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A study of circulating levels of IL-17 in Egyptian patients with Behcet's disease and its association with disease manifestation

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Abstract

Behcet's disease (BD) is a vascular inflammatory illness with different clinical presentations and incompletely understood mechanisms. Interleukin-17 (IL-17) is suggested to take part in BD inflammatory process but the exact role in different disease manifestation is still unclear. This case-control study aimed to investigate the correlation between IL-17 levels and the symptoms of BD. This study included 30 individuals diagnosed with BD and 15 apparently healthy volunteers, age and sex matched, as controls. Complete clinical assessment with consideration for clinical manifestations was performed. Laboratory markers for BD activity including erythrocyte sedimentation rates and C-reactive protein (CRP) were evaluated. Serum IL-17 level was measured using an enzyme-linked immunosorbent assay. The serum IL-17 levels in patients and controls differed significantly (p< 0.001). Both the duration of BD illness and CRP showed a significant positive correlation with serum IL-17 (p= 0.048 and p<0.001, respectively). Furthermore, compared to patients with uveitis and controls, individuals with skin manifestations had significantly greater serum IL-17 levels (p<0.001). In conclusion, serum IL-17 in BD patients especially in those with skin manifestations had significant correlation with disease activity. These results confirm the suggested role of IL-17 in augmenting the inflammation of BD and support the treatment with anti-IL-17 specific therapy for resistant cases of BD especially cases with skin symptoms.

Keywords: Behcet's disease, Disease manifestations, Interleukin-17, Mucocutaneous, Uveitis.

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Introduction

Behcet's disease (BD) is an inflammatory vascular condition that can affect any size or type of vessels.[1] Although the clinical presentation of BD quietly varies, recurrent mucocutaneous and skin lesions constitute the common clinical hallmark that usually occurs before other organ manifestations.[2] The exact cause for the disease is not fully known but different theories suggest that various infectious agents and genetic variants might potentially cooperate to trigger the innate hyper inflammatory state that sustained by the adaptive immune response.[3]

The human leukocyte antigen (HLA) genes, including HLA-B51 are a key genetic component.[4] Endoplasmic reticulum aminopeptidase 1 (ERAP1), interleukin (IL)-23/IL-17 pathway and tumor necrosis factor (TNF) signaling are set of susceptibility variants identified outside the HLA region.[5, 6] When HLA-B51 and ERAP1 variations interact, it throws off the balance of T cells, which activates the T-helper 1 (Th1) and Th17 pathways while suppressing regulatory T cells (Treg cells). This causes neutrophil activation and organ invasion.[2, 5] Th17 cells constitute the main effector arm of neutrophil activity. IL-17 is the primary Th17 cell-derived cytokine that can enhance inflammatory cytokine production, neutrophil activation, antibody production and adhesion molecules expression.[7]

In BD, dysregulation of the Th17 immune response is suggested to have an essential part to play in the process of illness onset and progression. However, investigations on levels of IL-17 in the blood of BD individuals have yielded mixed results.[8] Moreover, the exact role in disease activity and different disease manifestation is still unclear limiting the use of anti-IL17 as line of therapy for BD. Thus, this case-control study was performed as an attempt to evaluate serum IL-17 in individuals with BD and identify any correlations with the most frequent disease manifestations.

Patients and Methods

This case-control study included 30 BD patients. Participants were chosen from the outpatient clinic of Tanta University's Department of Physical Medicine, Rheumatology, and Rehabilitation. Patients who met the criteria set forth by the International Committee for the Diagnosis of Behcet's Disease (ICBD) were considered for inclusion.[9]

Patients who did not have BD were those with a score below 3. A probable diagnosis of BD was indicated by a score of 3, while a confirmed diagnosis of BD was given by a score of 4 or above. (Table 1)[9]

Table 1. The international criteria for Behçet disease scoring system.

