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Original Research Article

ATOPY IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER INVESTIGATION OF PREVALENCE

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Abstract

Background: In this study we compared FMF patients with healthy controls to show the prevalence of atopy and allergic diseases. **Materials and Methods:** Eosinophil percentage, total IgE level, cow's milk specific IgE, egg white specific IgE, wheat flour specific IgE and respiratory function tests were evaluated in both groups. **Result:** Atopy was detected in 10 cases (16,4%) in study group and 5 (8,2%) cases in control group. In study group 5 patients (8,2%) and in control 2 (3,3%) patients had allergic disorder (p=0.272). White egg specific IgE was positive in study and control group in 3 (5%) and 11 cases (18%) respectively (p=0.044). Specific IgE of wheat flour and cow's milk were similar between in control and study group. Serum total IgE level was higher in controls than study group (p=0.009). **Conclusion:** In this study, it was observed that the frequency of atopy and allergic diseases did not increase in FMF patients.

INTRODUCTION

Familial Mediterranean fever (FMF; recurrent polyserositis, periodic disease) is an autosomal recessive hereditary disease which primarily affects populations surrounding the Mediterranean basin. It is characterised by recurrent attacks of fever and peritonitis, pleuritis, arthritis, or erysipelas-like skin disease.[1] The onset of clinical manifestations begins before the age of 5 in 65% of FMF cases and before 20 years of age in 90% of cases.[2] Disease flares generally occur within variable intervals from once weekly to once a year and last for one to three days.[3] The most terrifying complication of FMF is renal amyloidosis due to ongoing inflammation; fortunately, it was suggested that colchicine treatment decreased amyloidosis rate to 8.6% in a large FMF cohort from Turkey.[4]

The pathogenesis of FMF has not been clearly elucidated. It is known that the disease is caused by the MEFV (Familial MEditerranean FeVer) gene mutation located on the short arm of the 16th chromosome.[5,6] It has been determined that the protein called pyrin or mareonostrin, encoded by MEFV, is present in polymorphonuclear leukocytes and myeloid bone marrow precursors and has an anti-inflammatory function. It is thought that abnormal pyrin protein, which is formed as a result of MEFV gene mutation, cannot suppress inflammation and causes clinical findings seen in FMF.[7,8]

Atopy is a hereditary predisposition to the development of IgE-related diseases such as allergic rhinitis, asthma and atopic dermatitis. The risk of allergic disease in a child approaches 50% when one parent is allergic and 66% when both parents are allergic. Allergic diseases arise from the acute or chronic exposure of a sensitized individual to a specific allergen by inhalation, ingestion, contact or injection. The atopic diseases are mainly mediated by Th2-type response and are associated with the production of proinflammatory cytokines, including IL4, IL5, IL6, IL9, IL10, and IL13.[9,10] Mutations in MEFV may result in defective inflammation suppression. Inflammation in FMF shows a Th1 polarization. The Th1 polarization in patients with FMF and carriers may be protecting them from diseases of pronounced Th2 response. There have been several studies showing reduced incidence of allergic patients due to TH1 polarization.[11,12]

The relationship between FMF and allergic diseases has been shown in some previous studies; Allergic diseases such as asthma, allergic rhinitis and atopic dermatitis have been reported to be less common in FMF patients compared to the entire population.[9,13-15] In studies on the subject, parameters such as skin prick test, total IgE level, eosinophil counts were used to determine the frequency of atopic disease. However, serum specific IgE levels, which are a more specific parameter, have a higher diagnostic value and a lower frequency of false positivity, were not evaluated.

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In this study, it was aimed to investigate the possible relationship between FMF and allergic diseases, to evaluate the prevalence of atopy and allergic diseases compared to the control group using various parameters such as egg white specific IgE, cow milk specific IgE and wheat flour specific IgE among FMF patients.

MATERIALS AND METHODS

In this study, pediatric patients aged 5-18 years who were followed up with the diagnosis of 61 FMF at Bezmialem Foundation University Medical Faculty Hospital, Department of Pediatric Nephrology were included. Healthy individuals with the impression of a healthy child at Bezmialem Foundation University were included in the control group. A questionnaire form was prepared and examined in all cases included in the study. Approval was obtained from Bezmialem Foundation University Clinical Research Ethics Committee for the study.

Demographic and clinical findings of all cases included in the study were determined with the prepared questionnaire forms. For this purpose age, gender, onset age of symptoms, age at diagnosis, duration of the disease, presence and type of genetic mutation, familial atopy history, presence of additional doctor diagnosed allergic disease (asthma, allergic rhinitis and atopic dermatitis) and chronic disease history (inflammatory bowel disease, asthma, obesity, type 1 DM, etc.) was questioned and recorded. Eosinophil percentage, total IgE level, cow's milk specific IgE, egg white specific IgE, wheat flour specific IgE and respiratory function tests (FVC, FEV1 and PEF) were evaluated in both control and FMF patients included in the study.

SPSS 20.0 program was used for the statistical analysis of the collected data. Chi-square test in comparison of categorical measurements between control group and patients in FMF group, Fisher's exact chi-square test in case of small expected numbers; In the comparison of numerical measurements, T test (Student's T test) was used in independent groups if the assumptions were provided, and the Mann Whitney-U test was used if the assumptions were not provided. Statistical significance level was taken as $p < 0.05$ in all tests used.

RESULTS

Sixty one children (28 boys, 33 girls) diagnosed as FMF with a mean (SEM) age of 9.9 years were included in the study. The mean age at diagnosis was found to be 7.3 years in the FMF group. The mean age of 61 patients (39 boys, 22 girls) in the control group was 6.7 years.

