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Serum Interleukin-33 in Behcet's Disease: Its Relation to Disease Activity and Clinical Manifestations

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Behcet's disease (BD) is a chronic systemic inflammatory disorder characterized by a course of remissions and exacerbations of unpredictable frequency and duration. Pro-inflammatory cytokines seem to be responsible for the enhanced inflammatory response in BD. Aim of the work: This study aimed to investigate serum levels of IL-33 in patients with Behcet's disease (BD) and their relationship to disease activity and clinical manifestations. Thirty patients with BD were enrolled and subjected to assessment of disease activity according to Behcet's Disease Current Activity Form (BDCAF) score. Serum IL-33 levels were determined using Enzyme-Linked-Immunosorbent Assay (ELISA). Thirty age and sex matched rheumatoid arthritis patients and thirty healthy volunteers were included in this study as control groups. Serum IL-33 level was 132.5 ± 19 pg/ml, 101.2 ± 20.1 pg/ml and 31.5 ± 10.5 pg/ml in RA, BD and healthy control groups respectively. IL-33 was significantly higher in BD patients (101.2 ± 20.1 pg/ml) as compared to healthy controls (31.5 ± 10.5 pg/ml) but lower than rheumatoid arthritis patients (132.5 ± 19.1 pg/ml). Levels of IL-33 were significantly increased in BD patients with skin lesions (Erythema nodosum & Acneiform lesions) and ocular lesions (retinal vasculitis) ($P < 0.05$), and a positive correlation was found between BDCAF score and IL-33 serum levels ($r = 0.9$, $P < 0.001$). In conclusions, serum IL-33 level is elevated in active BD patients with skin and ocular affection and correlates with disease activity.

Behcet's disease (BD) is a systemic relapsing chronic inflammatory disease of unknown etiology that presents with recurrent oral ulcers, genital ulcers, skin lesions and uveitis. A wide range of clinical features are observed, including involvement of the ophthalmic, musculoskeletal, vascular, central nervous and gastrointestinal systems (Kaburaki *et al.*, 2010).

Ocular involvement is reported in 30–70% of patients with Behcet's disease and is both more common and more severe in men than in women. Ocular disease is usually bilateral and characteristically occurs within 2–3 years of disease onset (Kural-Seyahi *et al.*, 2003), it is the presenting feature in 10–20% of patients. Chronic, relapsing bilateral uveitis involving both the anterior and posterior uveal tracts is a significant cause of morbidity. Anterior uveitis with mobile hypopyon, in which the

inflammatory exudate forms a visible layer of cells in the anterior chamber is characteristic sign of ocular Behcet's disease but is only observed in one-third of patients, together with posterior uveitis and retinal vasculitis, this may cause visual loss in up to 25% of patients, although prognosis is improving with the use of modern immunosuppressants (Muhaya *et al.*, 2000). Other ocular lesions include iridocyclitis, scleritis, keratitis, vitreous hemorrhage, optic neuritis, retinal vein occlusion and retinal neovascularization (Verity *et al.*, 2003).

Although the etiopathogenesis of BD remains uncertain, immunological abnormalities including innate and adaptive immunity in humoral and cellular immunity have been supposed to be the corner stone of the pathogenesis of BD (Pineton *et al.*, 2012).

A variety of cytokines such as IL -6, IL -17, IL -18 and IL-21 are increased in BD and

immune-modulatory cytokines are involved in disease pathogenicity and/or activity moreover the numerous polymorphisms of cytokine gene including TNF- α , IL-1, IL-12, and IFN- γ are also associated with the disease (Zhou *et al.*, 2012).

Interleukin 33 (IL-33) is a member of the IL-1 family, which is a ligand for the orphan receptor ST2 (also known as IL-1RL1). When IL-33 binds to ST2, it enhances inflammatory cytokines by activating nuclear factor- κ B and mitogen activated protein kinases (Na *et al.*, 2012). Both enhanced innate immunity and neutrophil hyperactivity with endothelial damage, which are part of BD pathogenesis, are related to elevated IL-33 levels (Pineton *et al.*, 2012).

IL-33 is widely expressed in many tissues such as the liver, lung, central nervous system, and multiple types of cells including epithelial cells, endothelial cells, smooth muscle cells, macrophages, and fibroblasts (Nile *et al.*, 2010).

