



Atopy in Children and Adolescents with Familial Mediterranean Fever

Ailesel Akdeniz Ateşli Çocuk ve Adolessanlarda Atopi

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ABSTRACT

Aim: To investigate the frequency of atopic disease, a prototype Th2 disease in patients with familial Mediterranean fever (FMF).

Materials and Methods: This study included 49 children with FMF and 30 age- and gender-matched healthy children. All participants were questioned about allergic diseases using the modified questions from ISAAC Study questionnaire. Total immunoglobulin (Ig) E levels and eosinophil counts were determined, and skin-prick test was performed.

Results: The skin-prick test showed no significant difference in the rate of positive response to at least one allergen in the children with FMF (10.2%) and the control group (10.0%). The rate of physician-diagnosed asthma, allergic rhinitis and eczema were similar in both groups. The answers given to the questions about allergic diseases were similar and there was no difference in the measurements of IgE levels and eosinophil counts of the two groups.

Conclusion: We determined that atopy frequencies were similar in children with and without FMF.

Key Words: Atopy, allergy, autoimmune, autoinflammatory, familial Mediterranean fever

ÖZET

Amaç: Ailesel Akdeniz ateşli (AAA) hastalarda Th2 hastalıklarının bir prototipi olarak atopik hastalık sıklığını araştırmak.

Gereç ve Yöntemler: Çalışmaya 49 AAA'lı çocuk ve onlar ile aynı yaş ve cinsiyette 30 sağlam çocuk alındı. Bütün katılımcılar modifiye edilmiş ISAAC anket formu kullanılarak sorgulandı. Toplam İmmünglobulin (Ig) E düzeyleri ve eozinofil sayıları belirlendi ve deri prik testleri yapıldı.

Bulgular: Deri prik testinde en az bir alerjene pozitif yanıt hızı AAA'lı çocuklarda (%10,2) ve kontrol grubunda (%10,0) istatistiksel olarak anlamlı farklı değildi. Her iki grupta doktor tanımlı astım, alerjik rinit ve egzema sıklığı benzer bulundu. İki grup arasında alerjik hastalıklar hakkındaki soruların yanıtları, IgE düzey ölçümleri ve eozinofil sayıları farklı bulunmadı.

Sonuç: Çalışmamızda atopi sıklığı açısından AAA'lı çocuklar ve sağlıklı kontroller arasında anlamlı bir farklılık saptanmadı.

Anahtar Kelimeler: Atopi, alerji, otoimmün, otoenflamatuvar, ailesel Akdeniz ateşi

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in MEFV, a gene which encodes pyrin and localizes on the short arm of chromosome 16p13. Mutations in the MEFV lead to uncontrolled neutrophil activation and cause the autoinflammatory phenotype of FMF (1-3). It mainly occurs in populations from the Mediterranean basin, mainly Turks, Levantine Arabs, Sephardic Jews, Druze, and Armenians (4,5).

Atopic disorders comprise allergic asthma, allergic rhinitis and atopic eczema. The atopic state is determined by skin-prick tests to common allergens, by the presence of allergen-specific IgE in their serum, and by the elevation of the total serum IgE (6). The pathogenic features of atopic disorders are elevated levels of IgE and a characteristic T helper cell cytokine pattern. It has been reported that the cytokine pattern of autoimmune and inflammatory diseases is Th1 pattern, whereas that of atopic disorders is Th2 (7,8). The Th1/Th2 antagonism suggests that the prevalence of atopy should be decreased in autoimmune and inflammatory

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disease. However, new T cell helper groups have been described recently, and it has been reported that Th 17 is more effective than Th1 on especially autoimmune and inflammatory illness (9).

The aim of this study was to determine whether or not an inverse relationship existed between atopic disease with a Th2 response and FMF.

Materials and Methods

The study was approved by the local Ethics Committee and was conducted in accordance with the guidelines proposed in the Helsinki Declaration. Informed consent forms were obtained from children (older than 12 years of age) and/or legal guardians.

Patients

Forty-nine FMF patients and 30 gender-matched healthy controls were enrolled in the study. A questionnaire about allergic asthma, allergic rhinitis and eczema was filled by the patients and the healthy control group. The questionnaire was modified from The International Study of Asthma and Allergies in Childhood (ISAAC), previously translated into Turkish (10). Skin-prick test was done to all the children, their eosinophil counts and total IgE levels were determined. Children with any chronic disease and acute infection were excluded from the study. All FMF patients were on Colchicine and in attack free period. All cases were clinically interviewed. Additionally, MEFV gene mutations of patients were taken from medical records.

