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Prevalence of Allergic Diseases in Patients with Common Autoinflammatory Diseases

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ABSTRACT

Objective: Autoinflammatory diseases are driven by abnormal activation of the innate immune system. Although allergic diseases are known to be mediated by the T helper 2 response, new mechanisms are put forward about the activation of innate immunity during exposure to allergens in recent years. Familial Mediterranean fever (FMF) and Behçet's disease (BD) are the commonly seen autoinflammatory diseases in Turkey. It was aimed to determine the prevalence of allergic diseases in BD and FMF and contribute to explaining the relationship between autoinflammation and allergic diseases in this survey.

Materials and Methods: The study included 42 patients with BD, 40 with FMF, 20 with other rheumatic diseases, and 20 healthy controls who had volunteered for allergic evaluation. Patients were questioned about allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, venom allergy, and food-drug allergy. The same prick test panel was used for all patients to investigate the presence of atopy.

Results: Although the rate of allergic diseases and the blood eosinophil rate were significantly higher in patients with FMF and Behçet's disease, which are commonly seen as autoinflammatory diseases, atopy rates were similar in all groups. The prevalence of allergic rhinitis and any allergic diseases was significantly higher in the FMF and BD groups (p: 0.03 and p: 0.02, respectively). In the multiple logistic regression model of the presence of any allergic disease, none of the factors was associated with allergic diseases.

Conclusion: The prevalence of allergic diseases in patients with FMF and BD was found to be higher than in those with other rheumatic diseases and the control group but atopy rates were similar in all groups. The autoinflammatory diseases are not protective in terms of allergic sensitization and allergic rhinitis. This may be the result of recent advances in the innate immune sensing system.

Keywords: Allergic diseases, autoinflammatory diseases, familial Mediterranean fever, Behçet's disease, atopy

INTRODUCTION

Pathogenic inflammation arises through aberrant, antigen-independent activation of the immune system in autoinflammatory diseases. Thus, they may broadly be considered to represent a primary disease of innate immunity, although cells more typically associated with adaptive immunity (e.g. lymphocytes) may also contribute to autoinflammation. Patients refer with recurrent systemic inflammation and some organ-specific comorbidities. These diseases are mediated by the overproduction of various cytokines including IL-1, IL-18, IL-6, TNFα, and type I interferon. Familial Mediterranean fever (FMF) is the most frequent autoinflammatory disease that is characterized by episodes of fever and serositis. The MEFV gene is identified as the responsible gene for this disease. It encodes pyrin, which an important player in the innate immune system and a component of the inflammasome. Inflammasomes are multiprotein complexes that have a major role in both the innate

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and adaptive immune system (1). The most important inflammasome is leucine-rich repeat/pyrin domain-containing-3 (NALP-3). It is required for the synthesis of interleukin-1β that is mentioned in the pathogenesis of FMF and other autoinflammatory diseases (2). A NALP-3 gene polymorphism is associated with an increased risk of atopic dermatitis, and activation of inflammasomes triggers childhood allergic respiratory diseases (3,4). Consequently, inhibition of NALP3 inflammasome seems to be an attractive strategy for treating allergic diseases. It is shown in animal models that activation of inflammasomes resulted in an increased inflammatory response to cause atopic symptoms (5, 6).

Although Behçet's disease is defined as vasculitis, it is accepted as an idiopathic autoinflammatory disease due to the systemic inflammation and diffuse organ involvement it causes (7). There may be a mixture of Th1 and Th2 activity and increased activity of Th17 cells in Behçet's disease.

Also, Th2 and Th17 inflammatory pathways are reciprocally regulated in the samples of asthmatic patients (8). Type II cytokine suppression promotes Th17 responses, displaying that patients with asthma may benefit from combined therapy targeting both Th2 and Th17 responses.

This study, it was aimed to determine the prevalence of allergic diseases in patients with BD and FMF and compare them with the patients with other rheumatic diseases and healthy controls.

MATERIAL and METHODS

The study included 40 patients with BD, 42 with FMF, and 20 with other rheumatic diseases (15 rheumatoid arthritis, 5 systemic sclerosis) who were followed up in the rheumatology clinic and volunteered for allergic evaluation and 20 healthy controls between July 2017 and January 2019 in Osmangazi University, School of Medicine, Department of Rheumatology. Patients with other rheumatic diseases such as rheumatoid arthritis and systemic sclerosis, which are known as Th1-related diseases and in which allergic diseases are less common, were included in the group with other rheumatic diseases.

