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Cytokine, C-Reactive Protein, and Heat Shock Protein mRNA Expression Levels in Patients with Active Behçet's Uveitis

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Background: To investigate the gene expression levels of interleukin 10 (IL10), IL18, interferon gamma (IFNG), IFN-gamma receptor (IFNGR), C-reactive protein (CRP), and heat shock protein 70 (HSP70) in patients with active Behçet's uveitis.

Material/Methods: Forty patients with Behçet's disease diagnosed according to the International Study Group criteria and 30 healthy individuals were included in the study. IL10, IL18, IFNG, IFNGR, CRP, and HSP70 gene expression levels were compared.

Results: Expression levels of IL18, IFNG, IFNGR, and CRP were significantly higher in patients with active Behçet's uveitis than in control subjects (P<0.01 for all), whereas no significant differences were found in IL10 and HSP70 gene expression levels (P>0.01 for both).

Conclusions: IL18, IFNG, IFNGR, and CRP gene expression is significantly increased in active Behçet's uveitis. There was no significant difference between active Behçet's uveitis patients and controls in terms of IL10 and HSP70 gene expression levels. We conclude that drugs prescribed to Behçet's patients with active uveitis downregulate gene expression.

MeSH Keywords: Behcet Syndrome • HSC70 Heat-Shock Proteins • Interleukins

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Background

Behçet's disease (BD) is an inflammatory condition characterized by recurrent episodes of oral aphthous ulcers, ocular and cutaneous lesions, and genital ulcerations [1]. Behçet's disease is associated with gastrointestinal, cardiac, renal, neurologic, vascular, cutaneous, and ocular disease and can cause arthritis

BD is more prevalent in the Middle East, along the Mediterranean coast, and in Central Asia. Turkey, where the disease was first described, has the highest reported prevalence, in the range of 110–420 per 100 000 inhabitants. In comparison, the National Study Group for BD in Portugal reported a prevalence of 2.5 per 100 000 inhabitants. Although regional prevalence varies widely, BD occurs in nearly all parts of the world [2,3]. The disease affects both sexes approximately equally and typically emerges between the ages of 20 and 40 years. Male sex and early onset are considered indicators of poor prognosis. The disease is a major cause of morbidity, both with skin and mucosal involvement, and in cases with involvement of other organs and systems [3–5].

The etiology of BD is not fully understood. Currently, the most supported hypothesis is that BD is an abnormal immune response in individuals genetically predisposed to the disease and is triggered by viral, bacterial, and other environmental antigens or autoantigens like heat shock proteins (HSPs) [6,7].

Th1 and Th2 cells are responsible for the secretion of different cytokines. IL-2 and IFN-γ, are typically produced by Th1 cells, while IL-4, IL-5, IL-6, IL-10, and IL-13 are secreted by Th2 cells [8–11]. Cross-regulation of the Th1 and Th2 cell subsets results in a Th1/Th2 balance, which has an important role in immune regulation. Numerous studies have implicated Th1/Th2 imbalance in autoimmunity. Previous studies have demonstrated that various inflammatory cytokines and chemokines secreted from mononuclear phagocytes and neutrophils, such as IFN-gamma, TNFα, IL-1, IL-2, IL-6,IL10, IL-8, IL-12, and IL-17, are increased in patients with BD. It has also been shown that the serum of BD patients induces pro-inflammatory activation of human peripheral blood macrophages. Furthermore, the IL-1 cytokine family has a central role in regulating immune and inflammatory responses, and increases serum levels of other cytokines (e.g., IL-8) which are reliable markers of BD activity [2,12,13].

IL10, a major Th2-type cytokine, plays a role in the inhibition of Th1 cell-derived cytokines and suppresses Th1 immunologic responses. A significant association has been observed between IL-10 and BD. A Behçet's-associated IL10 polymorphism (rs1518111 A allele) has been shown to cause significantly diminished IL-10 production in response to various stimuli compared to other gene variants. It is believed that diminished IL-10 production results in dysregulation of the inflammatory response and leads to the development of BD [14–19].