Signs/Symptoms	Number (points)
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test	1

The following equation was used for sample size calculation:

$$n = 2\left[\frac{(Z_{\alpha/2} + Z_{\beta}) * \sigma}{\mu_1 - \mu_2}\right]^2$$

Where: n = sample size. Zα/2 = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail). Zβ = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%). σ = the estimate of the standard deviation of the duration of post-operative hospital stay. μ1 = mean for IL- 17 levels in patients. μ2 = mean for IL- 17 levels in healthy controls.

Patients were selected considering the main manifestation of BD and divided equally into two groups either for skin or eye manifestation. The control group composed of 15 apparently healthy individuals who were age and sex-matched to the BD individuals.

Exclusion criteria included any patient with other autoimmune or inflammatory disease presented with skin or ocular manifestations like (Systemic Lupus Erythematosus (SLE), Spondyloarthritis) and BD patients on biological therapy and patients with both skin and eye manifestation.

All patients were assessed clinically concerning age, sex, disease duration, medical history, clinical manifestations and complete rheumatologic examination. Erythrocyte sedimentation rates (ESR) and C-reactive

protein (CRP) were assessed as markers for Behcet's disease activity.

Serum samples were obtained by centrifugation of five milliliters of venous blood at 1000 rpm for 15 minutes. The samples were stored frozen in simple sterile tubes at -80˚C.

Serum IL-17 was assessed for all participants by an enzyme-linked immunosorbent assay (ELISA) technique using human IL-17 ELISA commercial kits (Cat. # 201-12-0143; SunRed Biotechnology Company, Shanghai, China), according to the manufacturer's instructions. The ELISA results were recorded using a microplate reader (Stat Fax®2100, Fisher Bioblock Scientific, France) at 450 nm with a correction wavelength set at 570 nm.

Statistical Analysis

The obtained data were statistically evaluated using the Statistical Package for the Social Sciences (SPSS), IBM software program version 20.0. Quantitative data were characterized using the mean and standard deviation (SD). In order to compare the means of quantitative variables that were normally distributed in two distinct groups, we used an independent T- test. The categorical variables of the various groups were compared using the chi-square test. For the purpose of detecting correlation between two quantitative parametric variables, the Pearson correlation coefficient test was used. A p-value ≤0.05 was considered significant.

Results

In this study 30 patients with BD were enrolled. Of these, 22 (73.3%) were males and 8 (26.7%) females with a mean age of 36.8±8.7 years and a mean disease duration of 3.3±2.5 years. In addition, 15 apparently healthy subjects with mean age of 37.2± 6.9 years were enrolled as normal controls. Of these, 5 (33.3%) were females and 10 (66.7%) males, (Table 2).

The distribution of clinical characteristics of our patients (considering symptoms overlap) and their medical treatment are delineated in Table 3.

There were 15 patients presented with skin manifestations (some patients had more than one manifestation at the same time); 10 (66.6%) patients had erythema nodosum, 8 (53.3%) had folliculitis, 5 (33.3%) with recurrent skin ulcers and 6 (40%) with pustular nodular lesions. Six patients had neurological manifestations; 1 (16.7%) patient had cavernous sinus thrombosis and cerebral aneurysms, 2 (33.3%) had headache and 3 (50%) with peripheral neuritis. Arthritis was presented in 10 patients, mainly oligoarticular affecting the ankle, knee and wrist joints. Furthermore, 15 patients were presented with ocular manifestations as bilateral posterior uveitis, (Table 3).

Regarding laboratory data, the mean ESR and CRP of our patients were 32.1±6.2 and 18.4 ± 5.97 respectively. The immunological investigation revealed a remarkable disparity in IL-17 concentrations. Patients demonstrated significantly and markedly elevated IL-7 levels (69.75 ± 10.1 pg/ml) in contrast to the control group (15.39 ± 5.9 pg/ml), ($p < 0.001$). Table 2

Table 2. Demographic and laboratory data of the studied groups.

