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RESEARCH ARTICLE

IL-17, IL-10, IL-6, and IFN-γ in Egyptian Behçet's disease: correlation with clinical manifestations

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ABSTRACT. There are a limited number of studies that report the polarization of the immune system toward the production of T helper 1 (Th1), Th2, or Th17-type cytokines in patients with Behçet's disease (BD). Here, we aimed to detect the presence of various cytokines in serum samples of Egyptian BD patients and to determine the correlation between their production levels and clinical manifestations. To that aim, serum levels of IFN-γ, IL-10, IL-6, and IL-17 measured by ELISA were determined in BD patients with active or inactive disease to evaluate their clinical relevance. The results of the present study show significantly elevated levels of IL-17 and IL-6, as well as a reduction in IL-10, and no change in IFN-γ, in sera of BD patients, as compared to the healthy control group. Moreover, IL-6 serum levels were increased in BD patients in active stages of disease and correlated with arthritic manifestations. On the other hand, IL-10 serum levels were significantly decreased in patients with gastrointestinal tract complications. Furthermore, a positive correlation was observed between IL-10 serum levels and ocular manifestations in BD patients, in contrast to those of IL-17, showing no correlation with the different clinical manifestations. Taken together, the magnitude of IL-6 serum levels could be a potential marker for arthritic manifestations and disease activity, whereas those of IFN-γ, IL-10, and IL-17 cannot be considered predictors for different clinical manifestations in patients with BD.

Key words: Behçet's disease, cytokines, clinical manifestations, Th1, Th2, Th17

Behçet's disease (BD) is a multisystem inflammatory autoimmune disease characterized by recurrent oral apthous ulcers, genital ulcers, skin lesions, and ocular inflammation [1, 2]. It can frequently involve the joints in addition to vascular, neurological, and gastrointestinal systems [3, 4]. Cytokines and helper T cells play a crucial role in the inflammatory responses in BD [5, 6]. Elevated or altered levels of specific cytokines have been found in patients with Behçet's disease [7, 8]. The helper T cells are divided into Th1, Th2, and Th17 cells according to their cytokine secretion.

Th1 and Th17 cells were found to be involved in the development of several diseases because of their respective proinflammatory cytokines, interferon-γ (IFN-γ) and Interleukin-17 (IL-17). Th17 that produces IL-17 was found to be increased and activated in BD patients [9-11]. IFN-γ is a lymphokine that acts as an immunomodulator [12], proinflammatory cytokine [13] as well as antagonizing the function of IL-17, which is a critical pathogenic cytokine in autoimmune disease [14]. IFN-γ can reduce the pathways and the production of pathogenic autoantibody that plays an important role in autoimmune disease [13].

Interleukin-10 (IL-10) is a cytokine with broad anti-inflammatory properties; it was originally described as a T helper (Th2) derived cytokine and induced by Th17 cells in chronic inflammation for a feedback regulation [15]. IL-10 involved in the down regulation of autoimmune disease [16], inhibiting the production of IFN-γ [17] and could restrain the pathogenic role of Th17 cells [16]. Also, IL-10 has a negative effect on the generation of Th1 cells, thus helping in the polarization of a helper T-cell response toward a Th2 type [18, 19]. IL-6 is a key cytokine in BD as it plays a role in the differentiation of CD4+ T cells to Th17 cells [20, 21]. It has been proved in previous studies that IL-6 is one of the inflammatory cytokines secreted mononuclear phagocytes and neutrophils in patients with BD [22]. We aimed in our study to observe the aspects IFN-γ, IL-10, IL-6, and IL-17 in Egyptian Behçet's disease and their correlation with different clinical patterns.

SUBJECTS AND METHODS

Patient characteristics

Sixty-four patients with BD were recruited from the Department of Rheumatology at El-Kasr El-Aini Hospital (50 men and 14 women; mean age 34.1 ± 10.70) and were diagnosed according to the International Study Group (ISG) for Behçet's disease

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criteria (ISG for Behçet's Disease, 1990) [23]. Twenty age and gender-matched healthy control subjects were included in the study. Patients who had other autoimmune diseases, infection, or malignancy were excluded from the study. Informed consent was obtained from all subjects. The onset of the syndrome was defined as the time when the patient fulfilled the diagnostic criteria.

