The prevalence of atopy in patients with familial Mediterranean fever and Behçet's disease

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ABSTRACT

Objectives. *The purpose of this study is to investigate the prevalence of atopy in patients with Behçet's disease (BD) and familial Mediterranean fever (FMF).*

Methods. *In this study, 42 BD patients, 40 FMF patients and 49 healthy subjects were included. The skin test was applied to the whole group. If one or more allergen response was equal or greater than histamine response, it was accepted as atopy. At the same time, total serum IgE and peripheral blood eosinophil levels were also determined.*

Results. *The frequency of atopy was found to be 2.4% (1/42 patients) in BD patients and 5% (2/40 patients) in FMF patients and 16.3% (8/49 individuals) in healthy controls. In the BD patients, positivity to skin prick test was significantly lower than the control group (p=0.035). The mean serum total IgE level and eosinophil counts did not differ between the three groups. In 33.3% of BD patients, 39.8% of FMF patients and 20.8% of controls levels of IgE lower than 20 kU/L were found (both groups p<0.05).*

Conclusion. *The related conditions with Th-2 cell response such as atopy seem to be low frequency in BD and FMF patients.*

Introduction

The atopic disorders are associated with T helper 2 (Th2) cells characterised by production of interleukin 4 (IL4). Key pathogenetic features of atopic disorders such as asthma, allergic rhinitis, and atopic dermatitis depend on IL4 for the class switching of B cell responses to secrete IgE antibodies (1). Interferon gamma (IFN-γ) produced by Th1 cells, is a proinflammatory cytokine which helps B cells to produce autoantibodies and promotes macrophage-rich inflammatory reactions while inhibiting IgE dependent, eosinophil-rich reactions. They also activate monocytes to produce TNF-α and IL1, which are known to be important in synovitis, and Th1 cells can themselves make TNF-β. A number of inflammatory diseases have been shown to be driven by a strongly dominated Th1 response (2).

Familial Mediterranean fever (FMF) is characterised by recurrent attacks of fever and serositis (3). The gene responsible for FMF, entitled MEFV, encodes a leucocyte and monocyte specific inflammatory regulator, and its mutations cause the autoinflammatory phenotype of FMF (4). Centola *et al*. have shown that MEFV expression was increased by INF-γ and that it may have a place in the Th1 mediated response (5).

Behçet's disease (BD) is a chronic multisystemic vasculitis of every size and type vessels with unknown etiology. It is believed that the disease is triggered in genetically susceptible individuals by environmental factors, such as infectious agents (6). On the other hand, there have been strong evidences that Th1 type cytokines play an important role in the immunopathogenesis of inflammation in BD (7). It has been reported that naive $CD4^+$ T cells excessively responded to Th1 cytokines in patients with BD (8). Recently, it has been noted that the prevalence of Th-2 cell- mediated disease, such as atopic diseases, could be low in Th-1 cell-mediated disease, including rheumatoid arthritis (RA), and multiple sclerosis (MS). In the current study, atopic disease was found in 7.2% of BD patients, showing a significantly lower prevalence compared with controls (21.4%, p=0.012) (9).

There are only limited details available on the prevalence of atopy in BD and FMF patients. Therefore, this study was carried out in order to investigate the prevalence of atopy in patients with BD and FMF.

Material and methods

In this study, 42 patients who had been

diagnosed with BD according to International Study Group criteria (10), and 40 patients with FMF were enrolled. Forty-nine individuals without BD, FMF or any other inflammatory rheumatic diseases were included as the control group. For the last 3 weeks none of them had taken antihistamines or other drugs that could affect the results of the prick test. Informed consent was obtained from each patient and the study protocol was approved by the local ethics committee of Kocaeli University.

Laboratory

Levels of serum total IgE (Neopharma, Sweden) were measured in all patients by ImmnoCap technic. Complete blood count was done by Cell Dyn 3700 autoanalyser (Abbott, USA).

Skin Prick Test (SPT)

All the patients with BD and FMF, and controls were prick tested with 26 aeroallergens including common allergens of *Dermatophagoides pteronyssinus, D farinae*, grass mix, weed mix, tree mix (Alk-Abello, Denmark). Allergens were performed by Quintest applicator (HollisterStier, USA). After 20 min interpretation of SPT was evaluated by the same physician in each group. Patients with a wheal reaction equal to or greater than histamin response, to one or more of the allergens tested, were considered to be atopic. The test was evaluated by the same physician who was blinded to the diagnosis of the study groups.

Statistical analysis

Statistical analysis was performed by using the SPSS 13.0 program for Windows. Numeric parameters of groups were compared using ANOVA. Chi-square test and, when needed, Fisher's exact test were used for comparison of proportions.

Results

In the BD group (F/M: 19/23), the mean age was 36.5±11.8 years (min-max: 16-46, median: 35), and in the FMF group (F/M: 19/21), the mean age was 27.6±8.45 years (min-max: 18-60, median: 27.5). In the control group (F/M: 25/24) the mean age was 30.2±6.4 years (min-max: 20-51, median: 28). None of the patients nor the control group had atopic history, and there was no history of atopy in their family (Table I).

Table I. The demographic characteristics of FMF, BD and control groups.