Patients were evaluated by the single responsible researcher at the Osmangazi University School of Medicine, Department of Immunology and Allergy, and medical histories were taken. Physical examination, demographic characteristics, current allergic diseases (asthma, allergic rhinitis, atopic dermatitis, venom allergy, food-drug allergy), and the drugs used by the patients were recorded. Any allergic disease was defined as at least one positive history of the three most common allergic diseases (asthma, allergic rhinitis, and dermatitis).

The diagnosis of rhinitis and asthma was made by allergists in the allergy clinic based on international and national asthma/rhinitis guidelines (GINA, ARIA, and national guidelines)

A standard skin prick test with common aeroallergens was applied to all patients who were not on antihistamines and whose skin was suitable for the test to determine the atopic status of the patients,

The skin prick test was performed with positive-negative control, grass mixture, weed mixture, tree pollen mixture, *Dermatophagoides pteronyssinus, Dermatophagoides farinea,* molds *(Alternaria alternata, Cladosporium*), and cat allergens. The patients with a wheal reaction ≥ 3 mm, after subtraction of the reaction from the negative control, to one or more of the allergens tested, were considered to be atopic.

Statistical Analysis

The statistical analysis was performed using SPSS version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Numeric values with normal dispersion were expressed as means ± SD, and non-normally distributed variables were given as median values (Q1-Q3). Categorical variables were given as n (%). All directional p values were two-tailed and significance was assigned to values lower than 0.05.

The Shapiro Wilk's test was used to investigate the suitability of the data for normal distribution. Pearson Chi-Square, Pearson Exact Chi-Square, and Fisher Exact Chi-Square analyses were used for the analysis of the cross tables. The association between any allergic disease and FMF, BD, control, and other rheumatic disease was adjusted for age, sex, atopy, and eosinophilia in the logistic regression analysis models. Odds ratios and 95% CI were calculated (Table I)

The local ethics committee of Eskişehir Osmangazi University approved the study protocol (Approval number: G.241). Written informed consent was obtained from all participants.

Table I: Multiple logistic regression model for the presence of any allergic disease and related factors.

Allergic disease		B	S.E.	Wald	p	OR 95% C.I. for OR	Lower	Upper
Step 1	Age	0.01	0.02	0.53	0.47	1.01	0.98	1.05
	Sex	-1.32	0.57	5.33	0.02	0.27	0.09	0.82
	FMF			3.17	0.37			
	BD	-0.42	0.54	0.60	0.44	0.66	0.23	1.89
	Control	-21.1	11158,68	0	1	0	0	0
	Other	-1.37	0.77	3.16	0.08	0.26	0.06	1.15
	Atopy	1.21	0.65	3.47	0.06	3.35	0.94	11.96
	Eosinophilia	0	0	0.13	0.72	1	1	1
	Constant	-0.80	0.88	0.81	0.37	0.45		
Step 5	Sex	-0.89	0.52	2.98	0.08	0.41	0.15	1.13
	Constant	-0.65	0.25	6.68	0.01	0.52		
Step 6	Constant	-0.90	0.22	17.4	0.00	0.41		

RESULTS

The study included 122 patients who were followed-up at the rheumatology clinic (40 with FMF, 42 with BD, 20 healthy controls, and 20 with other rheumatic diseases). Of note, most of the patients were female (60% in the FMF group, 57.1% in the BD group, and 70% in the control group). The mean ages of these groups were similar.

In the group with other rheumatic diseases, 95% of patients were female and the mean age was significantly higher than in the other groups (51.6±15.8, p<0.002).

The occurrence of allergic rhinitis differed significantly between the groups (35% in the FMF group, 28.6% in the BD group, and 30% in the other rheumatic disease group, p= 0.03). The occurrence of any allergic disease differed significantly between groups (37.5% in the FMF group, 31% in the BD group, and 30% in the other rheumatic disease group, p= 0.02)

There was no difference in the frequency of asthma, venom allergy, and food and drug allergy.

Atopy rates were not statistically significantly different between the groups (control group (20%), FMF group (10%), the BD group (18.4%), and the other rheumatic disease group (10%)) (P=0.63). However, the family history of any allergic diseases was more prevalent in the FMF group (42.5%) compared to the BD group (28.6%) and the control (10%) and the other rheumatic disease groups (10%) (p=0.008). Although family history of allergic diseases and blood eosinophil rates were significantly higher in the FMF and BD groups, atopy rates were similar in all groups.

The data on age, sex, family history of allergic disease, atopy status, blood eosinophil rate, and allergic diseases are summarized in Table II and Figure 1.

