Serum Tumor Necrosis Factor-Alpha in Patients with Behcet's Disease

Thesis Submitted for Partial Fulfillment of Master Degree in Internal Medicine

By

Zeinab AL-Hussien Mohamed Al-Nahas; M.B.B.Ch

Under supervision of

Manal Mohamed Abd El Moniem

Professor of internal medicine

Cairo University

Olfet G- Shaker

Professor of medical Biochemistry

Cairo University

Hussein Ossama Elwan

Lecturer of General Surgery

Cairo University

Cairo University

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Abstract

In this study, all our patients were males with age ranged from 16 to 54 years and disease duration ranged from 1.0 to 252 months. The disease activity using Behcet's disease activity index was ranged from 1 to 7. According to clinical activity 20 patients had active disease while 10 patients had inactive disease.

Key word: BDEL –TAL- **Necrosis-** BDCAF

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LIST OF ABBREVIATIONS

ADMA	Asymmetric dimethylarginine
ALT	Alanine Transaminase
ASK 1	Apoptosis signal-regulating kinase 1
BD	Behcet's disease
BDAI	Behcet's disease activity index
BDCAF	Behcet’s Disease Current Activity Form
CBC	Complete blood count
CD	Cluster of differentiation
CNS	Central nervous system
CRP	C-reactive protein
DBP	Diastolic blood pressure
DD	Death domain
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
ELISA	Enzyme linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FADD	Fas-Associated protein with Death Domain
GI	Gastrointestinal
HAV	hepatitis A virus

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HB	Hemoglobin
HLA	Human leukocyte antigen
hs-CRP	High sensitive C- reactive protein
HSP	Heat-shock proteins
HSV-1	Herpes simplex virus-1
IBDDAM	Iranian Behcet's Disease Dynamic Measure
IKK	Inhibitor of Kappa kinase
IL	Interleukins
INF	Interferona
IQR	Inter quartile range
ISGBD	International Study Group (ISG) for Behcet's Disease
JNK	C-Jun N-Terminal kinase
LT	Lymphotoxin
MCP-1	Monocyte chemoattractant protein-1
MICA	Major histocompatibility complex class I chain-related gene A
MKK	Mitogen-activated protien kinase Kinase
mRNA	Messenger Ribonucleic acid
NFkB	Nuclear Factor Kappa light chain enhancer of activated B cell
NK cells	Natural killer cells
NO	Nitric oxid

RAS	Recurrent aphthous stomatitis
RPE	Retinal pigmented epithelial
SBP	Systolic blood pressure
SD	Standard of deviation
SPSS	Statistical Package of social science
TACE	TNF alpha converting enzyme
Th1 type	T helper type 1
TLC	Total leukocytic count
TNF	Tumor necrosis factor
TNF-R	TNF receptor
TRADD	TNFR-associated death domain protein
TRAFs	TNF receptor-associated factors
sTNF	Soluble Tumor necrosis factor
VEGF	Vascular endothelial growth factor

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Introduction

Behcet's disease (BD) is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthae and any of several systemic manifestations including genital apthae, ocular disease, skin lesions, neurologic disease, vascular or arthritis. The underlying cause of Behcet's disease is unknown. The disorder may represent aberrant immune activity triggered by exposure to an agent in patients with a genetic predisposition to develop the disease. (**Yurdakul et al., 2004)**

Considering the evidence of activation of immune system in BD, pro-inflammatory cytokines and mediators may affect the course of the disease. Chemotactic and phagocytic activities of neutrophils in patients with BD have been reported to be high and tumor necrosis factor alpha (TNF-α) is a major factor modulating inflammatory responses and is known to be increased in inflammatory diseases. Recent studies showed increased TNF-α level in BD patients, especially in the exacerbation period**. (Everklioglu et al.,2002)**

The enhanced inflammatory reaction in BD appears to be mediated by cytokines derived from T helper type I lymphocyte, including TNF-α.

TNF-α is produced by monocyte as part of the inflammatory cascade in BD and concentration of TNF and soluble TNF receptors are increased in the serum of patients with active disease. It has been demonstrated that the T lymhocyte expressing the gamma delta receptor in BD is activated in vivo and produces increased amounts of TNF-α and interferon gamma compared with healthy controls. **(Yamashita et al., 1997)**

Aim of the Work

Our aim is to evaluate the significance of tumor necrosis factor alpha (TNF-α) in Behcet's disease (BD) and the association of elevated level related to indices of inflammation in BD.