IL-18 is secreted by T cells, activates natural killer (NK) cells, and stimulates the release of IFN-gamma. It inhibits IL-12 and IFN-γ and suppresses production of IL-10. As a result, IL-18 promotes the differentiation of Th0 cells to Th1. Serum IL-18 levels are increased in most BD patients, and this elevation has been implicated in the etiopathogenesis of the disease [20–22].

Diagnosis is based on the criteria of the International Study Group for Behçet's Disease. Elevated serum levels of biochemical parameters such as cytokines [23–26] and CRP have been proposed as markers of disease activity [23,27].

HSPs are a family of proteins that exert immunostimulatory effects and may have regulatory functions in immune response pathways. Furthermore, they have been proposed as a source of cross-reactivity that could link infection and autoimmunity. Previous studies indicate that heat shock protein 70 (Hsp70) has both pro-inflammatory and anti-inflammatory properties. Its pro-inflammatory functions include binding to receptors on antigen-presenting cells, stimulating cytokine secretion, and facilitating antigen presentation). As an anti-inflammatory regulator, Hsp70 inhibits the release of inflammatory mediators. HSPs seem to have a role in the etiology of BD, but the nature of this involvement is not fully understood [23,28–34].

The basic goal of treatment approaches in BD is to suppress inflammation in the early stages and to control the symptoms and complications that may arise in certain organs.

Considering the role of cytokines and HSPs in inflammation pathways and possibly in the etiopathogenesis of BD, as well as their role as markers of disease activity, the present study was conducted to investigate expression levels of the genes encoding IL-10, IL-18 IL18, (IFNγ, IFNγR, CRP, and Hsp70.

Material and Methods

Study design

Forty patients (21 male, 19 female; mean age 31.3±42.5 years) diagnosed with BD in the Dermatology and Ophthalmology Departments according to the International Study Group criteria (ISGC) and a control group comprising 30 healthy unrelated individuals with no systemic disease (12 male, 18 female; mean age 21.8±34.8 years) were included in the study. The clinical and laboratory data of all study participants were recorded (Table 1). Twenty-eight of the BD patients were receiving only colchicine, while 12 were receiving immunosuppressive

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Table 1. Distribution of clinical and laboratory characteristics in patients with Behçet's disease.

Clinical and laboratory manifestation	BD N=40
Pathergy test positive	17
Oral aphthae positive	29
Skin lesion positive	4
Panuveitis positive	22
Posterior uveitis positive	18
HLA-B51 positive	11
Colchicine	28
Cyclosporine	12

Table 2. PCR components and volumes in cDNA synthesis from RNA.

cDNA PCR components	Volume (µl)
Buffer	4
Deoxynucleotide mix	2
RNase inhibitor	0.5
Reverse transcriptase	0.5
Mix total	7
mRNA+ ddH_2O + Random primer	13
Reaction total	20

Table 3. PCR thermal cycle steps in cDNA synthesis from RNA.

Step	Temperature	Time	Cycle number
1	25°C	10 min	1
2	55°C	30 min	1
3	85°C	5 min	1
4	4°C	∞	1

(i.e., cyclosporine) agents. Blood samples were obtained from all patients and control subjects.

RNA isolation, cDNA synthesis, and mRNA expression analysis

Total RNA was isolated using a MagNA Pure LC instrument and mRNA was purified from the total RNA using an Oligo-dT kit (Roche). RNA concentration was measured using a NanoDrop spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA). RNA samples were stored at –80°C until analysis. A

Table 4. Composition of PCR reactions for *IL10*, *IL18*, *IFNG*, *IFNGR*, *CRP*, and *HSP70*.