Skin-prick Tests

Skin-prick tests for aeroallergens were performed on all children with 28 common aeroallergens belonging to 7 groups; house dust mites (*dermatophagoides farinae*, *dermatophagoides pteronyssinus*), trees I (alder, *corylus*, *populus*, *ulmus*, *salix*), trees II (*betula verrucosa*, *fagus sylvatica*, *quercus robur*, *platanus orientalis*), herbs (*artemisia vulgaris*, *urtica dioica*, *taraxacum vulgare*, *plantago lanceolata*), mixture of grasses (*holcus lanatus*, *dactylis glomerata*, *lolium perene*, *phleum pratense*, *poa pratensis*, *festuca pratensis*), animal epithelia (cat hair, dog hair and sheepwool) and cereals (barley, oat, rye, wheat) (Allergopharma, Hamburg, Germany). Histamine and saline were used as positive and negative controls, respectively.

A drop of each allergen extract was placed on the volar surface of the left forearm and was penetrated with a staller point. After 15 minutes, the wheal reaction was measured as the mean of the longest diameter and the diameter perpendicular to it. A wheal response ≥ 3 mm than the negative control with surrounding erythema was considered positive. Atopy was defined as the presence of at least one positive reaction to these allergens.

Eosinophil Counts

The peripheral blood eosinophil was counted in blood samples containing EDTA using an automated hematology analyzer (Pentra DX 120). Blood sampling of all subjects was performed at the same time daily to avoid diurnal variation of

eosinophil count. Eosinophilia was defined as an eosinophil count >300 cells per microliter.

Serum IgE

Total IgE levels were measured by Architect ci1600 (Abbott, Barcelona, Spain). Normal serum IgE levels are given by the manufacturer as <15 IU/ml for age 1-12 months, <60 IU/ml for 1-5 years, <90 IU/ml for 6-9 years, and <200 IU/ml for 10-15 years. IgE levels above the age specific normal range will be referred to as 'elevated' IgE from here on.

Statistical Analysis

All statistical analyses were performed using computer software (SPSS for Windows version 20.0). For the tests of normality, we used Kolmogorov-Smirnov test for nominal variables. Continuous variables were compared by one-way analysis of variance (ANOVA), Student's t-test, Mann-Whitney-U or Kruskal-Wallis according to distribution of values. Chi-square test or Fisher's exact test for comparison of qualitative data were used in the evaluation of results. Statistical significance was determined as $p < 0.05$.

Results

There was no significant difference in age and sex between FMF patients and controls. The mean age was 11.8 ± 3.1 years and 12.6 ± 3.0 years, respectively (Table I). Mean age at the onset of the symptoms was 6 ± 3.65 years (min-max.=1-13), mean age of diagnosis was detected as $8,37 \pm 3,36$ years (min-max.=3-15).

The most common MEFV variant patterns seen were homozygous of M694V (24.5%), heterozygous of E148Q (16.6%) and heterozygous of M694V (12.2%). Fifteen of the children, the homozygous variants of MEFV (13 patients: M694V/M694V, one patient: M680I/M680I, one patient: M697V/M697V) were found. In the rest of the patients, the heterozygous and compound heterozygous (8 patients: E148Q, 6 patients: M694V, 4 patients: M694V, 2 patients: F479L/M694V, 2 patients: M694V/V726A, 1 patient: A744S, 1, 1 patient: 680I/M694V, 1 patient: M694I, 1 patient: M694V, 1 patient: M680I, 1 patient: V726A, 1 patient: E 148Q/M694V, 1 patient: P369S) were found. The minor variant, R202Q, was detected in 2 patients (Table II).

The rate of physician-diagnosed asthma, allergic rhinitis and atopic dermatitis were similar in both groups. There was no difference between the 2 groups based on the answers of other questions about asthma allergic rhinitis, and atopic dermatitis (Table II).

In the study group, Eosinophilia was detected in 3 and elevation of serum Ig E was detected in 8 patients. In the control group, eosinophilia was not observed while elevation of serum IgE was observed in 4 children. No difference in blood eosinophilia and elevation of serum IgE was observed between children with FMF and healthy children ($p > 0.05$) (Table III).

Five children in the study group and 3 in the control group were found to be positive in at least one skin-prick test to allergens that included mixture of grasses, cereals, mites and

animal epithelia. The most common allergen noted by skin-prick test was house dust mites. Others were occasionally positive. There was no significant difference in skin-prick test between the groups ($p>0.05$) (Table III).

