's patients with uveitis was 31.94 ± 9.40 years, Behcet's patients without uveitis was 33.27 ± 9.84 years and idiopathic uveitis cases was 34.9 ± 12.96 years. Regarding the one-way analysis of variance (ANOVA), no statistically significant difference was found among the 3 groups based on age ($P = 0.69$). Moreover, age in all 3 groups had a normal distribution ($P = 0.69$, $z = 0.7$). The patients' clinical data are displayed in Table 1. The mean duration of the disease in groups A, B, C was 10.3 ± 2.1, 11.8 ± 3.3 and 11.4 ± 1.2 months respectively.

Regarding sex, 51.1% of the patients were male. The 3 groups showed no difference based on sex ($P = 0.8$, $\chi^2 = 0.4$) and it had normal distribution in all 3 groups ($P = 0.61$, z=0.9).

As presented in Table 1, except for uveitis, no significant difference in other BD manifestations was detected in groups A and B.

The mean serum hs-CRP level was 6.95 ± 3.65 mg/mL, showing a normal distribution ($z = 1.2$). Hs-CRP also had normal distribution among the three groups ($P = 0.08$, $z = 1.2$). The mean hs-CRP in group A was 6.4 ± 3.2, in B was 6.4 ± 3.8 and in group C was 6.9 ± 3.9 mg/mL. The comparison of hs-CRP serum levels in the 3 groups is demonstrated in Table 2. Based on the one-way ANOVA, the difference in the mean serum hs-CRP levels among those groups was not statistically significant ($P = 0.69$).

Furthermore, no significant difference in dosage of prednisolone was achieved between the groups A and B ($P = 0.6$). Also we found no difference in the dosage of cytotoxic drugs between those 2 groups ($P = 0.9$).

We had measured HSP27 in those patients in our previous study on the same serum samples. Detail of results has been presented in the study of Adam et al (4). Here we briefly present the correlation between HSP27 and hs-CRP. HSP27 and hs-CRP both had a normal distribution, therefore Pearson correlation test was applied which showed no significant correlation ($P = 0.6$, $r = 0.45$)

Discussion

Hs-CRP, a plasma protein produced by the liver, may play some roles in several autoimmune diseases by activating the classical complement pathway and inactivating the alternative pathway (16). It is controversies about the correlation between increasing the level of CRP and activity of the disease (17, 18).

In the present study we observed no significant difference in circulating hs-CRP in active uveitis patients compared with those without uveitis. Besides, the level of hs-CRP showed no statistically significant difference between Behcet's patients and those with idiopathic uveitis. As mentioned before, limited studies on this subject are available in the literature.

Mesquida et al found that hs-CRP exacerbates the inflammatory burst by increasing the secretion of Th1 and Th17-proinflammatory cytokines, which are considered to play a critical role in development of BD. They reported higher hs-CRP levels in BD patients with uveitis compared to healthy controls (13). In a study

Table 1. Distribution of Clinical Manifestations in Behcet's Disease Patients With (A) and Without Uveitis (B) Using Yate Correction

Clinical Manifestation	Group A n = 31 No. (%)	Group B n = 37 No. (%)	*P* Value
Positive for pathergy test	28 (90.3)	33 (89.2)	0.23
Positive for oral aphthae	27 (87)	34 (91/9)	0.41
Positive for genital aphthae	11 (35.4)	22 (59.5)	0.08
Positive for arthritis	6 (19.3)	11 (29.7)	0.35
Positive for skin lesion	12(38.7)	13(35.1)	0.67

Table 2. Comparing Mean hs-CRP Serum Levels Between the Studied Groups (Tukey Test)

First Group	Second Group	Mean Difference Between 2 Group	Standard Deviation	*P*	Assurance Interval	
					Upper Bound	Lower Bound
A	B	3.082	1.261	0.2	5.345	-1.236
	C	4.131	1.347	0.2	5.278	-1.986
B	A	4.778	1.752	0.1	6.125	0.341
	C	3.361	1.102	0.1	4.759	0.839
C	A	4.716	1.283	0.1	6.264	-1.847
	B	5.849	1.3292	0.1	7.253	0.739

performed by Khairallah et al, "it was concluded that a better understanding of the process of auto-immunity and the role of cytokines responsible for tissue damage in BD and uveitis in general will allow new, more specific and effective therapeutic approaches to emerge in the near future" (7). These differences may be due to the chronicity of uveitis, ethnic factors; or difference in medications because most of such cases were not treated with any cytotoxic drugs due to long-standing remission. Based on the our previous study on these patients for HSP27, we found that BD patients with uveitis had higher HSP27 values than idiopathic group (9). We found no correlation between HSP27 and hs-CRP in BD patients. To our knowledge, this is likely the first report on this correlation.

Hs-CRP activates the classical complement pathway by binding to multivalent ligands (e.g., damaged cell membranes). It can also regulate the alternative complement pathway by recruitment of factor H besides minimizing the damage caused by autoimmune reactions (19,20). Tissue injury, infection and any inflammation could increase the level of hs-CRP (5). Hs-CRP has 2 isoforms: pentameric CRP which is expressed in tissues and monomeric CRP that is found in plasma that plays a major role in biological events. In the current study we measured only the serum level of hs-CRP, which may be the reason for finding no difference in it between groups A and B. Mi et al observed differences between etiologies and ethnicity, pointing toward potential susceptibility variations. There was an upward trend of idiopathic causes, possibly due to better control of systemic and infectious etiologies (21).

Conclusion

This study had some limitations such as small number of participants in each group and cross-sectional manner of the study. However, the strong points of the study were sampling before starting pulse therapy, including idiopathic uveitis group, the same distribution of other organ involvements in two BD groups.

Taken together, this cross-sectional study showed that hs-CRP does not have any relation with uveitis in BD patients, so it is not suggested in the diagnosis or prediction of developing uveitis in BD. Further studies are needed to determine the difference in hs-CRP level among different ethnicities and the correlation between other factors such as heat shock protein 70 and hs-CRP.

Conflict of Interests

All authors have no conflicts of interest.

Ethical Issues

The study protocol was approved by the Research Council Ethics Committee of Mashhad University of Medical Sciences. An informed consent was provided by each participant prior to study entrance.

Financial Support

Research Council of Mashhad University of Medical Sciences supported the study (grant No. 910277).

Acknowledgments

This article was extracted from a student thesis prepared by Mr. Zeid Zerehsaz to fulfil the requirements for obtaining specialty degree in Internal Medicine. We would like to thank the Research Council of Mashhad University of Medical Sciences for its financially support of this study. We are also grateful to all patients for their kind participation. Dr. Habibolah Esmaily was also appreciated because of helping in statistical analysis of our data.

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