Detailed clinical characteristics were recorded for each patient. Skin lesions (pseudo-folliculitis and erythema nodosum-like) were reported. The involvement of peripheral joints documented by a rheumatologist was noted. All the patients underwent complete ophthalmic examination and fundus fluorescein angiography. The diagnosis of vascular involvement was made on clinical signs, by Doppler ultrasonography and/or angiography using computed tomographic or magnetic resonance techniques where appropriate. When central nervous system (CNS) involvement was suspected from the history and the clinical examination, CT scan, cerebrospinal fluid examination, and/or MRI were performed to confirm the clinical findings. Other clinical manifestations, such as cardiopulmonary, intestinal, and kidney involvement, were also registered. The pathergy test was performed using a 20-gauge sterile needle on the forearms and the result was read 48 hours later by the same investigator. If a papule or a pustule formed at the site of the needle prick, the test was considered positive.

At the time of blood sampling, patients with two or more lesions in the previous 4 weeks (including oral ulcers, genital ulcers, skin lesions, uveitis, vascular, arthritis, gastrointestinal lesions, central nervous system lesions, and pulmonary involvement) were regarded to have active disease [24]. Almost all patients, except seven cases, were on a treatment specifically for BD (including colchicine, prednisone, azathioprine, thalidomide, cyclosporine, cyclophosphamide, and methotrexate). Routine laboratory investigations were collected from the patients' records.

Table 1
Demographic, clinical features and laboratory data of 64 patients with BD.

Parameter	Value
Demographic DATA	
Age (mean ± SD)	34.1 ± 10.70
Disease duration (mean ± SD)	
Male/female	50/14
Clinical involvement	
Oral ulcers (%)	64 (100%)
Genital ulcers (%)	60 (93.8%)
Ocular involvement (%)	37 (57.8%)
Skin lesion (%)	37 (57.8 %)
Vascular (%)	18 (28.1 %)
Neuro (%)	15 (23.4 %)
Arthritis	17 (26.6 %)
GIT (%)	3 (4.7%)
Chest (%)	4 (6.2%)
Active patients (%)	28 (43.8%)
Laboratory investigations	
ESR mmHg/hr (mean ± SD)	37.85 ± 20.40
Haemoglobin gm% (mean ± SD)	13.34 ± 1.3
WBC 1,000/mm^3 (mean ± SD)	8.86 ± 4.4
Neutrophils 1,000/mm^3 (mean ± SD)	58.82 ± 11.4
PLT 1,000/mm^3 (mean ± SD)	269.51 ± 57.3

All data are presented as mean ± SD.

Cytokine assay

The levels of circulating cytokines [IFN-γ (0.195-100 ng/mL) and IL-10 (0.195-100 ng/mL)] were determined in plasma of patients and controls by ELISA as previously described [25, 26] with slight modifications. Commercial DuoSet ELISA kits were used for the detection of total concentrations of IL-6 (9.38-600 pg/mL) (R&D System, Inc., Minneapolis, MN), IL-17 (less than 10 pg/mL) (RayBiotech, Inc. Norcross, GA) according to the manufacturer's instructions. Briefly, samples or standards were added to a coated microtiter plate and incubated for 2h at room temperature and then overnight at 4°C. Free sites were blocked with 5% fetal bovine plasma (FBS). Biotinylated polyclonal antibody was added for 2h at 37°C. At the end of the incubation period, streptavidine conjugated to horseradish peroxidase was added to the wells. After additional 1h incubation, hydrogen peroxide (H_2O_2) and tetramethylbenzidine (TMB) substrate solution (1:1) were added. The reaction was stopped by 1M HCl stopping buffer. The absorbance of each well was measured at 450nm using a microplate reader (SunriseTM, Tecan Group Ltd. Männedorf/Switzerland). Each plasma sample was analyzed in duplicates. The ELISA reader-controlling software (Softmax) readily processes the digital data of a raw absorbency value into a standard curve from which cytokine concentrations of unknown samples can be derived directly.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 19 (LEAD Technology Inc., Charlotte, NC, USA) was used to analyze the data. Data were presented as means with their corresponding standard error (SE) among different groups followed by independent T test. Also, spearman's rank correlation was used to examine the relationship between two continuous variables. Chi square test was performed to categorical data. *P*-values less than 0.05were considered significant level.

