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COULD THE RELATIONSHIP BETWEEN CRP AND ALBUMIN / GLOBULIN RATIO BE A CLINICAL ACTIVATION INDICATOR IN BEHÇET'S DISEASE?

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ABSTRACT

Aim: The aim of the study was to analyse the relationship between the sedimentation rate and Albumin/Globulin (A/G) ratio along with the CRP level which is considered as an indicator of Behçet's disease (BD) activation. **Method:** Fifty patients who were diagnosed with BD were included in this study. CRP levels, sedimentation rate, total protein and albumin levels of patients were retrospectively checked. The patients were classified into two groups: group 1 (0 – 0.8 mg/dl) consisting of those with CRP levels within the normal range and group 2 consisting of those with CRP levels higher than the normal range (CRP> 0.8 mg/dl). **Results:** There was a statistically significant difference between patients in group 2 and those in group 1 with respect to the sedimentation rate ($p = 0.001$) and A/G ratio ($p = 0.002$). Additionally, there was a statistically significant negative correlation between A/G ratio and both CRP levels ($r = -0.405$, $p = 0.004$) and sedimentation rates ($r = -0.592$, $p = 0.000$). **Conclusion:** We believe that in addition to CRP levels, the sedimentation rate and A/G ratio, which are frequently used in clinical evaluation and are easily accessible, may be utilised as indicators of BD disease activity. Therefore, further investigations are needed to clarify the role of these mediators in the BD.

KEYWORDS: Behçet's disease, C-reactive protein, Albumin/Globulin ratio.

INTRODUCTION

Behçet's disease (BD), which includes oral ulcers, genital ulcers and uveitis as its classical symptoms as defined by Hulusi Behçet, is a chronic recurrent vasculitis that has an effect on many organs and systems. The most prevalent clinical symptoms are considered to be caused by vasculitis, and the disease is clinically characterised by recurrent painful mucocutaneous ulcers.

The aetiology of the disease, which typically affects young adults and is prevalent among males, is unknown, and it has been suggested that the disease has genetic, infectious and immune mechanisms.[1] Similar to that observed in other autoimmune diseases, in persons with genetic predisposition, the disease may occur because of abnormal activity triggered by bacterial and viral agents along with some chemicals and heavy metals.[2] Detection of immunoglobulin and immune complexes as well as an increase in complement and acute-phase protein levels support the role of autoimmunity in aetiology.[3]

Because there is no consensus over the autoimmune origins of BD, it is evaluated as an auto-inflammatory disease which encompasses a larger group that is distinct from classical immune diseases, such as autoimmunity, allergy and immune deficiency.[4,5]

There is no pathognomonic laboratory test for diagnosing BD; therefore, the diagnosis is based on clinical findings. Moreover, because of a lack of any specific laboratory test, the evaluation of the disease activity is rather performed based on clinical characteristics of the disease.[6,7]

Even though many parameters including cytokines such as IL- 6 and acute-phase proteins such as C-reactive protein (CRP), lipoprotein-A and complement levels are used as activity indicators of BD, there is no specific indicator related to disease activation.[8-11]

CRP, as an acute-phase reactant, is a non-specific indicator used for diagnosing various diseases, such as infectious, autoimmune and rheumatologic diseases; for determining the severity of the disease and for treatment follow up. CRP levels exhibit a correlation with the inflammation level during the early stage of the disease.[12]

The erythrocyte sedimentation rate (ESR) is an indicator of the acute-phase reaction. In the course of an inflammatory reaction, ESR is affected by many factors

including the plasma albumin level. However, CRP is a much better indicator of inflammation than ESR as it is more sensitive to the changes in the clinical state and it responds faster.[13]

The serum albumin level, a negative acute-phase reactant, is a strong prognostic indicator that demonstrates the results of the disease related to the infection because it decreases as a response to the acute period of the infection.[14] The albumin level is associated with the chronic nature of the disease and is an indicator of the state of inflammation.[15]

The albumin/globulin (A/G) ratio is an index calculated from total protein and albumin levels and reveals the state of inflammation. Generally, there is a decrease in the A/G ratio during chronic infections, hypergammaglobulinemia, nephrotic syndrome, cirrhosis of the liver and collagen tissue diseases.[16] However, studies on the use of the A/G ratio as an inflammatory marker in rheumatologic diseases are limited. The aim of the present study was to analyse the relationship between the sedimentation rate and A/G ratio along with the CRP level which is considered as an indicator of BD activation.