Behcet's Disease

Introduction

Behçet disease (BD) was named in 1937 after the Turkish dermatologist Hulusi Behçet (1889–1948), who first described the triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis. **(Behçet et al., 1937)**

Behcet's disease (BD) is a multisystemic autoimmune inflammatory disorder characterized by vasculitis of unknown origin. BD shows a heterogeneous pattern of organ involvement that occurs in recurrent episodes of acute inflammation throughout the course of disease. **(Sakane et al., 1999)**

Epidemiology

Although cases of Behcet's disease were reported from all around the world, it is more prevalent in Far East (Japan, Korea); Middle East (Iran, Iraq, Israel, Saudi Arabia, Kuwait, Syria) and countries around Mediterranean see (Turkey, Italy, Egypt, Greece, Morocco, Algeria, Tunis). Therefore, Behcet's disease occurs most commonly in the countries along the ancient "silk road". Turkey has the highest prevalence: 80 to 370 cases per 100,000 populations. **(Kaklamani et al., 1998)**

The prevalence in Japan, Korea, China, Iran, and Saudi Arabia ranges from 13.5 to 20 cases per 100,000, whereas it is lower in Western countries 0.64 per 100,000 in the United Kingdom and 0.12 to 0.33 per 100,000 in the United States. In Berlin, Germany, the prevalence among citizens of Turkish origin is 21 per 100,000, which is lower than that in Turkey but far higher than that among German natives (0.42 to 0.55 per 100,000). **(Zouboulis et al., 1997)**

But prevalence and incidence estimates in Egypt are still unavailable. **(El Menyawi et al., 2009)**

Sex:

Behçet's disease is somewhat more common among females in Japan and Korea, whereas males are more frequently affected in Middle Eastern countries. **(Nakae et al., 1993)**

Age:

The mean age at onset of BD is most commonly in the third or fourth decade of life. **(Kastner, 1997)**

Familial inheritance:

The frequency within families is 2 to 5 percent, except in Middle Eastern countries, where it is 10 to 15 percent. Although the rate of concordance among twins is not known. Epidemiologic findings suggest that both genetic and environmental factors contribute to the development of the disease. **(Zouboulis et al., 1997)**

Clinical manifestations

A diagnosis of Behçet disease is based on clinical criteria because of the absence of a pathognomonic laboratory test. The period between the appearance of an initial symptom and a major or minor secondary manifestation can be up to a decade in many cases.

The revised 1987 criteria of the Japanese group **(Mizushima)** have been widely applied. **(Mizushima et al., 1988)**

More recently, the diagnostic criteria of the International Study Group for Behçet Disease have been applied to establish a firmer diagnosis. Therefore, the authors recommend that both sets of criteria be applied concurrently until a more exact system is devised. **(International Study Group for Behcet's Disease,. 1990)**

Diagnostic criteria from the Behçet syndrome research committee of Japan (1987 revision) are as follows:

Major features

- Recurrent aphthous ulceration of the oral mucous membrane.
- Skin lesions: Erythema nodosum–like lesions, subcutaneous thrombophlebitis, folliculitis (acnelike lesions), cutaneous hypersensitivity.
- Eye lesions: Iridocyclitis, chorioretinitis, retinouveitis, definite history of chorioretinitis or retinouveitis.
- Genital ulcers.

Minor features

- Arthritis without deformity and ankylosis.
- Gastrointestinal lesions characterized by ileocecal ulcers.
- Epididymitis.
- Vascular lesions.
- Central nervous system symptoms.

Interpretation:

- Complete: Four major features.
- Incomplete: (1) 3 major features, (2) 2 major and 2 minor features, or (3) typical ocular symptom and 1 major or 2 minor features.
- Possible: (1) 2 major features or (2) 1 major and 2 minor features.

International criteria for the classification of Behçet disease (1990) are as follows : (very strict for research purposes)

- Recurrent oral ulceration: Minor aphthous or major aphthous or herpetiform ulceration observed by a physician or reported reliably by a patient that recurs at least 3 times in 12-month period.

Plus 2 of the following:

- Recurrent genital ulceration: Recurrent genital aphthous ulceration or scarring, especially males, observed by a physician or reliably reported by a patient.
- Eye lesions: (1) Anterior uveitis, posterior uveitis, and cells in vitreous upon slit-lamp examination or (2) retinal vasculitis observed by physician (ophthalmologist).
- Skin lesions: (1) Erythema nodosum–like lesions observed by physician or reliably reported by a patient, pseudofolliculitis, and papulopustular lesions or (2) acneiform nodules consistent with Behçet disease, observed by a physician, and in postadolescent patients not receiving corticosteroids.
- Positive pathergy test: An erythematous papule larger than 2 mm at the prick site 48 hours after the application of a 20- to 22-gauge sterile