IL-33 mainly localizes to the nucleus, but under appropriate signal stimulation such as inflammation, IL-33 is in response processed and passively released from necrotic cells or actively secreted into the extracellular milieu (Haraldsen *et al.*, 2009) and functions through binding to its receptor ST2 as a pro-inflammatory cytokine that participates in the development and progression of many diseases, including collagen-induced arthritis (Palmer *et al.*, 2009), anaphylactic shock (Pushparaj *et al.*, 2009), inflammatory bowel disease (Seidelin *et al.*, 2010), autoimmune hepatitis, and ischemia reperfusion injury (Verity *et al.*, 2003).

This study aimed to investigate serum levels of IL-33 in patients with Behcet's disease (BD) and their relationship to disease activity as well as different clinical manifestations.

Subjects and Methods

Study Approval

The study was approved by the Ethical Committee of Benha University. All subjects gave written informed consent before participation in the study.

Subjects

Thirty BD patients diagnosed according to the International Study Group Criteria for BD (ISGC 1990), thirty rheumatoid arthritis patients diagnosed according to the American College of Rheumatology (ACR) revised criteria (Arnett *et al.*, 1988), and thirty age and sex matched apparently healthy volunteers were included in the study. They were recruited from the inpatient and outpatient clinics of Rheumatology, Rehabilitation & Physical Medicine, Ophthalmology and Dermatology & Andrology departments of Benha University hospitals in the period between June 2014 and January 2015. The practical part of the study was done at Medical Microbiology and Immunology Department, Benha Faculty of Medicine.

Patients were excluded from the study if they had other illnesses that might affect the results of the study such as malnutrition or body mass index (BMI) less than 19, diabetes mellitus, hyperlipidemia, end stage renal failure, chronic hepatitis, cardiovascular diseases, thyroid dysfunction, cancers, psoriasis, inflammatory bowel disease and other rheumatic diseases, as well as pregnant and lactating women.

Methods

All BD patients were subjected to the: Full history taking, and thorough clinical examination with stress on dermatological, locomotor, vascular and ophthalmologic examination.

-Skin pathergy test was done as described by Altac *et al.*, (1982).

- Assessment of disease activity was carried out according to Behcet's Disease Current Activity Form (BDCAF) score (Suzuki *et al.*, 2006) in which scoring depends on the symptoms present over the 4 weeks prior to assessment, the patient was assessed for: headache, mouth ulcers, genital ulcers, skin lesions (Erythema & skin pustules), joint involvement (arthralgia & arthritis), gastrointestinal symptoms (nausea/ vomiting/abdominal pain & Diarrhoea with altered/frank blood per rectum), and symptoms of involvement of the major vessels (chest pain, breathlessness, coughed up blood, pain/swelling/discoloration of the face or the arm, or the leg,) nervous system (blackouts, difficulty with

speech, difficulty with hearing, blurring of/double vision, weakness/loss of feeling of face, weakness/loss of feeling of arm, weakness/loss of feeling of leg, memory loss, loss of balance), the eyes (a red eye, painful eye, blurred, reduced vision). Scores of 0 to 1 are given based on the existence or absence of symptoms or findings, and the total points possible are between 0 and 12.

About 5cc of venous blood was collected by sterile venipuncture, allowed to clot; and sera were separated and kept frozen at -20°C till used.

Laboratory procedures included the following:

- 1) Erythrocyte sedimentation rate (ESR) by the Westergren method; recorded in mm/1st h.
- 2) C-reactive protein (CRP) by latex agglutination slide test.
- 3) Measurement of Serum IL-33

Human IL-33 was measured in serum using a commercially available ELISA kit (Human IL-33 ELISA Kit eBioscience, Austria) according to the manufacturer's protocol. In principle, it is an antigen detection immunoassay, utilizes the quantitative technique of a "Sandwich" enzyme-linked immunosorbent assay in which, wells of kit's microplates are already coated with antibodies (primary antibodies) specific for particular epitopes on human IL33. Briefly, diluted serum samples were incubated in the wells which were then repeatedly washed to remove unbound proteins. Biotinylated conjugated anti-Human IL33 antibody (secondary antibody) specific for the target epitopes were added into the microwells, incubated and then washed. Streptavidin horse radish peroxidase enzyme conjugated to the constant heavy chain of the secondary antibody was added into the microwells, incubated and the wells were washed again. The bound conjugate was developed as a coloured product (corresponding to the antigen concentration) by adding substrate. After the color is completely developed, the enzymatic reaction was terminated by addition of an acid solution. The optical

density (OD) of each microwell was measured at 450 nm. Obtained optical density values, were converted into pg/mL by the Bio Rad ELISA data analysis software. The cut-off value was calculated as the mean absorbance value of the negative controls plus three standard deviations.