MATERIALS AND METHODS

This study included 50 (18 male and 32 female) patients diagnosed with BD according to the International Study Group for BD criteria, who were routinely followed up in Faculty of Medicine, Education and Research Hospital Internal Diseases polyclinic, who regularly came for clinical controls between January 2015 and July 2017 and whose records were available. Patients who demonstrated to have one of the symptoms of oral aft or genital ulcers, joint pains or one of the eye symptoms specific to BD within the last week during physical examinations at the time of their application were classified as active patients. CRP levels, sedimentation rate, total protein and albumin levels of the patients were retrospectively checked. In our clinical laboratories, ranges of 0 – 0.8 mg/dl for CRP levels, 2 – 20 mm/h for sedimentation rate, 6.4 – 8.3 g/dl for total protein levels and 3.5 – 5 g/dl for total albumin levels were regarded as the normal value range. Patients were classified into two groups: group 1 (CRP negative group) consisting of those with CRP levels within the normal range (0 – 0.8 mg/dl) and group 2 (CRP positive group) consisting of those with CRP levels higher than the normal range (CRP > 0.8 mg/dl). Patients who had other rheumatologic and systemic diseases, active infections and nutritional disorders satisfied the exclusion criteria and were excluded from the study. Approval for the study was obtained from the ethics committee of University, Faculty of Medicine.

In our hospital, CRP levels were analysed using a serology autoanalyser (Beckman Coulter, IMMAGE, 800 version, USA) via the nephelometric method; the sedimentation rate was analysed using a fully automatic sedimentation device (Alifax brand Test 1 TH version, USA) via the Westergren method and total protein and albumin levels were analysed using a biochemistry autoanalyser (Abbott brand C- 16000 version, USA) via the photometric method.

Statistical Methods: To evaluate the assumption of normality in the data, the Kolmogorov–Smirnov test was used; and to describe the data, frequency (percent), mean±SD, median, and range were used. For evaluation of the differences between the two groups, we utilized t-test, statistical significance was set at $p< 0.05$. Pearson and Spearman's correlation test was used for to correlate the variables and $P< 0.05$ indicated statistical significance. All statistical analysis were performed by SPSS software (Version 21.0, Microsoft Co. Chicago, IL, USA).

RESULTS

Our study included 18 male (36%) and 32 female (64%) patients, and the mean age was 37.6 ± 10.7 (minimum 18 and maximum 61) years. Mean ± S.D values for total protein/albumin levels, sedimentation rate and A/G ratios of both groups are summarised in **Table 1**. We evaluated if there was any statistically significant differences between these two groups with respect to sedimentation rate, total protein/albumin levels and A/G ratios. Consequently, there was a statistically significant difference between the sedimentation rate ($p = 0.001$), total protein/albumin ($p = 0.002$) levels and A/G ratio ($p = 0.002$) of patients in group 2 and those in group 1 (**Table 2**). There was a statistically significant negative correlation ($r = -0.405$, $p = 0.004$) between the CRP levels and the A/G ratio and a statistically significant positive correlation ($r = 0.471$, $p = 0.001$) between the CRP levels and the total protein/albumin levels (**Table 3**). Similarly, there was a statistically significant negative correlation ($r = -0.602$, $p = 0.000$) between sedimentation rates and A/G ratio and a statistically significant positive correlation ($r = 0.611$, $p = 0.001$) between sedimentation rates and the total protein/albumin level (**Table 3**).

Table 1: Analysis of biochemical parameters of divided by CRP levels.

	CRP * Group	N	Mean	Std.Deviation
	1	33	1.7981	0.12659
Total Protein/Albumin				
	2	17	1.9455	0.1817
	1	33	11.1212	9.21533
Sedimentation				
	2	17	21.1765	10.731
	1	33	1.285	0.21122
Albumin/Globulin Ratio				
	2	17	1.0908	0.18568

** Group 1= CRP< 0.8; Group 2= CRP> 0.8; CRP: C-Reactive protein.*

Table 2: Comparison of groups according to CRP values.

	CRP Group	P* Value
	<0.8	
Albumin/Globulin Ratio		0.002
	>0.8	
	<0.8	
Total Protein/Albumin		0.002
	>0.8	
	<0.8	
Sedimentation		0.001
	>0.8	

*CRP: C-Reactive protein; *Independent sample t test*

Table 3: Correlations between values.

	CRP	Sedimentation
r	-0.405	-0.592
Albumin/Globulin Ratio		
P	**0.004**	**0.000**
r	0.0471	0.592
Total Protein/Albumin		
P	**0.001**	**0.000**

P<0.05: Statistical significant

DISCUSSION

Albumin and globulin are the two main components of serum proteins. Albumin levels are associated with the chronic nature of the disease and represent an inflammatory state.[17,18] The importance of albumin levels in estimating the outcomes of a chronic and inflammatory disease is also well-known.[14,15,19,20] Hypoalbuminemia is particularly prevalent in patients with cancer and is also associated with chronic inflammation.[21] Moreover, increased globulin levels can serve as a chronic inflammation marker and indicate the cumulative exposure of various proinflammatory cytokines.[22] A/G levels not only reflect the nutritional state but also indicate systemic inflammation.[23] In the present study, we found that the A/G ratio along with the CRP level was reliable as indicators of BD activation.

