THE RELATIONSHIP BETWEEN DISEASE ACTIVITY AND ASO AND CRP LEVELS IN BEHÇET'S DISEASE

BEHÇET HASTALARINDA HASTALIK AKTİVİTESİNİN ASO VE CRP DEĞERLERİ İLE İLİŞKİSİ

Erdal PALA[1], Ceren ÇİMEN[1]

ABSTRACT

Objective: Behçet's disease (BD) is a complex inflammatory condition affecting multiple systems, with an unclear etiology. Since BD is characterised by remissions and attacks, there is no specific marker that accurately reflects the severity of the disease. The objective of this study was to examine the correlation between C-reactive protein (CRP) and antistreptolysin-O (ASO) levels and disease activity in BD patients.

Materials and methods: Our study was retrospective. The files of patients with BD who were admitted to our dermatology clinic between January 2023 and January 2024 were retrospectively analyzed. Socio-demographic characteristics, CRP and ASO levels were recorded and the relationship with disease activity was analyzed. Behçet's Disease Current Activity Form (BDCAF) was used to assess Behçet's disease activity. The study data were analyzed using SPSS V20 (Released 2018, IBM, NY, USA) software.

Results: The study included 100 patients with BD. 71% (n=71) of the patients were female. The mean age was 37.9±13.1 years for females and 34.5±9.8 years for males. Oral aphthae were found in 94%, genital ulcers in 70%, and papulopustular lesions in 68% of patients with BD. Neurological, gastrointestinal and vascular involvement were less common. Of the 100 patients with Behçet's disease, 4% (n=4) had central nervous system involvement, 1% had gastrointestinal system involvement and 4% (n=4) had vascular system involvement. Eye involvement was detected in 5 male patients and 17 female patients. The Pathergy test was positive in 40% (n=40) of the patients. The mean ASO value of patients with active Behçet's disease were 157.65 IU/ml, which was statistically more significant than the ASO values of patients with inactive Behçet's disease ($p<0.05$). Mean CRP levels in patients with active Behçet's disease were 4.39 mg/L. It was statistically higher than the mean CRP levels of inactive Behçet's patients. ASO and CRP levels were statistically significantly correlated with disease activity ($p<0.05$). No statistically significant difference was found between ASO levels and age, whereas the relationship between CRP levels and age was statistically significant ($p<0.05$).

Conclusions: Our study demonstrated a statistically significant correlation between ASO and CRP levels and BD activity. We suggest that serum ASO and CRP levels should be routinely checked in patients with BD to assess disease activity and to identify the presence of infection as a potential triggering factor.

Keywords: Behçet's disease, C-Reactive Protein, Antistreptolysin O, Inflammation mediators, Severity of illness index

ÖZET

Amaç: Behçet hastalığı multisistemik inflamatuar bir hastalıktır ve etiyolojisi henüz net olarak tanımlanamamıştır. Behçet hastalığı remisyon ve ataklarla seyreden bir hastalık olduğu için, hastalığın şiddetini tam olarak yansıtan spesifik bir belirteç bulunmamaktadır. Bu çalışmadaki amacımız Behçet hastalarında C-reaktif protein (CRP) ve ASO (Antistreptolizin-O) değerleri ile hastalık aktivitesi arasındaki ilişkiyi araştırmaktır.

Materyal ve metot: Çalışmamız retrospektif olarak gerçekleştirilmiştir. Ocak 2023-Ocak 2024 tarihleri arasında dermatoloji kliniğimize başvuran Behçet Hastalarının dosyaları retrospektif olarak taranarak hastaların sosyodemografik özellikleri, ASO ve CRP düzeyleri kaydedilerek hastalık aktivitesi ile ilişkisine bakılmıştır. Behçet hastalığının aktivitesini ölçmek için Behçet Hastalığı Güncel Aktivite Formu (BDCAF) kullanıldı. Çalışma verileri SPSS V20 (Released 2018, IBM, NY, ABD) yazılımında analiz edilmiştir.