RESULTS

Patients characteristics

All patients (64) have oral ulcer (100%), 60 patients have genital ulcers (93.8%), 37 patients have ocular manifestations (57.8%), 37 patients have skin manifestations (57.8%), 18 patients have vascular manifestations (28.1%), 15 patients have neurological manifestations (23.4%), 17 patients have arthritis (26.6%), 3 patients have GIT manifestations (4.7%), 4 patients have chest manifestations (6.2%). Patients with two or more lesions in the previous 4 weeks were regarded to have active disease; there were 28 patients

in active state (43.8%) and 36 patients in inactive state (56.2%) at the time of blood sampling (*table 1*).

Soluble cytokine levels in BD patients and healthy controls

As shown in *figure 1*, BD patients showed a significant increase in serum levels of IL-17 (*figure 1A*) and IL-6 (*figure 1B*) cytokine compared to control group ($P < 0.041$ and $P < 0.0001$ respectively). On the other hand, serum level of IL-10 has shown a significant lower level in BD patients when compared to control group ($P < 0.001$) as shown in *figure 1C*. Also, serum level of IFN-γ was slightly elevated in BD patients but was not significant from the control group (*figure 1D*). The Th17 cytokine IL-17 has shown a negative correlation with the Th1 cytokine IFN-γ ($r = -0.336$, $P < 0.001$), (*figure 2A*) and a significant negative correlation between IL-6 and IL-10 has been observed ($r = -0.323$; $P < 0.01$) (*figure 2B*).

Soluble Cytokine Levels in BD Clinical Manifestations

As BD is a heterogeneous disease, further analysis was performed to compare the level of soluble cytokines in BD patients in the presence and absence of some clinical manifestations at the time of blood sampling (*tables 2-5*). IL-6 was increased in active disease patients compared to those in inactive stage, at $P < 0.05$. IL-10 was decreased in patients with GIT manifestations compared to those with no manifestations ($P < 0.05$) and was increased insignificantly in patients with eye manifestations. This study showed no significant differences in IL-17 level neither in relation to any specific organ involvement nor to the clinical activity of disease. Also, this study showed that patients with ocular and chest manifestations had significant decrease in IFN-γ levels than those without (at $P < 0.05$ and $P < 0.01$ respectively).

Correlation between Cytokines and BD Laboratory Investigations and Clinical Manifestations

Our study showed a positive correlation between IL-6 and ESR ($r = 0.38$; $P < 0.001$), disease activity ($r = 0.270$, $P < 0.05$), and arthritic manifestations ($r = 0.260$, $P < 0.05$). Moreover, a negative correlation was observed between IFN-γ and ocular manifestation ($r = -0.325$, $P < 0.01$). Also, a positive correlation was detected between IL-10 and ocular involvement ($r = 0.250$, $P < 0.05$). On the other hand, there was no correlation between IL-17 and specific organ involvement. These results are presented in *table 6*.

DISCUSSION

The main idea of our study was built on investigating a set of cytokines in BD patients with different clinical manifestations, in order to assess any potential correlation between these circulating cytokines, and the clinical features of disease. Several studies reported the involvement of specific cytokines as mediators in BD [27, 28]. Cytokines involved can be categorized into different types such as Th1, Th2, and Th17. These different cytokines play an important role in disease pathogenesis [28, 29]. Our results showed an increase in IL-6 levels in BD patients compared to the control group, which is in accordance with earlier studies that were reported in patients suffering from BD in Turkey