In the FMF group, 2 patients had asthma, one patient had allergic rhinitis, and 2 patients had atopic dermatitis. The frequency of allergic diseases in the FMF group was 8.2%. In the control group, 2 children (3.3%) were allergic, including asthma in one case and atopic dermatitis in one case. There was no statistical significance in terms of allergic diseases between the groups ($p > 0.05$). Familial atopy was detected in 10 patients in the FMF group and 5 patients in the control group. There was no statistically significant difference between the two groups ($p = 0.27$).

In the group of FMF patients, 7 patients (11.5%) had concomitant chronic diseases (obesity in two patients, asthma in two patients, inflammatory bowel disease in two patients and type 1 diabetes in one patient). In the control group, no case with chronic disease was detected. As a result of the statistical analysis, the difference between the two groups was found to be significant ($p = 0.013$).

While the average total IgE value of 59 patients in the FMF group was 72.8 Ku / L, it was 98.8 Ku / L in the control group. The difference was statistically significant ($p = 0.009$) When the eosinophil count and respiratory function test parameters (PEF, FEV1 and FVC) were compared, there was no statistically significant difference between the two groups included in the study. [Table 1]

Table 1: Comparison of total serum IgE, eosinophil, PEF, FEV1 and FVC values in FMF and control groups

	FMF **Mean±SD	Control **Mean±SD	*p
Total IgE	72,85±154,0	98,8±153,7	0.009
Eosinophil (%)	2,33±2,33	3,5±3,6	0.073
PEF (%)	71,4±20,1	78,4±34,4	0.863
FEV1 (%)	85,3±14,9	83,6±18,2	0.590
FVC (%)	76,3±19,1	80,6±16,6	0.283

Table 2: Specific IgE (cow's milk, wheat flour and egg whites) positive incidence rates in FMF and control groups

	FMF *n:61	Control *n:61	**p
Cow milk specific IgE	0 (%0)	3 (%4,9)	0.244
Egg white specific IgE	3 (%5)	11 (%18)	0.044
Wheat flour specific IgE	0 (%0)	2 (%3,4)	0.244

In the FMF patient group in which cow milk specific IgE was studied, none of the patients had cow milk specific IgE positive. In the control group, 3 patients (4.9%) were found to be sensitive to cow's milk. In the statistical study, no significant difference was found ($p = 0.44$). Egg white specific IgE was positive in 3 patients in the FMF group and in 11 patients in the control group. When the statistical analysis was done between the groups, it was found that the difference between the two

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groups was significant (p=0.044). Wheat-specific IgE was not detected in any of the 61 patients in the FMF group; In the control group, 2 patients were positive (3.4%). There was no significant difference between them (Table 2, p = 0.244).

DISCUSSION

FMF is the most common disease in the group of periodic fever syndromes, with an autosomal recessive inheritance, which is common in our country and in our region, typically with attacks with fever, abdominal pain, joint findings and skin findings. As a result of our study, we can say that allergic diseases and atopy are seen less frequently in FMF patients compared to the general population. Similarly, it has been suggested in previous studies that FMF disease is protective against allergic diseases.[9,15-18]

In the study of Saçkesen et al,[9] it was suggested that the prevalence of atopy and allergic rhinitis was less frequent in FMF patients compared to the general population. The prevalence of additional allergic diseases and familial atopy in FMF cases included in the study was found to be 6.7%. In our study, the prevalence of additional allergic diseases and familial atopy was found to be 8.2% and 16.4%, respectively. This result can be explained by the higher prevalence of atopy in our region where environmental allergens are more common. In both studies conducted by Danon et al,[16] and Özyılkan et al,[17] a significantly lower prevalence of asthma was found compared to the control group. In our study, no significant difference was found between the control and FMF groups in terms of asthma prevalence.

In the study of Yazıcı et al,[15] the prevalence of atopy was investigated by using skin prick test, serum eosinophil and IgE levels. The prevalence of atopy was found to be 5% in the FMF group and 16.3% in the healthy group. There is no significant difference between the FMF group and the control group in the percentage of eosinophils and serum total IgE levels. In the study of Saçkesen et al,[9] no significant difference was found between the groups in terms of serum total IgE levels. In our study, a statistically significant decrease in IgE level was found in the FMF group (p = 0.009). The percentage of eosinophils in the FMF group was 2.3% on average and 3.5% in the control group. However, despite the high rates of eosinophils in the control group, no significant difference was found (p = 0.07).

In our study, egg white specific IgE was found to be significantly higher in the control group compared to the FMF patient group, which is a finding that supports the study of Saçkesen et al.[9] However, in this study, specific IgEs, which are a more specific indicator of allergic disease and atopy, were not investigated, only serum total IgE level was examined. In our study, there was no difference between the wheat flour specific IgE and cow milk specific IgE levels between the control group and the FMF group. The fact that these parameters, which rank first among food allergens, are not significantly different between the groups indicates the need for more research on FMF etiopathogenesis.

In the study conducted by Demir et al,[19] small intestine biopsy was performed in 41 FMF patients with capsule endoscopy method. Mucosal damage was detected in 44% and edema in 29%. Current findings have been associated with the autoinflammatory process. In our study, chronic disease was found in 11.5% of FMF patients, and this is a result that supports this study.

CONCLUSION

In conclusion, in this study, it was observed that the frequency of atopy and allergic diseases did not increase in FMF patients. However, the low serum total IgE and egg white specific IgE levels in FMF patients suggest that atopy is less common in FMF patients. Further studies, with more cases and using more parameters to detect atopy, will provide more detailed and precise information on the subject.

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