Multiple logistic regression analysis models were built to adjust for the associations between any allergic disease, and FMF, BD, and other rheumatic disease using the control group selected as the reference group. After adjusting for age, sex, atopy, eosinophilia, in the multiple logistic regression analysis models, the presence of any allergic disease was not associated with any of these factors (Table I).

DISCUSSION

This is the first adult study comparing the frequency of allergic diseases in FMF, BD, other rheumatic disease group, and healthy control groups. Although the prevalence of allergic rhinitis and any allergic disease was higher in the FMF and BD groups compared to the ones in the other groups, the frequencies of asthma, venom allergy, and food and drug allergy were not statistically significantly different.

Allergic diseases are thought to be driven by Th2-related responses. Activated Th2 cells are considered to

Table II: The demographic features of the patients

	FMF (n=40)	BD (n=42)	Control (n=20)	Other rheumatic disease (n=20)	p
Female n (%)	24 (60)	24 (57.1)	14 (70)	19 (95)	**0.02**
Age (years)	38.2±13.3	41.8±11.1	39.1±13.6	51.6±15.8	**0.002**
Family history of allergic disease n (%)	17 (42.5)	12 (28.6)	2 (10)	2 (10)	**0.008**
Atopy n (%)	4 (10)	7 (18.4)	4 (20)	2 (10)	0.63
Eosinophil count (median Q1-Q3)	100-300	75-200	100-187.5	75-125	**0.016**
Eosinophilia rate (median Q1-Q3 %)	1.4-3.6	1-3	0.83-2.1	0.58-1.55	**0.002**
Asthma n(%)	1 (2.5)	3 (7.1)	0	1 (5)	0.74
Allergic rhinitis n (%)	14 (35)	12 (28.6)	0	6 (30)	**0.03**
Dermatitis n (%)	0	1 (2.4)	0	3 (15)	**0.028**
Venom allergy n (%)	1 (2.5)	0	0	0	0.656
Food allergy n (%)	0	0	0	2(10)	0.058
Drug allergy n (%)	4 (10)	4 (9.5)	0	2 (10)	0.57
Any allergic disease* n (%)	15 (37.5)	13 (31)	0	6 (30)	**0.02**

*Any allergic disease is defined as at least one positive history of the three common allergic diseases (asthma, allergic rhinitis, and dermatitis)

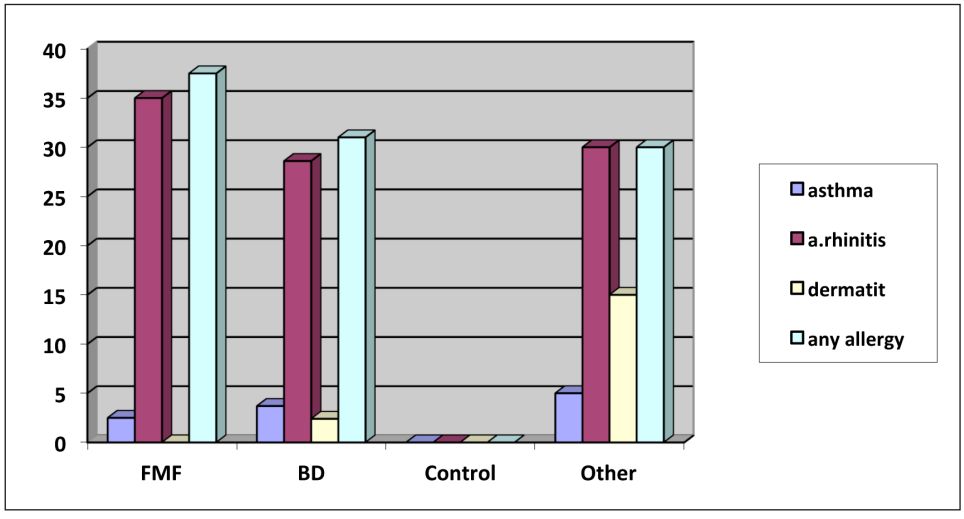

Figure 1. Prevalence of allergic diseases in different groups.

decrease Th1 differentiation. Moreover, the predominance of the Th1 response may be a possible protector against allergic diseases. Thereby, the incidence of atopic diseases is known to be lower in Th1-related diseases (such as rheumatoid arthritis (RA) and multiple sclerosis) than in controls (9, 10). In a study by Verhoef et al., hay fever was found to be lower in RA patients than in non-RA patients (4% vs. 8%) (9). In our study, the prevalence of allergic rhinitis was 30% in the other rheumatic diseases group that was similar to the one in the BD group. On the other hand, chronic inflammatory conditions and especially asthma and allergic rhinitis are associated with an increased risk of rheumatoid arthritis (11). There are still conflicting results about allergic diseases in rheumatoid arthritis patients. However, recent studies have shown that there is a relationship between these two pathways with the discovery of Th17, new signal molecules (toll-like receptors, NOD-like receptors, caspase pathway, and inflammasomes (12).