PCR components	Volume (µl)
ddH_2O	5
Probe Master Mix LC 480	10
Mix total	15
cDNA	5
Reaction total	20

Table 5. Roche LightCycler 480 Real-Time PCR program used in gene expression assay of *IL10*, *IL18*, *IFNG*, *IFNGR*, *CRP*, and *HSP70*.

Step	Temperature	Time	Cycle number
Preincubation	95°C	10 min	1
Amplification	95°C	10 s	45
	60°C	30 s	
	72°C	1 s	
Cooling	40°C	30 s	1

Transcriptor First-Strand cDNA synthesis kit (Roche) was used to synthesize cDNA from the isolated RNA samples (Tables 2, 3). IL10, IL18, IFN-γ, IFN-γR, CRP, and HSP70 expressions were analyzed using a Roche LightCycler 480 Real-Time polymerase chain reaction (PCR) device (Tables 4, 5). Two reference genes (β_2M and G6PD) were used in the analysis. Statistical analyses were performed using the SPSS (version 17.0 for Windows; SPSS Inc., Chicago, IL, USA) software package.

Results

Clinical characteristics and laboratory findings of the patients with Behçet's disease are summarized in Table 1.

There were significant differences IL18, IFN-γ, IFN-γR, and CRP gene expression levels between patients with active Behçet's uveitis and control subjects, but no significant differences were seen in IL10 and HSP70 gene expression levels (Table 6).

Discussion

The etiopathogenesis of BD has not been fully elucidated, but environmental, genetic, and immunologic factors may have important roles in its development [2,35].

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Table 6. *IL10*, *IL18*, *IFNG*, *IFNGR*, *CRP*, and *HSP70* gene expression levels in patients with active Behçet's uveitis and a control group.

Gene expression	BD N=40 median (min–max)	Control group N=30 median (min–max)	P value
IL10	9.13 (0.25–15.41)	7.24 (1.21–18.91)	>0.01
IL18	1.86 (1.12–9.56)	10.57 (3.81–15.52)	<0.01
IFNG	2.27 (0.63–7.28)	6.42 (5.21–13.01)	<0.01
IFNGR	4.02 (0.01–6.12)	4.41 (1.05–7.67)	<0.01
CRP	0.03 (0.14–2.37)	14.41 (2.539–14.58)	<0.01
HSP70	6.61 (0.12–11.21)	5.12 (0.44–13.08)	>0.05

Pro-inflammatory cytokines are elevated in BD patients, especially in the active phase of the disease. Significant lymphocyte and neutrophil infiltration is seen in affected organs. Current evidence indicates that active lymphocytes direct inflammation and activate neutrophils and endothelial cells. Overexpression of cytokines, particularly those involved in Th1-mediated inflammation, combined with genetic predisposition, is believed to be responsible for the increased inflammatory reaction [3,6,12,13].

Colchicine therapy is used to treat BD patients and is known to block cytokine synthesis through antimitotic and antifibrotic mechanisms. We also showed in our study that the IL18, IFN-γ, IFN-γR, and CRP genes were downregulated in our patient group.

There are several SNP studies on IL10 in the literature which confirm the link between IL-10 and BD. In addition, a meta-analysis including a total of 2430 patients and 2660 healthy controls showed that the IL23R/IL12RB2 gene region (rs924080), which did not reach significance at the genome level on initial analysis, was associated with BD and showed an association with this region in different ethnic groups. Aside from HLA class 1 region, novel connections between BD and IL-10 and IL23R/IL12RB2 genes identified in this comprehensive study present a breakthrough in our understanding of the development of the inflammatory reaction seen in BD [36–39].

There are numerous studies in the literature investigating IL-10 serum levels. Aridogan et al. and Guenane et al. reported elevated IL-10 serum levels in BD patients, while Sadeghi et al. found no significant difference in IL-10 serum levels between BD patients and a control group. In our study, we observed no significant difference in serum levels of IL-10 between patients with active Behçet's uveitis and control subjects [40–42].