	Patients (n=30)	Controls (n=15)	*p*-value
Age (years)	36.8±8.7	37.2± 6.9	NS[t]
Sex (Male/female)	22/8	10/5	NS[χ^2]
ESR	32.1± 6.2	14.1 ± 3.96	<0.001[t]
CRP	18.4 ± 5.97	3.4 ±1.1	<0.001[t]
Serum IL-17	69.75 ± 10.1	15.39 ± 5.9	<0.001[t]

t: Independent t test. χ^2: Chi square test $p > 0.05$ is not significant (NS).

Table 3. Clinical characteristics of the 30 patients group.

Clinical characteristic	Patient's n (%)
Oral ulcers	21 (70%)
Genital ulcers	19 (63.3%)
Skin involvement	15 (50%)
Neurological manifestation	6 (20%)
Uveitis	15 (50%)
Arthritis	10 (33.3%)
Corticosteroid therapy	23 (76.7%)
Colchicine treatment	21 (70%)
Azathioprine therapy	20 (66.7%)

n= number of patients.

Intriguingly, the research revealed a robust positive correlation between serum IL-17 and two critical parameters among BD patients: (disease duration and CRP levels). These correlations were statistically significant (p=0.048 and p< 0.001, respectively), as shown in Table 4 and Figure 1.

Table 4. Correlation between serum IL-17 and different parameters in the 30 patients group.

	r	*p* value
Disease duration	0.3634	0.048
ESR	0.054	NS
CRP	0.746	<0.001

r: Pearson correlation coefficient;
p > 0.05 is not significant (NS).

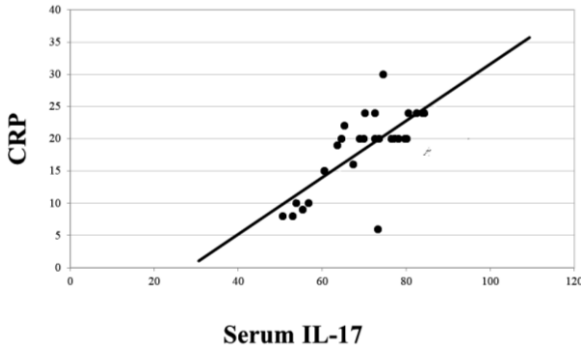

Figure 1. Correlation between serum IL-17 and CRP of BD patients.

The patient cohort was evenly distributed across two primary disease manifestation categories: uveitis and cutaneous symptoms. A comprehensive analysis demonstrated notable variations in IL-17 concentrations across these groups. Patients exhibiting skin manifestations displayed substantially higher IL-17 levels (78.2 ± 4.3 pg/ml) compared to those with uveitis (61.43 ± 6.4 pg/ml), (p < 0.001). Furthermore, the dermatological symptom group not only showed elevated IL- 17 levels compared to uveitis patients but also demonstrated significantly higher concentrations when contrasted with the control population (p < 0.001). Similarly, uveitis patients exhibited considerably elevated serum IL-17 levels (61.43 ± 6.4 pg/ml) relative to controls (15.39 ± 5.9 pg/ml), (p < 0.001), Figure 2.

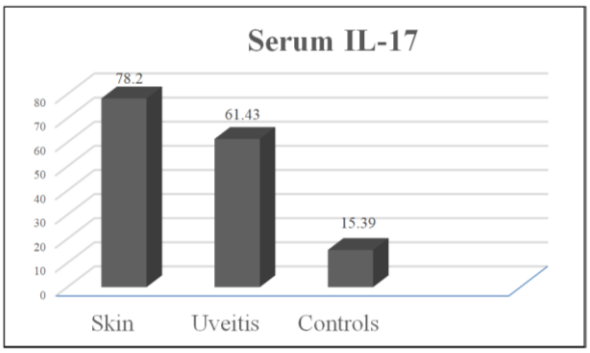

Figure 2. Mean levels of serum IL-17 in patients with skin manifestation, patients with uveitis and controls.