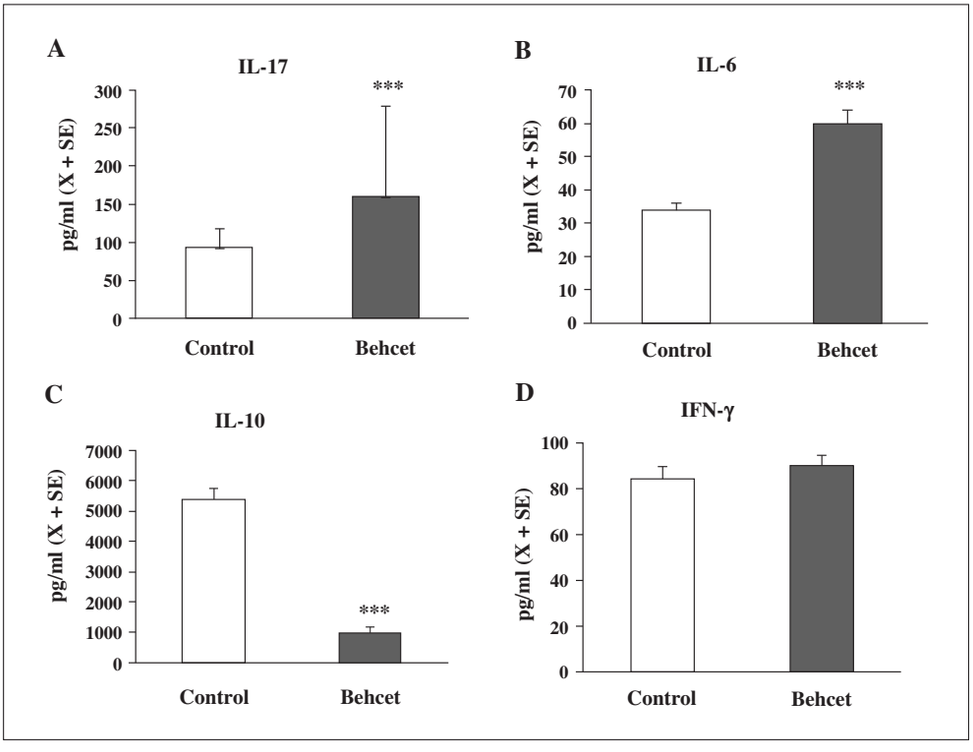

Figure 1
Serum levels of IL-17 **(A)**, IL-6 **(B)**, IL-10 **(C)** and IFN-γ in the patients with Behcet's disease.in comparison to control group. Results are expressed as mean ± standard error. Asterisk (*) denotes statistically; significance from normal controls; ***P<0.001.

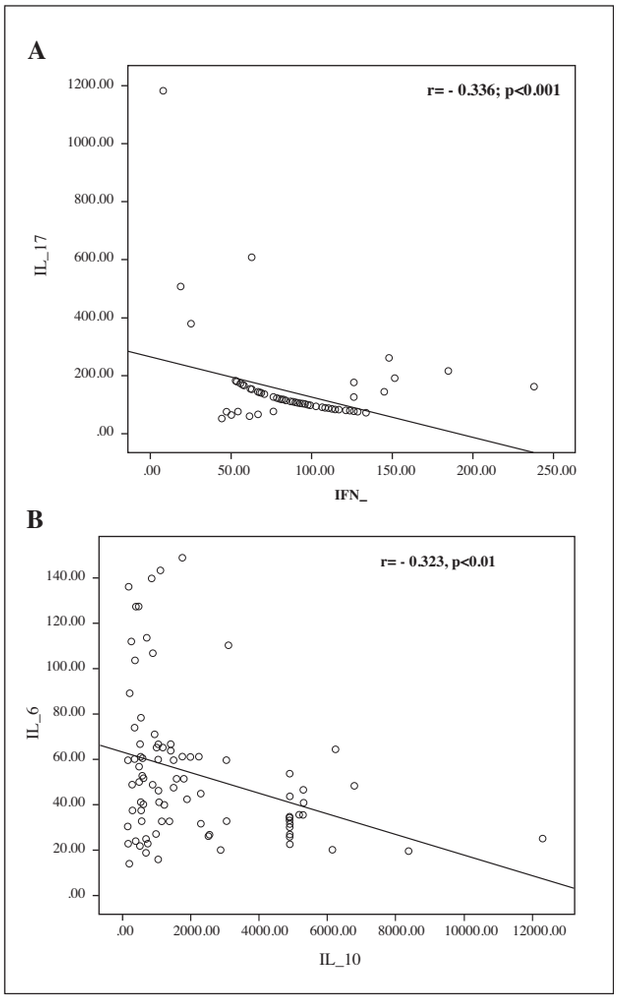

Figure 2
A) A negative correlation between IL-17 and IFN-γ (r = -0.336, P<0.001), **B)** A negative correlation between IL-6 and IL-10 (r = -0.323; P<0.01).

