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Adaptive ımmune system evaluation in familial mediterranean fever: clinical and ımmunological analysis

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Abstract
Background: Familial Mediterranean Fever is a common genetic autoinflammatory disease prevalent in the Mediterranean region. The clinical course of the disease is characterized by fever and serositis attacks. While defects in the innate immune system are known to play a role in the pathogenesis of the disease, the impact of the adaptive immune system remains unclear. Therefore, the main objective of this study is to analyze the adaptive immune system cells in FMF patients and investigate their relationship with the disease.
Methods: Our study includes 88 FMF patients with confirmed MEFV gene mutations. The demographic characteristics, clinical symptoms, genetic profiles, treatment methods, and any accompanying diseases of the patients were thoroughly examined. Additionally, lymphocyte subpopulations were analyzed using flow cytometry, and inflammatory markers and immunoglobulin levels were evaluated.
Results: Significant differences were observed in the distribution of adaptive immune system cells in FMF patients compared to the healthy reference group. In the analysis of lymphocyte subgroups, levels of CD3, CD4, CD19, CD16+56+, CD3CD4CD45RACD31, CD4+CD45RA+, CD8+CD45RA+, CD19+CD27+IgD+IgM+, CD19+CD27+IgD-IgM-, and CD19+CD38+CD21 were found to be lower compared to healthy individuals. Additionally, CD8, CD19+CD27-IgD+, and CD3/CD8/TCRGD cells were found to be higher. Moreover, in FMF patients with accompanying diseases, CD3, CD4, and CD19 values were statistically lower ($p<0.001$).
Conclusion: This study reveals that adaptive immune system cells are affected in FMF patients, suggesting their significant role in the disease's pathophysiology. Immunological evaluations should be prioritized in the management of FMF, enabling personalized treatment plans for more effective outcomes.

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Introduction

The European Society for Immunodeficiencies (ESID) classifies Familial Mediterranean Fever (FMF) as one of the autoinflammatory syndromes. FMF is an inherited immune disorder characterized by episodes of fever and sterile inflammation.[1] The most common mutation in this disease occurs in the 781-amino-acid segment of the MEFV gene, which encodes the immunoregulatory molecule pyrin protein. Pyrin plays a critical role in the innate immune system by interacting with caspase-1 and other inflammatory components. This interaction regulates the production of inflammatory factors such as IL-1ß and is part of the multiple protein complexes known as inflammasomes. These complexes have important functions in both the innate and adaptive immune systems.[2]

A study involving 2000 genetically confirmed FMF patients has shown frequent associations of FMF with various diseases, such as cardiovascular diseases, vasculitis, and inflammatory bowel disease.[3] These findings suggest that FMF may not only be an autoinflammatory disease but may also involve other disease processes triggered by systemic inflammation. Understanding the etiopathogenesis of FMF is crucial for the clinical improvement of patients. In this context, studies focusing on blood cells, such as erythrocyte indices, monocytes, and neutrophils, which are associated with the activity and severity of the disease, have become important in current research.[4] However, the role of lymphocytes and their subsets (T, B, NK, naive, and memory cells) in the pathogenesis of FMF has not been fully elucidated. The current literature is limited in this regard, and further investigation into this area is warranted. A detailed examination of lymphocytes and other immune cell subsets is important for understanding the complex pathology of FMF and may lead to the development of innovative approaches for the treatment and management of the disease.

In this study, we aim to evaluate the interactions of the immune system in patients diagnosed with FMF by analyzing lymphocyte subsets at our clinic.

Methods

Study population and design

A study was conducted on a total of 88 patients who were clinically diagnosed with Familial Mediterranean Fever (FMF) and underwent MEFV gene mutation analysis at the Pediatric Allergy Immunology Clinic. These patients were subsequently followed up. Detailed records of the patients' age, gender, date of diagnosis, medical history, and family history were documented. The symptoms and clinical findings of each patient at the time of admission were determined through a comprehensive physical examination and laboratory tests. The treatments received by the patients (colchicine, IVIG, and others) were thoroughly reviewed.

Within the scope of the research, peripheral blood samples obtained from the patients were analyzed for lymphocyte subset parameters, such as CD3 (T cells), CD4 (Helper T cells), CD8 (Cytotoxic T cells), CD19 (B cells), CD16+56+ (Natural killer cells), CD3CD4CD45RACD31 (New thymic emigrants), CD4+CD45RA+ (Naive T4), CD8+CD45RA+ (Naive T8), CD19+CD27-IgD+ (Naive B), CD19+CD27+IgD+IgM+ (Nonswitched B), CD19+CD27+IgD-IgM- (Switched B), CD19+CD38+CD21 low, and CD3/CD8/TCRGD using flow cytometry. Additionally, inflammatory markers and immunoglobulin levels of the patients were evaluated.