Bulgular: Çalışmaya Behçet hastalığı tanısı olan 100 hasta dahil edilmiştir. Hastaların %71'i (n=71) kadındı. Yaş ortalaması kadınlarda 37,9±13,1, erkeklerde 34,5±9,8 idi. Behçet hastalarının %94'ünde oral aft, %70'inde genital ülser, %68'inde papülopüstüler lezyon tespit edildi. Nörolojik, gastrointestinal sistem ve vasküler sistem tutulumları daha az oranda görüldü. Çalışmaya katılan 100 behçet hastasının %4'de (n=4) santral sinir sistemi tutulumu, %1'de gastrointestinal sistem tutulumu, %4'de (n=4) vasküler sistem tutulumu mevcuttu. Göz tutulumu ise erkek hastaların 5'de, kadın hastaların 17'de tespit edildi. Hastaların %40'da (n=40) paterji testi pozitif olarak tespit edildi. Aktif Behçet hastalığı olanların ortalama ASO değerleri 157,65 IU/ml bulunmuş olup inaktif Behçet hastalarının ASO değerlerine göre istatistiksel olarak daha anlamlı idi ($p<0,05$). Aktif Behçet hastalarında ortalama CRP seviyeleri 4,39 mg/L olarak tespit edildi. İnaktif Behçet hastalarının ortalama CRP seviyelerine göre istatistiksel olarak daha yüksekti. Hastaların ASO değerleri ile yaş arasında istatistiksel olarak anlamlı bir fark bulunmazken,
CRP değerleri ile yaş arasındaki ilişki istatistiksel olarak anlamlıydı ($p<0,05$).

Sonuçlar: Çalışmamızda Behçet hastalarında ASO ve CRP değerleri ile hastalık aktivitesi arasında istatistiksel olarak anlamlı bir ilişki olduğu saptanmıştır. Behçet hastalarının hem hastalık aktivitesini takip etmede hem de olası bir tetikleyici faktör olarak bir enfeksiyon varlığının belirlenmesi için serum ASO ve CRP değerlerinin rutin kontrollerde bakılması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Behçet Hastalığı, C-Reaktif protein, Antistreptolisin O, İnflamasyon, Hastalık şiddet indeksi

Received:20.06.2024
Accepted:20.08.2024
Published:31.08.2024

How to cite: Pala E, Çimen C. The Relationship Between Disease Activity And ASO And CRP Levels In Behçet's Disease. SMJ 2024; 2(2): 3-11..

[1]Atatürk University, Faculty of Medicine, Department of Skin and Venereal Diseases, Erzurum, Turkey
*erdalpala2525@gmail.com
**Corresponding Author*