and Japan [30, 31], respectively. Moreover, the present study showed that the disease activity is correlated with the increased level of IL-6 and in patients with active stage, which is in agreement with earlier studies [32, 33]. IL-6 is a multifunctional pro-inflammatory cytokine with an important role in the regulation of immune response [34]. Earlier studies revealed that IL-6 is implicated and over expressed in the pathology of many autoimmune and inflammatory diseases, but overproduction of IL-6 might lead to abnormal B cell differentiation and antibody production [35]. Also, this study showed a negative correlation between IL-6 and IL-10, which could be explained that in normal state IL-10 inhibit inflammatory cytokines which lead to the down-regulation of immune responses [36]. This study showed that IL-10 was decreased in BD patients compared to control group so there was no inhibitory action on IL-6. The previous reason might explain the increased level of IL-6 and the negative correlation found between them and this is in agreement with an earlier study [37]. Moreover, our study revealed a positive correlation between IL-6 and arthritic manifestation and this is in accordance with Frikha *et al.* [38] who postulated that inflammation and synovitis are caused by persistent vasculitis that constitutes the primary pathology in BD. Accordingly, clinicians approved the use of an anti-IL-6 receptor antibody for the treatment of moderately to severely active rheumatoid arthritis [39]. Also, it was reported that the immune response in BD is related to either the Th1 pathway [40] or the increase in Th17 cytokines [41]. The present study did not show a significant difference in serum level of IFN-γ between BD patients and control groups and this might be attributed to the fact that IL-6 promotes Th2 cell differentiation and inhibits IFN-γ production [33]. IFN-γ is a protective cytokine in the development of an autoimmune response [13]. This might explain the nonsignificant difference between the levels of IFN-γ in BD patients and control groups. IFN-γ is a pro-inflammatory cytokine that plays a central role in inflammation and autoimmune disease [42]. On the other hand, IFN-γ is as a master regulator of inflammation and immune response [43, 44]. IFN-γ has a self-regulatory process that maintains the homeostasis of immune system, when body is in a state of inflammation high levels of IFN-γ will be secreted to down regulate that inflammation by activating the regulatory mechanisms that deliver a

Table 2
Association of the most common clinical findings of the disease with IL-6 in the patients with BD.

Clinical manifestations	**NO (%)**	**Median IL-6**		***P*-value**
		Present	**Absent**	
Oral involvement	64 (100)	60.74 ± 4.24	-	-
Genital involvement	60 (93.8)	44.8 ± 10.51	61.8 ± 4.45	0.20
Skin involvement	37 (57.8)	55.4 ± 6.1	64.6 ± 5.8	0.28
Ocular involvement	37 (57.8)	54.5 ± 5.08	69.28 ± 7.03	0.09
Vascular involvement	18 (28.1)	69.43 ± 9.04	57.34 ± 4.69	0.24
Neurological involvement	15 (22.3)	65.7 ± 7.96	59.2 ± 5.0	0.49
Articular involvement	17 (26.6)	71.37 ± 8.84	56.9 ± 4.74	0.16
Chest involvement	4 (6.26)	82.1 ± 22.3	59.3 ± 4.27	0.38
GIT involvement	3 (4.7)	102.7 ± 31.0	58.6 ± 4.09	0.29
Activity	28 (43.8)	71.06 ± 7.56	52.7 ± 4.37**	0.04

Results are expressed as mean pg/mL ± standard error. *$P < 0.05$; **$P < 0.01$.

Table 3
Association of the most common clinical findings and the disease with IL-10 in the patients with BD.