Statistical analysis

SPSS 15.0 for Windows software was used for statistical analysis. Descriptive statistics are presented as numbers and percentages for categorical variables, and as median, minimum, and maximum for numerical variables. Comparisons of numerical variables between groups were performed using Student's t-test when the normal distribution assumption was met, and the Mann-Whitney U test when it was not. Comparisons of proportions between groups were conducted using the Chi-square test. A significance level of $p<0.05$ was considered statistically significant.

Ethical approval

Our study was conducted with the approval of the Ondokuz Mayıs University Ethics Committee, the local ethics committee in the Department of Pediatrics at Ondokuz Mayıs University Faculty of Medicine, with approval number 2021000606-1. The research was initiated in accordance with the Helsinki Declaration, the Patient Rights Regulation, and general ethical principles.

Results

A total of 88 patients diagnosed with Familial Mediterranean Fever (FMF) at the Pediatric Immunology-Allergy Clinic of Faculty of Medicine were included in this study. The distribution according to age groups is as follows: 23 patients (29.41%) in the 1-4 year age range, 33 patients (42.35%) in the 5-9 year age range, 26 patients (32.35%) in the 10-18 year age range, and 2 patients (2.94%) in the 19-24 year age range. The mean age is 7 years and 7 months. The distribution of patients by gender includes 49 male patients (55.64%) and 39 female patients (44.36%). The rate of patients resulting from consanguineous marriages within the family is approximately 5.68%. The demographic characteristics of the patients are presented in Table 1, while the 24 patients with additional diseases other than FMF are listed in Table 2.

In the detailed evaluation of lymphocyte subsets in patients, median values (with minimum-maximum ranges) were examined (Table 3). These values were compared with reference values[5] from the healthy population and analyzed by separating patients into those with additional diseases (Group 1) and those without (Group 2). In Group 1, CD3, CD4, and CD19 were significantly lower ($p<0.01$) (Table 4).

When evaluating the patients' immunoglobulin levels, IgG deficiency was detected in 9.09%, IgA deficiency in 4.55%, and IgM deficiency in 5.68% of the cases.

Table 1 Demographic data of patients.

Symptoms	n	%
Fever	73	83.0
Abdominal Pain	34	38.6
Mouth Ulcer	33	37.5
Stomachache	47	53.4
Diarrhea	17	19.3
Rash	17	19.3
Fatigue	15	17.0
Loss of Appetite	14	15.9
Sore Throat	7	8.0
Headache	3	3.4
Joint Swelling	3	3.4
Constipation	4	4.5
Sweating	1	1.1
Physical Examination		
Tonsillitis	14	15.9
Urticaria	6	6.8
LAP (Lymphadenopathy)	5	5.7
HSM (Hepatosplenomegaly)	2	2.3
Arthritis	1	1.1
Heart Murmur	1	1.1
Serous Fluid in Ear	1	1.1
Hemangioma	1	1.1
Ptosis (Drooping Eyelid)	1	1.1
Diaper Dermatitis	2	2.3
Acid	1	1.1
Consanguinity		
None	83	94.3
Present	5	5.7
Family History		
None	83	94.3
Both Parents FMF	1	1.1
Both Parents + Sibling FMF	1	1.1
Mother + Sibling FMF	1	1.1
Sibling FMF	2	2.3
Treatment		
Colchicine	86	97.7
IVIG	20	22.7
Deposalin	17	19.3
Steroid	11	12.5
Trimethoprim	10	11.4
Colchicine Resistance		
None	87	98.9
Present	1	1.1
Surgery		
None	80	90.9
Appendectomy	1	1.1
Appendectomy + Adenoidectomy	1	1.1
Appendectomy + Adenoidectomy + Inguinal hernia op.	1	1.1
Adenoidectomy	3	3.4
Inguinal hernia op.	1	1.1
Ileus attack	1	1.1

Table 2 Other diseases.

Other diseases	N:24
Common variable immunodeficiency (CVID)	3
Unknown cause immunodeficiency	2
Asthma + IgA deficiency	2
Autoimmune lymphoproliferative syndrome (ALPS)	1
Autoimmune neutropenia	1
ADHD + hypogammaglobulinemia	1
Bronchiectasis	1
Ulcerative colitis	1
Severe combined immunodeficiency (SCID)	1
Hypogammaglobulinemia	1
PFAPA + hypogammaglobulinemia	1
Mevalonate kinase deficiency (MVK)	1
Vitiligo + IgA deficiency	1
Duchenne muscular dystrophy (MD)	1
Kabuki syndrome	1
X-linked chronic granulomatous disease (X-CGD)	1
Mastocytosis	1
Celiac disease + hypogammaglobulinemia	1
Down syndrome + hypogammaglobulinemia	1
Osteomyelitis	1

Table 3 Immunological profile values according to lymphocyte subsets in FMF patients.