Introduction

Behçet's disease (BD) is a chronic auto-inflammatory disorder of unknown cause, characterised by periods of remission and flares. In addition to genital ulcers, skin manifestations, and eye manifestations, it can affect many other organs. Although Behçet's disease can occur worldwide, it is more common in countries along the Silk Road. The reported prevalence in Turkey is high, with more that 1 case per 1,000 people. Although Behçet's disease can develop at any age, the average age of onset is reported to be 30 years (1). The aetiopathogenesis is not fully understood, with various mechanisms such as genetic, epigenetic, infectious, immunological, and environmental factors being emphasised (2). Studies on the role of microorganisms in the exacerbation of BD were first conducted by Professor Dr. Hulusi Behçet (3). It has been suggested that a potential immune response in genetically predisposed individuals could be triggered by a cross-reaction between heat shock proteins from specific streptococcal species and human heat shock proteins. Following this cross-reaction, stimulation of the Toll-like receptors (TLRs) can lead to increased T-cell expression. Both innate and adaptive immune responses likely contribute to the development of BD (4). Microbial lipopolysaccharides can elevate various proinflammatory cytokines by activating the autoinflammatory response through TLRs and inflammasomes, leading to the production of interleukin-1β (IL-1β). Research indicates elevated expression of proinflammatory cytokines like IL-6, IL-8, IL-1α, IL-1β, and tumor necrosis factor (TNF) in BD, alongside decreased levels of the anti-inflammatory cytokine IL-10. (5,6). ASO (antistreptolysin-O) is used to diagnose poststreptococcal disease. High levels of ASO are found after streptococcal infection of the upper respiratory tract. ASO levels start to rise approximately 1 week after infection. Recent studies have shown that streptococcal infections play a rolein the etiology of BD. In BD, sensitivity to streptococcal antigens is suggested to influence the manifestation of symptoms (7). C-reactive protein (CRP) is synthesized by the liver as a positive acute-phase reactant and serves as a highly sensitive marker for inflammation and tissue damage. CRP levels are elevated in infections, inflammatory diseases, trauma, malignancy, and cardiac pathology. Parameters including erythrocyte sedimentation rate (ESR), CRP, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio have been employed to assess disease activity in BD. One study found a weak to moderate statistical association between disease activity and CRP (8). Although there are very few studies in the literature investigating the relationship between ASO levels and BD, we did not find any study investigating the relationship between the activity of the disease and ASO levels. Although the etiopathogenesis of Behçet's disease is not fully known, exacerbation of disease activity may occur due to infectious causes. ASO and CRP levels, which can be an indicator of infections, may be important in monitoring the activity of Behçet's disease. Identifying and treating a source of infection that can activate Behçet's disease can put Behçet's disease into remission. Therefore, we think that ASO and CRP, like many other markers used in monitoring the activity of Behçet's disease, can be used as markers for monitoring the disease activity. Based on this, our study aimed to explore the correlation between BD activity and ASO and CRP levels.

Material and methods

Design of the study

This was a retrospective, single-center study, employing a cross-sectional design.

Ethical approval

Our study was in accordance with the tenets of the Declaration of Helsinki and had local ethics committee approval (07.06.2024/376)

Participants and study protocol

Between January 2023 and January 2024, 100 active and inactive patients with Behçet's disease (BD), aged 18 to 70 years, who visited to the Behçet's outpatient clinic of our hospital were, included in the study. BD diagnosis was established based on the International Behçet's Disease Diagnostic Criteria.Patients with 1 major criterion and at least 2 minor criteria during examination were diagnosed with Behçet's disease (major: oral aphthae, minor: genital ulcers, eye findings, skin findings, positive pathergy test). A pathergy test was performed to support the diagnosis. The forearm areas were

punctured with 20-gauge needles at multiple sites at a depth of 5 mm. The test was considered positive after 24 and 48 hours if a papule or pustule appeared at the tested site. The Behçet's Disease Current Activity Form (BDCAF) scale was used to assess disease activity in patients previously diagnosed with BD during routine check-ups. BDCAF asked about headache, oral ulcer, genital ulcer, erythema, pustules, inflammatory arthralgia, arthritis, abdominal pain, nausea-vomiting, diarrhea-significant rectal bleeding, eye involvement, central nervous system involvement, and large vessel involvement other than intracranial and vascular disease in the past four weeks due to BD. The presence of each clinical symptom was scored as 1 point and an index score was calculated using 12 points. Demographic characteristics of the patients were documented in a patient record form. Patient records were retrospectively reviewed and symptoms, BDCAF score, ASO and CRP levels were recorded from the date of presentation. Our hospital's laboratory reference values were used to evaluate the test results. Accordingly, CRP (C-reactive protein) <5 mg/L and ASO (antistreptolysin-O) 0-200 IU/mL were accepted as normal values. Biochemical analyses of CRP and ASO were performed using an electrophotometric method on a Roche® instrument. Patients under 18 and over 70 years of age, patients with acute infections, a known history of malignancy, pregnancy and lactation, or any other known inflammatory dermatological disease were excluded from the study.

