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Is there any difference regarding atopy between children with familial Mediterranean fever and healthy controls?

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Abstract

Introduction: There are only a few studies regarding the prevalence of atopy in Familial Mediterranean fever (FMF) patients, and their results are conflicting.

Methods: In this study children with the diagnosis of FMF were evaluated for the presence of atopy by comparing with controls. One hundred and eighteen children diagnosed as FMF and 50 healthy age and sex matched controls were enrolled. They were evaluated for the presence of rhinitis, atopic dermatitis, urticaria and asthma. Laboratory assessment was done by measuring IgA, IgM, IgG, IgE levels, total eosinophil count and by performing skin prick test (SPT) panels for common allergens to children with FMF and healthy controls.

Results: One hundred and eighteen children (61 girls and 57 boys) diagnosed as FMF with a median age of 120 ± 47 months (range 36–204 months) were compared with 50 healthy controls (31 girls and 19 boys) having a median age of 126 ± 37 (range 48–192 months). The mean percentage of total eosinophil count of patients was similar to that of the control group. The mean level of IgE was significantly higher in children with FMF than controls (136 ± 268 , 87 ± 201 , respectively; p values <0.05). The percentage of skin prick test positivity was similar for both patients and controls (13% and 8.2%, respectively; $p > 0.05$). The prevalences of atopic dermatitis, allergic rhinitis, and asthma in the patient group were 5.08%, 28.8%, and 15.25%, respectively, while the control group had the prevalences of 0%, 36%, and 14% respectively.

Conclusion: Children with FMF did not show an increase of atopic dermatitis, allergic rhinitis and asthma with respect to controls.

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease which is characterised by recurrent episodes of fever, abdominal pain, chest pain and arthritis. It is accepted to be the prototype of auto-inflammatory diseases.¹ In FMF, the MEFV gene mutations cause uncontrolled and persistent inflammation by the influence of protein pyrin. The effect of pyrin is still unclear but there is an agreement of increased processing and production of IL-1 β during attacks.^{2,3} According to the previous studies, Th1 cells were assigned to be the major inflammatory cells at play by promoting actions of macrophages and maintaining inflammatory response.⁴ But, rather than a simple Th1 influence at the pathophysiology of FMF, a more complex integration of cytokines like IL-6, IL-10, IL17 and TGF- β were suggested.^{5,6} So besides Th1, more diverse cell populations, in particular TH17 and Tregs, were shown to play a role in FMF.^{7,8}

For a long while, allergic diseases were characterised by dysregulated Th2 responses, but accumulating knowledge suggests a considerable Th17 effect at the immunopathogenesis contributing to inflammation both by increasing inflammatory cell migration and to a lesser extent triggering Th2 directed responses.⁹

There are few studies showing the low prevalence of atopy in patients with FMF.^{10,11} But the changing knowledge about the Th1/Th2 paradigm and emergence of new perspectives in the immunopathogenesis of both FMF and allergic diseases led us to hypothesise the idea that as Th17 was playing a common role in both of these diseases, the prevalence of allergic diseases in FMF patients may not be different from the healthy population.

Methods

The study was approved by the institutional review board and fulfilled the ethical guidelines of the Helsinki Declaration (Edinburgh, 2000). Informed parental consent was taken from all the participants before inclusion. The study was planned as a prospective comparative cohort.

The study consisted of 118 children with FMF diagnosed and followed-up by a paediatric rheumatologist at the paediatric rheumatology out-patient clinic of Istanbul Kanuni Sultan Suleyman Education and Research Hospital, Turkey, and 50 age and sex matched healthy controls. Diagnosis of FMF was based on the Tel-Hashomer Criteria.¹² All patients were in clinical remission and all were taking colchicine. No patient or control was taking any other drug (especially no antihistaminic medication four weeks before their involvement in the study). Subjects had the results of genetic analysis for the most common FMF mutations in Turkey (M694V, M680I, V726A, E148Q, M694I). Routine screenings done at every visit, like complete blood count, erythrocyte sedimentation rate, C-reactive protein and serum amyloid A were recorded.

Children with FMF and the controls were referred to the paediatric allergy out-patient clinic. The diagnosis of allergy was made by paediatric allergy specialists. Skin prick tests were applied epicutaneously for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, tree pollens, grass and cereal pollens, animal danders, moulds, milk,

egg yolk and egg white (Allergopharma, Rheinbek, Germany). Histamine was accepted as positive control and saline as negative control. The test was considered positive if the mean wheal diameter was ≥ 3 mm compared with the negative control after 20 min. Eosinophil counts were measured using a complete blood cell autoanalyser. IgE levels were measured using nephelometric immunoassay. IgE levels above 100 IU/ml and eosinophil counts over 500/ μ L were regarded as above normal. Overall atopy was defined as the presence of at least one of asthma, allergic rhinitis or eczema.

Symptoms of any allergic disease were assessed using the ISAAC questionnaire form. The International Study of Asthma and Allergies in Childhood (ISAAC) is a standardised questionnaire designed to evaluate the prevalence and severity of symptoms of asthma, allergic rhinitis and atopic eczema. It had been previously validated among Turkish children.^{13,14} In this study, the questionnaires were asked face-to-face to parents of the participants and controls.

Asthma is defined as asthma diagnosed by a doctor or a diagnosis of allergic bronchitis and/or ≥ 3 bronchitis episodes, and wheezing or whistling in the chest or asthma crisis during the last 12 months. Allergic rhinitis is defined as experiencing problems with sneezing, or having a runny or blocked nose during the last six months without presence of the common cold or flu. Eczema is defined as recurrent erythema, and itching or rash over the body without fever in the last six months. Atopy in the family was defined as a positive history or diagnosis of asthma, rhinitis, and/or eczema in one or both parents.^{10,13,14}

Statistical methods

Statistical analysis was carried out using SPSS version 16.0 statistical package. The data were evaluated using descriptive statistical methods (mean \pm standard deviation, median, frequencies and percentages). Chi-square test was performed to compare the difference of frequencies of asthma, allergic rhinitis and atopy between patients and controls. A two-tailed p value less than 0.05 was considered statistically significant.

Results

This prospective cohort consisted of 118 patients and 50 controls. The median age and gender balance of the patient and control groups were similar (120 ± 47 months, 61 girls and 126 ± 37 months, 31 girls, respectively; both p values > 0.05). The demographic data, clinical findings, laboratory results and mutation analysis are shown in Table 1.

The prevalences of atopic dermatitis, allergic rhinitis, and asthma in the patient group were 5.08%, 28.8%, and 15.25%, respectively, while the control group had the prevalences of 0%, 36%, and 14% respectively. When compared with the control group, the children with FMF had non-significantly increased prevalences of atopic dermatitis, allergic rhinitis and asthma. The comparisons are summarised in Table 2.

The mean percentage of total eosinophil count of patients was similar to that of the control group. The mean level of IgE was significantly higher in children with FMF than

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