Statistical Analysis

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 20, qualitative data were expressed in number and percent, quantitative data were expressed in mean and standard deviation, In the statistical comparison between the different groups, the significance of difference was tested using ANOVA (analysis of variance) used to compare between more than two groups of numerical data, post-hoc test was used to detect significance difference in-between groups, Student t test used to compare between two groups of numerical data, correlation coefficient (r) test was used correlating different parameters. *P* value <0.05 was considered statistically significant.

Results

The study included 30 BD patients, 19 male (63.3%) and 11(36.7%) females. Their ages ranged from 20-50 years with a mean of 36.5 ± 9.8 years. Disease duration ranged from 3 to 12 years with a mean of 5.73 ± 3.5 years. Thirty rheumatoid arthritis patients {13(43.3%) male and 17(56.7%) female} with ages ranged from 24-48 years with a mean of 37.7 ± 10.2 years and thirty healthy volunteers {18 males (60%) and 12 females (40%)}, aged from 19-52 years with a mean of 35.3 ± 9.3 years were included in the study, Table (1).

Table 1. Age and sex distribution among patients with Behcet's disease, rheumatoid arthritis and controls

	BD (n=30)	RA (n=30)	Control (n=30)	<i>P</i> -value
Age (mean \pm SD)	36.5 \pm 9.8	37.7 \pm 10.2	35.3 \pm 9.3	NS
Sex				
Male	19(63.3%)	13(43.3%)	18(60%)	NS
Female	11(36.7%)	17 (56.7%)	12(40%)	

P > 0.5 is Not significant (NS)

Table (2) shows clinical manifestations of BD patients: Skin lesions: Oral aphthous ulcers 30 patients (100%), genital ulcers 27 patients (81%), skin pethargy test in 5 patients (15%),

Arthritis in 4 patients (12%), Ocular disorders in 18 (54%): uveitis in 13 patients (72.2%), optic neuritis in 2 patients (11.1 %) and retinal vasculitis in 3

Table 2. Clinical features of Behcet's disease patients.

Features	NO (30) (%)	%
Oral aphthous ulcers	30	100%
Genital ulcers	27	81%
Skin pethargy	5	15%
Arthritis	4	12%
Ocular manifestations	18	54%
Vascular lesions (Deep vein thrombosis)	1	3%
CNS manifestations	2	6%
Erythema nodosum	11	33%
Acneiform lesion	11	33%
Gastrointestinal manifestations	4	12%

Patient (16.7%) (Figure 1) displayed a picture of posterior uveitis (vitritis, vasculitis and optic neuritis) and its fluorescein angiography lesions (deep venous thrombosis) 1 patient

(3%), CNS manifestations 2 patients (6%), erythema nodosum, sterile pustules or papules in 11 patients (33%) and gastrointestinal manifestations in 4 patients (12%).

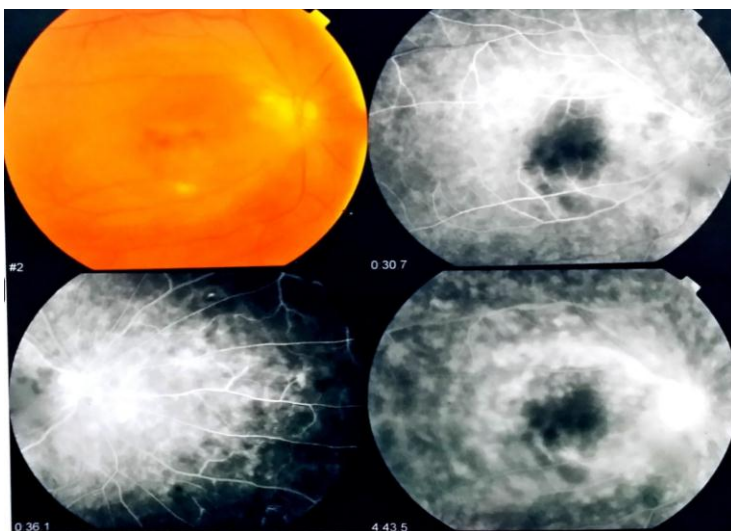


Figure 1. Retinal imaging of a Behcet's disease patient with Uveitis using fundus fluorescein angiography.