Statistical analysis

The study data were analyzed using SPSS V20 (Released 2018, IBM, NY, USA) software. Categorical data were presented as frequencies and percentages, while numerical data were reported as means and standard deviations. The Kolmogorov-Smirnov test, z-scores derived from skewness and kurtosis coefficients, and graphical methods were used to assess the conformity of numerical data to a normal distribution. The Mann-Whitney U test was used to analyze non-normally distributed continuous variables, while the Student's t-test was applied to normally distributed continuous variables. The Chi-squared test was used to analyze categorical data. Spearman correlation analysis was performed to assess the association between ASO and CRP levels. A significance level of $p<0.05$ was considered for all data.

Results

The study included 100 patients diagnosed with Behçet's disease (BD), of whom 71% (n=71) were female. The mean age among female participants was 37.9±13.1 years, while among male participants, it was 34.5±9.8 years. The mean ages of female and male patients did not differ significantly ($p>0.05$). Oral aphthae were found in 94%, genital ulcers in 70% and papulopustular lesions in 68% of BD. Oral aphthae and genital ulcers were more common in female patients than in male patients. Central nervous system, gastrointestinal, and vascular involvement were observed less frequently (Table 1). Central nervous system involvement was present in 4% (n=4), gastrointestinal system in 1% (n=1) and vascular system involvement in 4% (n=4) of our Behçet's patients. Eye involvement was found in 5 male and 17 female patients. Pathergy test was positive in 54.5% (n=24) of patients with active Behçet's disease. According to the BDCAF scale, 44% (n=44) of our patients were active and 56% (n=56) were inactive. The distribution of organ involvement in BD patients was similar between genders (Table 2). No statistically significant difference was observed between gender and the pathergy test regarding ASO values ($p>0.05$) (Table 3). The mean ASO level among the patients was 164.4±243.3 IU/ml. No statistically significant difference was observed between ASO levels and organ involvement ($p>0.05$) (Table 4). There was no statistically significant difference observed between ASO levels and age. The CRP levels of the patients were 25.7±91.8 mg/L. No statistically significant difference was observed between CRP levels and organ involvement ($p>0.05$) (Table 4). No statistically significant difference was observed between gender and the pathergy test regardingCRP levels ($p>0.05$) (Table 3). Additionally, the correlation between CRP levels and age was statistically significant ($p<0.05$, r:0.21), indicating a weak positive relationship. No statistically significant correlation was observed between the pathergy test and disease activity ($p>0.05$) (Table 5).

However, a statistically significant difference was detected in ASO and CRP levels regarding disease activity ($p<0.05$) (Table 6). A correlation between ASO and age was analyzed, but no statistically significant difference was found.

Tablo 1. Organ involvement among Behçet's disease patients

		n	**%**
Oral aphthae	Yes	94	94.0
	No	6	6.0
Genital ulcer	Yes	70	70.0
	No	30	30.0
Papulopustular lesion	Yes	68	68.0
	No	32	32.0
Eye	Yes	22	22.0
	No	78	78.0
Arthritis	Yes	59	59.0
	No	41	41.0
Erythema nodosum	Yes	41	41.0
	No	59	59.0
Central nervous system	Yes	4	4.0
	No	96	96.0
Gastrointestinal tract	Yes	1	1.0
	No	99	99.0
Vascular system	Yes	4	4.0
	No	96	96.0

Table 2. Organ involvement-gender relationship

		Gender				
		Male		Female		
		n	%	n	%	P
Oral aphthae	Yes	26	89.7	68	95.8	0.352
	No	3	10.3	3	4.2	
Genital ulcer	Yes	20	69.0	50	70.4	0.885
	No	9	31.0	21	29.6	
Papulopustular lesion	Yes	18	62.1	50	70.4	0.416
	No	11	37.9	21	29.6	
Eye	Yes	5	17.2	17	23.9	0.463
	No	24	82.8	54	76.1	
Arthritis	Yes	14	48.3	45	63.4	0.163
	No	15	51.7	26	36.6	
Erythema nodosum	Yes	8	27.6	33	46.5	0.081
	No	21	72.4	38	53.5	
Central nervous system	Yes	0	0.0	4	5.6	0.320
	No	29	100.0	67	94.4	
Gastrointestinal tract	Yes	0	0.0	1	1.4	
	No	29	100.0	70	98.6	
Vascular system	Yes	2	6.9	2	2.8	0.577
	No	27	93.1	69	97.2	