High-sensitivity CRP (hs-CRP) is an acute-phase reactant and a chronic inflammation marker. [24] The hs-CRP level is an indicator for estimating the risk or prognosis of various diseases, such as coronary artery disease, ischaemic stroke, sepsis and cancer,[25,26] and in some cases, other parameters besides CRP are required for evaluations. Accordingly, studies examining the role of CRP levels in various diseases have been conducted. In a study, Ranzani et al. evaluated the 90-day mortality rates of patients with sepsis after they were discharged from the intensive care unit, compared the CRP level with the CRP/albumin ratio and found that evaluation of the CRP/albumin ratio provided more accurate results than that obtained by evaluating only standard CRP levels as a long-term indicator of the prognosis.[27]

Jaehun Oh et al., in a retrospective study on the mortality risk in elder patients who were admitted to the hospital via emergency services, demonstrated that the hs-CRP/albumin ratio at the time of admittance to the emergency service was correlated with all-cause in-hospital mortality in patients aged > 65 years.[28]

Min Hyung Kim et al., evaluated the independent estimation of the 180-day mortality in patients with severe sepsis and septic shock in a retrospective cohort study within the course of approximately 6 years and found that the CRP/albumin ratio was an independent predictor of mortality in patients with severe sepsis or septic shock.[29]

The modified early warning score (MEWS) is a concept used for determining the degree of illness in patients with severe diseases in acute medical units.[30] Fairclough et al., in their study evaluating correlations between CRP and albumin levels with MEWS, demonstrated that even though an increasing CRP/albumin ratio was less sensitive compared with MEWS in terms of determining general mortality, it was more useful in acute inflammation of chronic diseases, particularly in elder patients.[31]

Sugimoto et al. stated that the A/G ratio decreased in patients with relapse ocular BD and in those who were undergoing infliximab treatment and that tracking the A/G ratio might be used as a biomarker for detecting relapses in patients with ocular BD.[16] In the same study, CRP levels in the patient group were detected to be slightly increased. In the literature review, we found no

study on the A/G ratio in patients with BD except for the aforementioned study which studied patients with relapsed ocular BD.

As observed in many studies conducted for evaluating the aforementioned disease activations, evaluation of easily accessible parameters that are frequently used in clinical evaluations will make implementation easier for BD. Therefore, we compared two different groups with normal and high CRP levels with their A/G ratio and sedimentation rates, which are frequently used in clinical evaluations and were easily accessible. We found that there was a statistically significant difference between the group with positive CRP level and the group with negative CRP levels with respect to the sedimentation rate, total protein/albumin levels and A/G ratios. We also found that in the group with positive CRP levels, the A/G ratio decreased and the total protein/albumin level and ESR rate increased and that as CRP levels and sedimentation rates increased, the A/G ratio decreased.

Although acute-phase proteins, immunoglobulin, complement, autoantibody, lymphocyte, surface indicator and cytokine levels are utilised as indicators of BD activity, there is no specific indicator for disease activation.

Melikoğlu et al. demonstrated that there is a correlation between disease activity and CRP and IL- 6 levels in patients with BD,[32] whereas Müftüoğlu et al. found that the relationship between emerging erythema nodosum, acute thrombophlebitis and arthritis, and high ESR and CRP positivity might be an indicator of general disease activity.[11] In a study, Gibson et al. reported that ESR and CRP levels increased during the acute or relapsed phase of BD and that leucocytosis and hypergammaglobulinemia were detected during the active period of the disease; however, these indicators did not have a strong correlation with disease activity.[33]

Similarly, in a study on patients with uveitis associated with BD, Mesquida et al. have reported that compared with the control and inactive disease groups, proinflammatory cytokine, such as IFN-γ, TNF-α, IL-17A and hs-CRP, levels from increased in patients with uveitis, and this increase was related to disease activity; however, most of the biomarkers were examined in experimental studies and they were difficult to test in a clinical setting.[16,34]

Based on the results of the present study, we believe that along with CRP levels, sedimentation rate and A/G ratio, which are frequently used in clinical evaluations and are easily accessible, may be used as indicators of BD activity.

CONCLUSIONS

Even though CRP levels are used as a sole indicator in some cases for evaluating the infection and inflammation state, disease activity and mortality, further studies on additional parameters are being conducted because of the need for supporting parameters. There are very few studies on supportive parameters along with CRP levels that are accepted as indicators of disease activity, and it is not easy to utilise many of the biochemical parameters for routine clinical use in the current conditions. Based on the results of the present study, we believe that biochemical markers, such as sedimentation rate and A/G ratio, which are routinely analysed in clinics along with CRP levels, may be important indicators for determining BD activity.

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