The figure shows that: Colour fundus; shows vitritis (hazy media), optic neuritis (swollen optic disc with blurred edge) and vasculitis. Fluorescein angiography: multiple hypofluorescent patches of retinal infarction in perifoveal area with late staining of nearby occluded retinal arteriole (occlusive vasculitis). Late staining of large retinal veins with evident periphlebitis. Late fuzzy hyperfluorescence over disc indicates disc edema (optic neuritis). Late hyperfluorescence at posterior pole is due to dye leakage from dilated macular capillaries with diffuse macular edema.

Mean serum levels of IL-33 were 132.5 ± 19 pg/ml, 101.2 ± 20.1 pg/ml and 31.5 ± 10.5 pg/ml in RA, BD and healthy control respectively. The difference between the three groups was statistically significant ($P < 0.001$), on detecting the differences between groups,

IL-33 was significantly higher in BD patients (101.2 ± 20.1 pg/ml) compared to healthy control (31.5 ± 10.5 pg/ml) ($P < 0.001$), and was significantly lower than rheumatoid arthritis patients (132.5 ± 19.1 pg/ml), ($P < 0.001$), Table (3).

Table 3. Comparison of serum IL-33 levels between patients with Behcet's disease, rheumatoid arthritis and controls

	BD (n=30)	RA(n=30)	Healthy control(n=30)	P value
IL-33(mean \pm SD)	101.2 ± 20.1 pg/ml *†	132.5 ± 19.1 pg/ml †	31.5 ± 10.5 pg/ml	<0.001

*significant difference from RA †significant difference from Control

Inter groups comparison were done by post- hoc test. $P < 0.5$ is significant

Table (4) shows that IL-33 serum levels were significantly elevated in BD patients with skin lesions in the form of (Erythema nodosum & Acneiform lesions) and retinal vasculitis ($P < 0.05$), while there were no increase in IL-33 serum levels with oral ulcers, genital

ulcers, arthritis, vascular lesions, CNS lesions or a positive skin pathergy test ($P > 0.05$).

There was significant positive correlation between BDCAS and serum IL-33 levels ($r = 0.9$, $P < 0.001$), Figure (2).

Table 4. Mean serum levels of IL33 according to clinical manifestations of Behcet's diseases

		Mean \pm SD	P-value
Genital ulcers	Present (n=27)	100.3 ± 22.1	NS
	Absent (n=3)	102.1 ± 21.7	
Skin pathergy	Present (n=5)	101.9 ± 19.9	NS
	Absent (n=25)	100.5 ± 21.3	
Arthritis	Present (n=4)	102.4 ± 19.8	NS
	Absent (n=26)	100 ± 22.1	
Ocular manifestations*	Present (n=18)	108.3 ± 18.9	<0.05
	Absent (n=12)	94.1 ± 16.8	
Erythema nodosum*	Present (n=11)	109.1 ± 19.9	<0.05
	Absent (n=19)	93.4 ± 18.1	
Acneiform lesion*	Present (n=11)	108.8 ± 17.2	<0.05
	Absent (n=19)	93.6 ± 19.1	

* $P > 0.5$ is Not significant (NS)

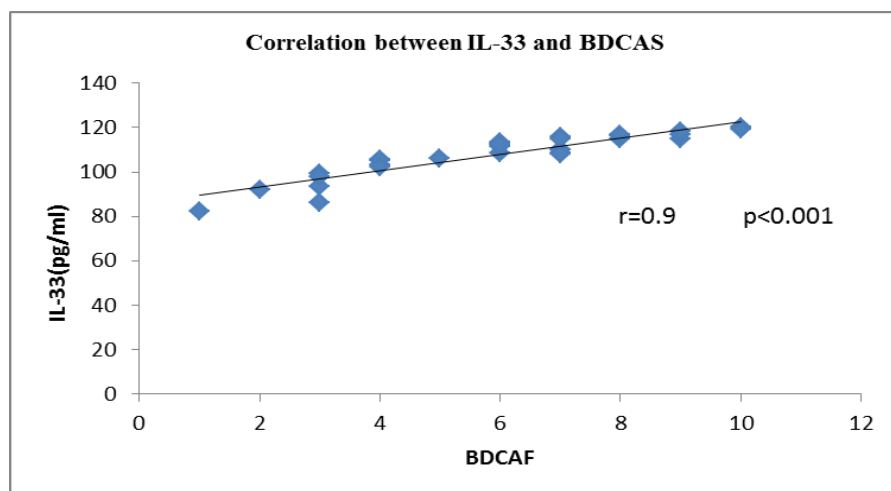


Figure 2. Correlation between serum level IL33 and Behcet's Disease Current Activity Form (BDCAF)