		FMF (n=40)	BD (n=42)	Controls (n=49)	*p*-value
Age		27.6 ± 8.45	36.5 ± 11.8*	30.2 ± 6.4	0.000*
Sex	Female	47.5% (19)	45.2% (19)	51% (25)	>0.050
	Male	52.5% (21)	54.8% (23)	49% (24)	

Table II. The results of atopy in FMF, BD and control groups.

		FMF (n=40)	BD (n=42)	Controls (n=49)	*p*-value
Eosinophil (/mm^3)		133.5 ± 95.8	133.95 ± 208.8	164.6 ± 98.3	>0.050
Total IgE (kU/L)		79.3 ± 163.8	79.9 ± 127.1	87.75 ± 105.8	>0.050
Prevalence of atopy		5% (2/40)	2.4% (1/42)*	16.3% (8/49)*	0.035*
Total IgE	<20	38.9% (14)	33.3% (12)	20.8% (10)	>0.050
(kU/L)	20-100	47.2% (17)	41.7% (15)	50% (24)	
	>100	13.9% (5)	25% (9)	29.2% (14)	

SPT (atopy) was positive in two of 40 FMF patients (5%), one of 42 BD patient (2.4%) and eight of 49 controls (16.3%); compared with controls, the BD patients patients had a significantly lower frequency of positive SPT (p=0.035). The other atopy parameters, including serum total IgE levels and peripheral blood eosinophil counts did not differ in FMF and BD when compared with controls. In 33.3% of BD patients, and 39.8% of FMF patients and 20.8% of controls was found lower levels of IgE than 20 kU/L (both groups p<0.05) (Table II).

Discussion

Th2 T cells are required for atopic responses, with an absolute requirement for IL4, the signature Th2 cytokine, in generating IgE responses. Th2 cells also make IL5, which is important for eosinophil activation. In contrast, Th1 T cells, via their production of interferon γ, are critical for protection against intracellular pathogens such as mycobacteria. A number of inflammatory diseases have been shown to be driven by a strongly dominated Th1 response (2).

A reduction in the prevalence of atopic diseases has also been clearly shown in some Th1 associated diseases, including adult RA (11). The other two diseases in which Th1 type cytokines play an important role in the immunopathogenesis of inflammation are FMF and BD (5, 9). In one study the prevalence of asthma was 2.96%, but was only 0.92% among patients with FMF (p<0.005) (12). Sackesen *et al*. reported that the prevalence of atopy (6.7%, 4/60 patients) in patients with FMF was significantly lower than in children (20.6%) of a population-based study (p<0.001) (1). In contrast to these studies, another study suggested that there were no statistically significant differences in the prevalence of asthma between FMF patients and their spouses or between parents and controls (13). In our study, the frequency of atopy was lower in FMF patients (5%) than in controls (16.3%), but this difference was not statistically significant.

There is limited information available on atopy in BD patients. Recently, it was reported that the frequency of positive SPT in 30 BD patients was lower than that in 30 healthy controls, but this difference did not reach a statistical significance (10% *vs*. 20%, p>0.05) (14). In another study, the frequencies of SPT positivity in patients with BD and in controls were 12.9% and 36.3%, respectively (p=0.001). It was reported that, the frequency of atopic diseases, including allergic rhinitis, bronchial asthma, and atopic dermatitis, in BD was lower than in the healthy controls (7.2% *vs*. 21.4%, p=0.012) (9). In our study, the frequency of atopy, Th-2 type cell-mediated conditions, was significantly lower in BD patients (2.4%) than in controls (16.3%) (p=0.035).

Atopy is commonly associated with high serum IgE levels. To date, the studies on serum IgE levels have shown the conflicting results in BD patients. Cengiz reported that serum total IgE concentrations were significantly higher in patients with BD than in the control group (132.36±9.39 *vs*. 42.94±4.59 IU/ml, $p<0.01$). He pointed out that there was a positive correlation between serum IgE concentrations and the duration of the disease (15). In addition, Kalpaklioğlu *et al*. reported that patients with active disease tended to have higher levels of serum total IgE, but the difference was not statistically significant (16). In contrast to these studies, Chang *et al*. reported that the mean values of serum IgE levels were significantly decreased in BD when compared with controls (mean, 105.8 *vs*. 193.4 IU/L, $p=0.03$) (9). In another study, Dinç *et al*. reported that serum total IgE levels were not elevated in BD (14). There was only one study about FMF and atopy, and in this study the mean value of IgE was not differ between FMF and the population-based study (35.0±5.3 *vs*. 43.9±3.1 kU/l, $p=<0.05$) (1). In our study, serum total IgE levels did not differ in FMF and BD when compared with controls.

In various studies, peripheral blood eosinophil counts did not differ between BD patients and controls, suggesting the absence of non-specific atopy in this syndrome (9, 14, 15, 17). Similarly to these results, in our study, peripheral blood eosinophil counts did not differ between FMF and BD when compared with controls. However, the number of study groups is the limitation of this study.

In summary, the current study revealed a lower prevalence of atopy in BD patients, corroborating the hypothesis that Th-1 cell mediated disorders protect against the development of Th-2 cell mediated diseases.

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