A meta-analysis of IL18 gene polymorphism in BD patients suggested that IL18 polymorphism had a minor role in the etiopathogenesis of the disease. In a study by Özyurt et al., BD patients exhibited significantly higher IL-18 serum levels compared to a control group. Musabak et al. reported that IL-18 was associated with disease activity. IL-18 levels in BD patients are also increased in the remission phase. Jang et al. reported that IL-18 levels in BD patients with two IL18 SNPs, -137 (G/C) and -607 (C/A), were not different from those of the control group, while BD patients with the GG genotype at position -137 exhibited significantly higher IL-18 levels. Similarly, Lee et al. clearly identified the SNP -607 CC genotype in BD patients. The patients with active Behçet's uveitis included in our study exhibited significantly lower IL18 gene expression levels compared to the control subjects [43–47].

IFN-γ is produced primarily by Th1 cells. Lymphocytes and NK cells not only stimulate cytotoxic effects, but also inhibit Th1 cell differentiation and Th2 polarization. The predominance of the Th1 immune response is also confirmed by the elevated levels of mRNA for the transcription factors interferon regulatory factor 1 (IRF1) and signal transducer and activator of transcription 1 (STAT1) and STAT4. This has been demonstrated in many previous studies (Albanidou-Farmaki et al. 2007; Buno et al. 1998; Dalghous et al. 2006; Natah et al. 2000) [43,48–50].

According to data in the literature, serum IFN-γ levels are elevated in BD. In our patient group, there was a significant difference in IFN-γ gene expression between BD patients and the control group. In a flow cytometry study on the IFN-γ gene in BD, Çetin et al. reported significantly increased IFN-γ expression in patients compared to controls [51].

In the present study, we also compared IFN-γR mRNA expression in patients with active Behçet's uveitis and the control group, and determined that BD patients had significantly lower IFN-γR mRNA expression levels. We believe the use of immune suppressors inhibits T cell activation and colchicine reduces IFNGR mRNA expression levels via its antimitotic effect. There are no other published studies concerning IFN-γR gene expression in BD, which makes our study a first in the literature.

CRP is a known acute- phase reactant and is elevated in various inflammatory conditions. CRP level can also serve as a

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marker of immune-mediated tissue damage. Our comparison of CRP mRNA expression levels in patients with active Behçet's uveitis and control subjects revealed a significant difference. There are many studies in the literature evaluating serum levels of this protein, with numerous authors reporting that serum CRP levels are elevated in patients with active BD (e.g., Karadağ et al., Müftüoğlu et al., Balta et al., Bekpınar et al., Adam et al.) [23,52–55].

HSPs, also referred to as stress proteins, are found in all prokaryotic and eukaryotic cells. They are stress-response immunoreactive proteins induced by environmental factors such as infection, trauma, and heat. These intracellular proteins exert both pro-inflammatory and anti-inflammatory effects, and are believed to play an important role in BD pathogenesis. We did not observe a significant difference in HSP70 gene mRNA expression levels between the active Behçet's uveitis patients in our study group and the control group. Karadağ et al. reported a significant increase in serum levels of Hsp70 in active Behçet's patients compared to patients with inactive disease and a control group. Sahaberi et al. analyzed serum levels of Hsp70 and anti-Hsp70 antibody in patients with and without Behçet's uveitis and determined that serum Hsp70 levels were higher in the patients with Behçet's uveitis, while there was no difference between groups in serum levels of anti-Hsp70 antibody. Relatively little information can be found in the literature concerning the relationship between Hsp70 and BD. There are various published studies of other HSPs, including numerous reports indicating that Hsp60-65 serum levels are elevated in BD [23,56–61].

Conclusions

The results of our gene expression study show that mRNA expression levels of IL18, IFNG, IFN-γR, and CRP are significantly reduced in patients with active Behçet's uveitis, but no statistically significant differences between groups were observed in mRNA expression levels of IL10 or HSP70 genes.

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