Table 3. The relationship between ASO-CRP values and gender and pathergy test

			Mean	Median	Standard Deviation	P
ASO Value	Gender	Male	185.67	101.00	386.85	0.721
		Female	155.67	100.00	153.50	
	Patergy Test	Positive	130.99	81.50	154.74	0.060
		Negative	181.57	110.55	277.64	
CRP Value	Gender	Male	16.47	3.78	37.38	0.787
		Female	29.45	3.00	106.41	
	Patergy Test	Positive	24.81	3.00	74.66	0.503
		Negative	26.14	3.06	100.09	

ASO: Antistreptolysin-O, CRP: C-Reactive Protein

Table 4. The relationship between ASO-CRP values and organ involvement

			Mean	Median	Standard Deviation	P
ASO Value	Oral aphthae	Yes	167.67	249.95	100.00	0.674
		No	112.67	78.66	93.50	
	Genital ulcer	Yes	140.94	131.62	100.00	0.712
		No	219.04	395.43	110.55	
	Papulopustular lesion	Yes	178.10	283.99	100.00	0.799
		No	135.19	115.65	105.55	
	Eye	Yes	191.56	171.64	165.95	0.083
		No	156.70	260.33	100.00	
	Arthritis	Yes	187.18	296.32	111.00	0.428
		No	131.55	131.38	91.80	
	Erythema nodosum	Yes	214.38	344.60	112.50	0.186
		No	129.62	126.92	95.50	
	Central nervous system	Yes	60.95	24.68	63.05	0.100
		No	168.68	247.34	101.55	
	Gastrointestinal tract	Yes	45.30	.	45.30	0.246
		No	165.57	244.19	100.00	
	Vascular system	Yes	118.57	78.78	99.40	0.986
		No	166.28	247.74	100.00	
CRP Value	Oral aphthae	Yes	26.79	94.63	3.00	0.805
		No	8.45	10.29	4.54	
	Genital ulcer	Yes	20.51	64.48	3.06	0.857
		No	37.76	136.71	3.00	
	Papulopustular lesion	Yes	22.05	65.58	3.00	0.346
		No	33.42	132.49	3.87	
	Eye	Yes	54.04	166.73	3.11	0.950
		No	17.69	54.50	3.00	
	Arthritis	Yes	28.14	105.16	3.00	0.360
		No	22.16	69.45	3.00	
	Erythema nodosum	Yes	29.11	82.57	3.00	0.820
		No	23.31	98.40	3.00	
	Central nervous system	Yes	2.68	1.41	2.97	0.423
		No	26.65	93.64	3.06	
	Gastrointestinal tract	Yes	3.00	.	3.00	0.849
		No	25.92	92.29	3.00	
	Vascular system	Yes	2.93	2.85	2.35	0.393
		No	26.64	93.64	3.00	

ASO: Antistreptolysin-O, CRP: C-Reactive Protein

Table 5. Association between pathergy test and disease activity

			Disease activity	
			Active	Inactive
Patergy test	Positive	n	24	16
		%	54.5	47.1
	Negative	n	20	40
		%	45.5	60.6

Table 6. The relationship between ASO-CRP values and disease activitiy

			Mean	**Median**	**Standard Deviation**	**P**
ASO value	Severity of Illness Index	Active	252.04	157.65	340.55	**<0.001**
		Inactive	95.49	80.50	69.71	
CRP value	Severity of Illness Index	Active	36.36	4.39	82.65	**0.033**
		Inactive	17.30	3.00	98.39	