Discussion

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family, which includes IL-1 and IL-18. IL-33 is considered to be crucial for induction of Th2-type cytokine-associated immune responses such as host defense against nematodes and allergic diseases by inducing production of such Th2-type cytokines as IL-5 and IL-13 by Th2 cells, mast cells, basophils and eosinophils. In addition, IL-33 is involved in the induction of non-Th2-type acute and chronic inflammation as a pro-inflammatory cytokine, similar to IL-1 and IL-18 (Keisuke *et al.*, 2010).

Increased serum level of IL-33 was documented previously in a variety of inflammatory diseases including RA (Talabot-Ayer *et al.*, 2012), systemic sclerosis (Manetti *et al.*, 2011), SLE (Yang *et al.*, 2011), ankylosing spondylitis (Li, *et al.*, 2013), inflammatory bowel disease (Latiano *et al.*, 2013), multiple sclerosis (Hamzaoui *et al.*, 2013), and henoch-Schönlein purpura (Chen *et al.*, 2013).

The results of our study demonstrated that IL-33 was significantly higher in BD patient (101.2±20.1pg/ml) compared to healthy

control (31.5±10.5pg/ml) and is significantly lower than rheumatoid arthritis patients (132.5±19.1 pg/ml).

This is in consonance with Hamzaoui *et al.*, 2013 who reported that serum IL-33 level was significantly higher in BD patients [159.65 ± 61.7 pg/mL] compared to healthy controls [70.03±25.95 pg/mL] ($P<0.0001$). While active BD patients expressed lower IL-33 levels than the control disease group, rheumatoid arthritis (RA) and multiple sclerosis (MS) patients [$P=0.00021$], this discrepancy may be due to genetic backgrounds.

Also Dae-Jun *et al.*, 2013 reported that serum levels of IL-33 was higher in patients with BD compared with those in normal controls (IL-33: 594.48 ± 175.04 pg/mL in BD and (224.23 ± 56.64 pg/ml) in normal controls [$P = 0.048$]. IL-33 expression in skin tissue, was higher in patients with BD compared with that in the normal controls

In contrast to our result, Koca *et al.*, 2014 investigated serum IL-33 level and IL-33 gene polymorphisms in a cohort of 117 patients with BD and 149 healthy controls (HC), serum

IL-33 levels was not significantly different ($P>0.05$) in the BD and control group .

The present study revealed that IL-33 serum levels were significantly increased in BD patients with skin lesions in the form of (Erythema nodosum and Acneiform lesions) and retinal vasculitis ($P<0.05$), while there were no increase in IL-33 serum levels with oral ulcers, genital ulcers, arthritis, vascular lesions, CNS lesions or a positive skin Pathergy test ($P> 0.05$). These results are in hand with these reported by Hamzaoui *et al.*, 2013 who found that patients with active BD with retinal vasculitis showed the highest serum IL-33 level and IL-33 mRNA expression in the skin lesions of patients with active BD was significantly increased compared to that in healthy skin biopsies ($P=0.00016$) in another study done by Hamzaoui, *et al.*, 2014 documented for the first time, that IL-33 is upregulated in the CNS of patients with neuro-behçet disease.

In this study, there was significant positive correlation between BDCAS and IL-33 ($r=0.9$, $P<0.001$). In agreement with our results Hamzaoui, *et al.*, 2013 reported that serum IL-33 level was significantly higher in active BD patients (159.65 ± 61.7 pg/mL) compared to inactive BD patients (85.57 ± 21.07 pg/mL) ($P<0.0001$) and healthy controls (70.03 ± 25.95 pg/mL) ($P<0.0001$). This may be explained by increased cytokines will increase the production of IL-33 in active BD. Since a variety of cytokines, including TNF- α , and IL-1B those are also associated with BD are documented to enhance the expression of IL-33 (Meephansan *et al.*, 2013).

In contrast, Koca *et al.*, 2014 reported that the level of IL-33 was significantly lower in the active BD (n=39) subgroup than inactive BD (n=46) subgroup (11.3 ± 9.3 vs. 13.7 ± 2 pg/ml, $P=0.02$). Also Dae-Jun *et al.*, 2013 found that serum IL-33 levels were not correlated with inflammatory markers, such as acute phase reactants or BD activity scores.

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