Clinical manifestations	NO (%)	Median IL-10		*P*-value
		Present	Absent	
Oral involvement	64 (100)	980.7 ± 88.32	-	-
Genital involvement	60 (93.8)	1,148 ± 642.4	969.5 ± 86.3	0.8
Skin involvement	37 (57.8)	980.7 ± 145.8	980.7 ± 111.2	1
Ocular involvement	37 (57.8)	1,116 ± 125.27	794.3 ± 112.7	0.06
Vascular involvement	18 (28.1)	837 ± 159.59	1,036 ± 105.67	0.3
Neurological involvement	15 (22.3)	833.2 ± 167.36	1,025 ± 103.4	0.33
Articular involvement	17 (26.6)	1,184 ± 180.3	906.6 ± 100	0.18
Chest involvement	4 (6.26)	644 ± 246	1,003.2 ± 92.43	0.24
GIT involvemen	3 (4.7)	617 ± 117.5*	998 ± 91.96	0.05
Activity	28 (43.8)	981 ± 147.28	979 ± 109.3	0.99

Results are expressed as mean pg/mL ± standard error. *$P < 0.05$; **$P < 0.01$.

Table 4
Association of the most common clinical findings of the disease with IL-17 in the patients with BD

Clinical manifestations	NO (%)	Median IL-17		*P*-value
		Present	Absent	
Oral involvement	64 (100)	160.9 ± 19.67	-	-
Genital involvement	60 (93.8)	238 ± 12.3	155.7 ± 19.54	0.55
Skin involvement	37 (57.8)	152.8 ± 18.71	166.8 ± 31.37	0.70
Ocular involvement	37 (57.8)	169 ± 31.05	148.7 ± 19.58	0.5
Vascular involvement	18 (28.1)	128 ± 9.62	173 ± 26.97	0.123
Neurological involvement	15 (22.3)	133 ± 10.22	169 ± 25.45	0.19
Articular involvement	17 (26.5)	223 ± 66.69	138 ± 10.96	0.22
Chest involvement	4 (6.26)	259.3 ± 117.0	154.3 ± 19.56	0.43
GIT involvement	3 (4.7)	146 ± 19.9	161 ± 20.6	0.6
Activity	28 (43.8)	185 ± 40.7	141 ± 14.8	0.32

Results are expressed as mean pg/mL ± standard error. *$P < 0.05$; **$P < 0.01$.

Table 5
Association of the most common clinical findings of the disease with IFN-γ in the patients with BD

Clinical manifestations	NO (%)	Median IFN-γ		*P*-value
		Present	Absent	
Oral involvement	64 (100)	90.0 ± 4.52	-	-
Genital involvement	60 (93.7)	78.7 ± 5.75	90.7 ± 4.80	0.146
Skin involvement	37 (57.8)	86.9 ± 6.80	92.21 ± 6.63	0.55
Ocular involvement	37 (57.8)	100.3 ± 6.01	82.4 ± 6.26 *	0.04
Vascular involvement	18 (28.1)	99.1 ± 7.61	86.4 ± 5.51	0.18
Neurological involvement	15 (22.3)	91.35 ± 9.1	89.5 ± 5.25	0.86
Articular involvement	17 (26.5)	81.57 ± 9.1	93.0 ± 5.1	0.28
Chest involvement	4 (6.26)	67.9 ± 6.81*	91.4 ± 4.7	0.027
GIT involvement	3 (4.68)	68.9 ± 11	91.0 ± 4.6	0.17
Activity	28 (43.7)	87.3 ± 8.3	92.0 ± 4.8	0.623

Results are expressed as mean pg/mL ± standard error. *$P < 0.05$; **$P < 0.01$.

Table 6
Correlation between plasma cytokine levels with features of BD patients and disease activity.