ASO: Antistreptolysin-O, CRP: C-Reactive Protein

Discussion

Our study aimed to investigate whether ASO and CRP levels could be used as markers to monitor the activity of Behçet's disease (BD). In our study, statistically significant higher ASO and CRP levels were found in patients with active Behçet's disease compared to those with inactive Behçet's disease. Based on this finding, we suggest that ASO and CRP levels serve as useful markers for monitoring disease activity in patients with Behçet's disease. Behçet's disease (BD) is an inflammatory disease whose etiopathogenesis is not fully understood but may be triggered by infectious and some environmental causes in individuals with a genetic predisposition. Although no specific microorganism has been pinpointed in the etiology of BD, it has been proposed that microorganisms might indirectly trigger the disease through compromised immune system function.. One study found that the onset of uveitis attacks in BD patients following hypersensitivity testing with streptococcal antigens suggested a possible role of streptococci in the etiology (9). Although many studies have investigated the relationship between antigenic stimuli from microorganisms and the etiopathogenesis of BD, few have examined the relationship between ASO levels and the disease. Similarly, while many studies have explored the relationship between BD activity and CRP levels, we found no studies that specifically investigated the relationship between ASO levels and BD. Microbiological studies have generally focused on ulcers, oral flora, and skin lesions. Potential triggering agents in the etiology of BD include streptococcal antigens, Staphylococcus aureus, Mycobacteria, Saccharomyces cerevisiae, Helicobacter pylori, Escherichia coli, Borrelia burgdorferi, and Mycoplasma fermentans (10). Although many parameters have been studied to monitor the activity of BD, there is still a need for parameters with high specificity and sensitivity that are easy and quick to use. One of the parameters used to monitor this activity is CRP. Since CRP can be elevated in various infectious and inflammatory diseases, its specificity as a marker for assessing BD activity remains controversial. Studies have demonstrated elevated CRP levels in patients with active BD compared to control groups (11). Another study reported that CRP levels were higher in BD patients with erythema nodosum and thrombophlebitis (8). In our study, we observed statistically significant elevations in CRP levels among patients with active BD compared to the inactive group.

However, unlike some reports in the literature, we did not find a correlation between CRP levels and specific symptoms of the disease. ASO is commonly utilized in diagnosing poststreptococcal diseases, often revealing a heightened ASO response subsequent to streptococcal upper respiratory tract infections (12). Streptococcal infections are considered pivotal in the etiopathogenesis of BD. Tonsillitis and dental caries have been observed to be common conditions among patients with BD (13). When we look at the literature, the number of studies investigating the relationship between ASO levels and BD is quite low. One study found that erythema nodosum-like lesions were more prevalent in BD cases with elevated ASO levels (14). Similarly, another study that investigated the levels of ASO in BD reported higher levels of ASO in patients with BD compared to control subjects. (15, 16). In our study, we found that both ASO and CRP levels were not related to the symptoms of BD, However, we observed statistically significant elevations in ASO levels among active BD patients compared to inactive ones. Thus, we propose that markedly elevated ASO levels could serve as a useful indicator for monitoring BD activity.

Strength and Limitations

Our study has several limitations. Firstly, it was retrospective and conducted at a single institution, which limits the generalizability of the results; therefore, prospective studies conducted across multiple centers are needed. Secondly, the lack of control groups in our study represents another limitation. Despite these limitations, a key strength of our study is that we have not identified any literature examining the relationship between BD activity and ASO levels. Furthermore, the inclusion of a relatively large number of BD patients enhances the robustness of our findings.

Conclusions

In summary, our study found higher ASO and CRP levels in patients with active BD compared to those with inactive disease, and we believe that ASO levels should be specifically monitored during disease activity follow-up. Although ASO and CRP levels have not been shown to be associated with various symptoms of BD, prospective studies with larger numbers of participants are needed to evaluate this. Based on these results, we suggest that initiating antibiotherapy in BD patients with high ASO levels may be beneficial in the management of BD.

Acknowledgements
None

Conflict of interest
None

Funding
None

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