Discussion

In this study, we investigated the frequency of allergic disease in children with FMF, an autoinflammatory disease. Skin-prick test positivity, elevation of IgE levels and eosinophilia were not significantly different in children with FMF and the control group.

Until now, only two studies investigating the relationship between atopy and FMF have been published. In the first of these studies, Sackesen et al. (11) reported that the prevalence of atopy (6.7%) in patients with FMF was significantly lower than that in healthy children (20.6%). However, in this study, the mean serum total IgE level counts did not differ between the groups, similar to our study. Eosinophil counts between the groups were not compared in this study. Recently, a second study examining the frequency of atopy in patients with Behçet disease and FMF has been published. In the FMF patients, positivity to skin-prick test was lower than the control group but the results were not statistically significant (12). Similar to our study, the mean serum total IgE level and eosinophil counts did not differ between the groups. However, this study was different from ours in that it was performed on adult patients.

What triggers the inflammation in FMF has not been clarified yet. Autoinflammatory diseases are associated with an inability to control inflammation caused by primary dysfunction of members of the innate immune system, such as neutrophils and monocytes/macrophages. FMF is caused by mutations in the MEFV gene, encoding pyrin, which is known to regulate the inflammasome, a platform for processing interleukin (IL)-1 β (13).

Cytokines are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, and cancer. The T helper cells are a type of T cell that play an important role in the immune system. Th1 type cells heavily produce inflammatory cytokine interferon (IFN) γ and induce the cellular immune response, while Th2 type cells heavily produce anti-inflammatory cytokine IL-4, IL-5, IL-13 and induce the humoral immune response (8). Th1 and Th2 are mutually inhibitory and show regulatory properties. They regulate the development and function of each other, and thus create a balance between the two types of cells. Th2 cells have been

	FMF (+) n=49	FMF (-) n=30	p
Age (years)	11.8 \pm 3.1	12.6 \pm 3.0	0.289
Gender (boy/girl)	22/27	13/17	0.892

FMF: Familial Mediterranean fever

recognized as inducing bronchial asthma, whereas Th1 cells trigger autoimmune and inflammatory diseases (7,8). Until recently, a lot of pathological conditions such as allergic and autoimmune diseases were based on the disruption of this balance. A few papers reported that FMF was driven by Th1 response (14,15).

	FMF (+) n (%)	FMF (-) n (%)	p
Responses for asthma			
History of current wheezing	4 (8.2)	0 (0)	0.292
History of ever wheezing	4 (8.2)	0 (0)	0.292
Doctor diagnosed asthma	2 (4)	0 (0)	0.523
Responses for allergic rhinitis			
Doctor diagnosed allergic rhinitis	2 (4)	1 (3.3)	1
Lifetimes rhinitis	6 (12)	1 (3.3)	0.243
Associated itchy eye	6 (12)	1 (3.3)	0.243
Responses for eczema			
Doctor diagnosed atopic dermatitis	0 (0)	0 (0)	
Chronic rash	0 (0)	0 (0)	
MEFV mutations			
<i>M694V/M694V</i>	13 (25.6)		
<i>E148Q</i>	8 (16.3)		
<i>M694V</i>	6 (12.2)		
<i>M694V</i>	4 (8.2)		
<i>F479L/M694V</i>	2 (4.1)		
<i>M694V/V726A,</i>	2 (4.1)		
<i>M680I/M680I,</i>	1 (2)		
<i>M697V/M697V</i>	1 (2)		
<i>A744S</i>	1 (2)		
<i>680I/M694V</i>	1 (2)		
<i>M694I</i>	1 (2)		
<i>M694V</i>	1 (2)		

FMF: Familial Mediterranean fever

	FMF (+) n (%)	FMF (-) n (%)	p
Prick test positive	5 (10.2)	3 (10)	1.000
Eosinophilia	3 (6)	0 (0)	0.284
Elevated IgE levels	8 (16)	4 (13)	0.501

FMF: Familial Mediterranean fever

In our study, the prevalence of atopy investigated by skin-prick test, serum IgE levels and eosinophil count in patients with FMF were similar to those in healthy controls. This finding is contrary to the opinion of the traditional inverse correlation between atopy and autoimmunity and inflammatory disease. Therefore, we suggest that FMF is different from Th1 type autoimmune disease or Th1 response.

Conclusion

Our results did not show antagonistic a relationship between FMF and atopic diseases driven by Th2 response. Further studies with a larger number of patients are necessary to determine the predominant cytokine profile in patients with FMF.

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