Clinical manifestations	IFN-γ r (*P*-value)	IL-10 r (*P*-value)	IL-6 r (*P*-value)	IL-17 r (*P*-value)
Gential	$r = 0.121$; $P = 0.343$	$r = 0.038$; $P = 0.763$	$r = 0.121$; $P = 0.343$	$r = -0.061$; $P = 0.631$
Skin	$r = 0.135$; $P = 0.286$	$r = 0.028$; $P = 0.825$	$r = 0.126$; $P = 0.326$	$r = -0.176$; $P = 0.163$
Ocular	$r = -0.325$; $P = 0.009$**	$r = 0.250$; $P = 0.046$*	$r = -0.207$; $P = 0.100$	$r = 0.048$; $P = 0.707$
Vascular	$r = 0.207$; $P = 0.101$	$r = -0.162$; $P = 0.201$	$r = 0.141$; $P = 0.266$	$r = -0.093$; $P = 0.464$
Neuro	$r = -0.026$; $P = 0.839$	$r = -0.130$; $P = 0.307$	$r = 0.139$; $P = 0.274$	$r = 0.039$; $P = 0.760$
Arthritis	$r = -0.184$; $P = 0.146$	$r = 0.184$; $P = 0.146$	$r = 0.260$; $P = 0.038$*	$r = 0.150$; $P = 0.236$
Chest	$r = -0.210$; $P = 0.096$	$r = -0.152$; $P = 0.230$	$r = 0.117$; $P = 0.357$	$r = 0.189$; $P = 0.135$
GIT	$r = -158$; $P = 0.212$	$r = -0.112$; $P = 0.378$	$r = 0.178$; $P = 0.159$	$r = 0.090$; $P = 0.479$
Activity	$r = -0.055$; $P = 0.668$	$r = -0.065$; $P = 0.611$	$r = 0.274$; $P = 0.049$*	$r = -0.038$; $P = 0.768$
Duration	$r = 0.159$; $P = 0.209$	$r = 0.094$; $P = 0.462$	$r = 0.226$; $P = 0.07$	$r = -0.113$; $P = 0.373$

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

negative feedback [44]. Additionally, this study showed a decrease in serum level of IFN-γ in ocular and chest involvement. This effect could be related to IL-10 that down-regulates the expression of NO that in turn antagonizes the effect of IFN-γ, which prompts a protective role of IL-10 [45]. Other studies are not in accordance with this study as they observed Th1 dominance in BD uveitis, but we found a decrease in serum level of IFN-γ in the active stage and an increase in the inactive stage [11, 46]. Ozdamar *et al*. in 2009 [47] found high levels of IFN-γ in the bronchoalveolar lavage from BD with pulmonary disease and this is not in accordance with our results as we detect a lower serum level of IFN-γ. This could be explained by the difference in type of samples (serum or bronchoalveolar lavage) and time of samples collection.

Additionally, the results of the present study showed an elevated level of IL-17 in BD compared to control group and this is in agreement with Chi *et al*. [9, 48]. Th17 cells produce a number of proinflammatory cytokines such as IL-17 and IL-22, whereas IL-6 is essential for their development [9, 49]. Recent data suggest that Th17 plays a crucial role in the pathogenesis of BD as it activates neutrophils. IL-6 plays a role in the differentiation of CD4+ T cells to Th17 cells in BD [20, 21]. The present finding showed an increase in serum level of IL-6 that is in agreement with Kim and Bettelli [20, 21]. Also, we observed a negative correlation between IL-17 and IFN-γ that is in agreement with Chi and Hamzaoui [9, 48] who reported an elevation in IL-23 and IL-17A but not IFN-γ.

The anti-inflammatory cytokine IL-10 is an immunosuppressive cytokine and involved in the down regulation of autoimmune disease; the decreased level of IL-10 contributes to the persistent inflammation found in BD patients [16, 50]. IL-10 shows a positive correlation with eye manifestation which could be attributed to the fact that IL-10 is a potential cytokine of protecting effect [28, 36]. The current study observed a decrease in serum level of IL-10 in BD patients compared to control group. Also, a decrease in serum level of IL-10 in patients suffering from GIT manifestations and a positive correlation were observed between IL-10 and patients with eye manifestation. These findings support those of Fitzgerald *et al*. [16] and Guo [50]. In contrast, however, Aridogan *et al*. [51] and Ben Ahmed *et al*. [40] observed an increased level of IL-10 in peripheral blood mononuclear cells from patients with BD.The reason for this discrepancy is at present not clear.

The present study revealed that Th2, Th17 cytokines are involved in the pathophysiology of BD disease except for IFN-γ that is a Th1 cytokine and this finding is in agreement with Vaccarino *et al*. [52]. However, these cytokines cannot be considered markers for the different clinical manifestations observed in BD patients apart from IL-6 that could be a potential marker for arthritic manifestations and disease activity.

CONCLUSION

BD is not uncommon in Egypt but there is little information of the involvement of cytyokinesin the pathogenesis of this heterogenous disease. Whereas IL-6 and IL-17 are potential markers for BD. IL-17, IL-10, and IFN-γ serum levels are not correlated with any of the different clinical manifestations of BD, except for IL-6 that could be a potential marker for arthritic manifestation and disease activity.

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