Discussion

BD emerges as a chronic vascular inflammatory disorder with complex and incompletely understood pathogenesis and treatment strategies.[10] The current investigation delves into IL-17, a pro-inflammatory cytokine potentially crucial in BD's mechanism and potential therapeutic targeting. Multiple research efforts have substantiated the significance of IL-17 in BD's immunological landscape.[11, 12]

The study by Gelmez et al., 2021,[13] documented increased IL-17 expressing natural killer cells and innate lymphoid cell 3 in BD patients. Deniz et al., 2017,[14] observed heightened IL-17 and IFN-γ release under Th-17 stimulating conditions, which trigger neutrophil activation and subsequent adaptive immune responses. Genetic influences potentially modulate IL-17 expression, with Jiang et al., 2015,[15] suggesting that IL-23 receptor gene polymorphisms might increase expressions of IL-17, IL-6, and TNF-α in BD.

The study by Ögün et al., 2019,[16] further explored cytokine dynamics in cerebrospinal fluid, examining IL-17 and IL-34's roles in active neuro-BD. In line with our results, they detected considerable elevation of IL-17 in patients compared to controls but they did not detect the same finding for IL-34 and attributed this difference to low sample size.[17, 18]

The current study revealed significant positive correlations between serum IL-17 levels and both disease duration and CRP, a critical inflammatory marker. Previous research supports this finding, as Hamzaoui et al., 2011,[19] demonstrated that plasma IL-17 levels and Th17 cell proportions significantly correlated with inflammatory markers in active BD patients. Also, Sonmez et al., 2018,[20] noticed the increased IL-17 in peripheral blood lymphocyte cultures of patients with active BD.

The study by Chi et al., 2008,[21] and Mesquida et al., 2014,[18] found elevated IL-17 levels in patients with active Behect's uveitis. Similarly, Ekinci et al., 2010,[22] detected significant higher IL-17 levels in active patients with ocular and mucocutaneous symptoms compared to inactive patients. The study by Wang et al., 2014[23] noticed the decreased IL-27 expression and elevated IL-17 production in patients with active BD suggesting that low IL-27 may enhance Th1 and Th17 cell response which augment inflammatory reaction of BD. However, Jadideslam et al., 2020,[24] and Küçükşahin et al., 2023,[12] could not detect significant correlation between IL-17 and parameters of BD activity despite the delineation of increased gene expression and serum levels of IL-17 in BD patients in contrast to controls.

Clinical manifestations showed intriguing variations. While patients were categorized into skin manifestation and uveitis groups, serum IL-17 levels remained markedly high in contrast to controls. Notably, skin manifestation groups displayed higher IL-17 levels than uveitis groups, aligning with earlier observations by Chen et al., 2011,[25] who highlighted IL-17A's role in inflammatory mediator secretion. The immunological mechanisms involve multiple cellular pathways. The study by Shimizu et al., 2012,[26] detected increased IL-17+CD4+ T cells in BD-related erythema nodosum, while NaSYet al., 2013,[27] reported elevated IL-17 expression in both CD4+ and CD8+ T cells during active BD. The study by Vural et al., 2021,[28] specifically identified expanding CD8+ T cells as primary IL-17A sources in BD skin lesions.

These comprehensive findings suggest potential therapeutic interventions. Di Scala et al., 2019,[29] and Fagni et al., 2020,[30] initially proposed and subsequently confirmed the potential of IL-17 antagonist secukinumab in treating refractory mucocutaneous BD. In conclusion, from the above results, we can conclude that IL-17 was significantly elevated in BD patients with more elevation in patients with skin symptoms besides correlation with disease activity. IL-17 may participate in disease pathogenesis and augment the inflammatory process. Targeting IL-17 by specific antibody therapy may provide a hope for resistant cases of BD especially cases with mucocutaneous disease.

Author Contributions

DH made the statistical analysis, NAS collected the samples and performed laboratory assessment, AME helped in clinical assessment of patients, ShAA collected the patients and, helped in clinical

assessments of them. All authors participated in writing and reviewing the paper before submission.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Local Research Ethical Committee of the Faculty of Medicine, Tanta University, Egypt (approval code: 36264PR821/8/24)

Informed consent

Every single patient who took part in this research gave their clear written consent to participate in the study.

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