The studies on patients with FMF have shown a low incidence of asthma. In the study of Sackesen et al., allergic

rhinitis, and atopy rates were lower in the children with FMF compared to the normal population, FMF was found to be protective in terms of atopic sensitization and allergic rhinitis (13). Aydogmuş et al. demonstrated that children with FMF had a non-significantly increased prevalence of atopic dermatitis (5.08%), allergic rhinitis (28.8%), and asthma (15.25%) compared to the control group, but atopy rates and mean eosinophil counts were similar (14). In a recent children study, Yildiz et al. demonstrated that the prevalence figures of asthma, atopic dermatitis, and allergic rhinitis were 4.2%, 0.72%, and 0.87%, respectively, and asthma was more frequent in those without the exon 10 mutation. They speculated that the MEFV mutation may have a protective effect against asthma (15). In the current study, the incidence of asthma, allergic rhinitis, venom allergy, drug allergy, and any allergic disease in FMF patients was 2.5%, 35%, 2.5%, 10%, and 37.5%, respectively. The presence of allergic rhinitis and any allergic disease in FMF was higher than that of our population rates but asthma prevalence was lower than that of our population. FMF gene mutations could not be recorded in this study, and this lower rate of asthma may be due to the protective effect of the MEFV mutation.

Behçet's disease is classically considered to be a Th1- and Th17-mediated disease; however, elevated serum levels of IL-6 or IL-10 are also seen, and these are associated with Th2 cytokines (16). In a study by Horie et al., the incidence of allergic diseases was 20.7% (1.4% atopic dermatitis, 10.2% allergic rhinitis, 5.4% asthma, and 8.5% food/drug allergy) in ocular Behçet's disease patients. The prevalence of allergic diseases was lower than in the Japanese population (17). Few studies have investigated the clinical features of atopic dermatitis in Behçet's disease. Although they reported a lower incidence, there was no significant difference between their clinical manifestations and disease severity (18, 19).

The prevalence of asthma all over the world is around 5-20%. However, there are differences between countries. In the multi-center PARFAIT study conducted in adults in our country in urban areas, the prevalence figures of asthma, allergic rhinitis, and eczema in males were 6.2%, 11.7%, and 6.6%, respectively; and in females, these were 7.5%, 17.0%, and 7.3% respectively (20). In the present study, the incidence figures of asthma, allergic rhinitis, dermatitis, drug allergy, and any allergic disease in the BD group were 7.1%, 28.6%, 2.4%, 9.5%, and 31%, respectively. Besides, the presence of allergic rhinitis and any allergic disease was significantly more common in the FMF and BD groups compared to the control group. The prevalence of asthma was similar to the one in our population but the prevalence of rhinitis was higher in the BD group compared to the one in the PARFAIT study.

There are confusing results about the eosinophil levels in Behçet's disease. In two studies from our country, eosinophil levels were similar to those in BD and control groups, whereas, in a study from Korea, it was found to be lower in the BD group than in the control group (21, 22). In our study, the number and rate of eosinophils were higher than those of the control and other rheumatic disease groups.

There are some limitations of this study. Firstly, our control group may not have a sufficient number of patients to reflect the normal population. Secondly, 80% of other rheumatic disease group had rheumatoid arthritis, as these patients generally use oral steroids, it may not be appropriate to compare eosinophilia between groups.

In this study, the incidence of allergic diseases was higher in patients with FMF and BD than in the control groups but atopy rates were similar in all groups. Lately, the Th1/Th2 paradigm is losing its significance. Particularly Th17 and Treg cell lineages were shown to be crucial in the pathogenesis of the autoinflammatory disease. Th17 cells are also one of the important components of allergic inflammation and asthma. This cell subpopulation is accepted as the major evidence of interaction between innate and adaptive immunity (14). Also, new researches on innate immunity and new signaling pathways show that they play a role in both autoinflammatory diseases and allergic diseases.

In conclusion, common autoinflammatory diseases such as Familial Mediterranean Fever and Behçet's disease are not protective in terms of allergic sensitization and allergic rhinitis in the adult population, which may be the result of increased innate immunity activation in autoinflammatory diseases.

CONFLICT of INTEREST

The authors declare no conflicts of interest relevant to this study. The local ethics committee of Eskişehir Osmangazi University approved the study protocol (Approval number: G.241).

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