Lymphocyte subset	Total%	Median % (Min-Max)
CD3 (T cell)	69	39-94
CD4 (helper T cell)	37.5	14-61
CD8 (cytotoxic T cell)	29	11-72
CD19 (B cell)	13	3-39
CD16+56+ (natural killer cell)	9.5	2-52
CD3CD4CD45RACD31 (recent thymic emigrant)	38	1-62
CD4+CD45RA+ (naive T4)	47	7-88
CD8+CD45RA+ (naive T8)	48	6-100
CD19+CD27-IgD+ (naive B)	80	40-99
CD19+CD27+IgD+IgM+ (non-switched memory B)	7	1-42
CD19+CD27+IgD-IgM- (switched memory B)	7	1-28
CD19+CD38+CD21 low	4	0-13
CD3/CD8/TCRGD	21	3-50

Table 4 Comparison of values of lymphocyte subsets between healthy reference (5) and groups with and without additional diseases.

n		Total		Group 1		Group 2		
		%	n	%	n	%	p	
CD3 (T cell)	Normal	76	86,4	18	75,0	58	90,6	**0,022**
	Low	9	10,2	3	12,5	6	9,4	
	High	3	3,4	3	12,5	0	0,0	
CD4 (helper T cell)	Normal	78	88,6	19	79,2	59	92,2	**0,032**
	Low	7	8,0	5	20,8	2	3,1	
	High	3	3,4	0	0,0	3	4,7	
CD8 (cytotoxic T cell)	Normal	75	86,2	18	75,0	57	90,5	0,157
	Low	2	2,3	1	4,2	1	1,6	
	High	10	11,5	5	20,8	5	7,9	
CD19 (B cell)	Normal	37	82,2	9	64,3	28	90,3	**0,009**
	Low	6	13,3	5	35,7	1	3,2	
	High	2	4,4	0	0,0	2	6,5	
CD16+56+ (natural killer cell)	Normal	41	89,1	11	78,6	30	93,8	0,186
	Low	3	6,5	2	14,3	1	3,1	
	High	2	4,3	1	7,1	1	3,1	
CD3CD4CD45RACD31 (recent thymic emigrant)	Normal	21	53,8	5	41,7	16	59,3	0,309
	Low	18	46,2	7	58,3	11	40,7	
CD4+CD45RA+ (naive T4)	Normal	25	62,5	6	50,0	19	67,9	0,269
	Low	13	32,5	6	50,0	7	25,0	
	High	2	5,0	0	0,0	2	7,1	
CD8+CD45RA+ (naive T8)	Normal	25	59,5	8	66,7	17	56,7	0,763
	Low	14	33,3	4	33,3	10	33,3	
	High	3	7,1	0	0,0	3	10,0	
CD19+CD27-IgD+ (naive B)	Normal	29	65,9	8	57,1	21	70,0	0,339
	Low	1	2,3	1	7,1	0	0,0	
	High	14	31,8	5	35,7	9	30,0	
CD19+CD27+IgD+IgM+ (nonswitched memorry B)	Normal	34	81,0	10	71,4	24	85,7	0,354
	Low	7	16,7	3	21,4	4	14,3	
	High	1	2,4	1	7,1	0	0,0	
CD19+CD27+IgD-IgM- (switched memory B)	Normal	26	61,9	11	78,6	15	53,6	0,116
	Low	16	38,1	3	21,4	13	46,4	
CD19+CD38+CD21 low	Normal	24	68,6	7	63,6	17	70,8	0,470
	Low	10	28,6	3	27,3	7	29,2	
	High	1	2,9	1	9,1	0	0,0	
CD3/CD8/TCRGD	Normal	19	44,2	8	57,1	11	37,9	0,235
	High	24	55,8	6	42,9	18	62,1	

Furthermore, among inflammatory markers, the proportion of patients with negative ANA was 32.26%, +1 was 9.68%, +2 was 12.90%, and +3 was 9.68%.

Discussion

Familial Mediterranean Fever (FMF) is classified as a genetically transmitted and congenital immune system anomaly. The pathogenesis of FMF is associated with mutations in the FMF gene. This gene encodes pyrin, a protein that regulates a cellular death process known as pyroptosis.[6] Pyroptosis facilitates the controlled death of infected or damaged cells in the body. Pyrin regulates this process to maintain inflammation under control. Mutations in the FMF gene can disrupt the function of pyrin, leading to uncontrolled inflammatory responses and the typical symptoms of FMF.

Among the characteristic features of the disease are fever, abdominal pain, chest pain, and arthritis.[7] In our study, the most common clinical symptoms observed in patients were fever (83%), recurrent abdominal pain (53.4%), joint pain (38.6%), and oral ulcers (37.5%).

Studies on the pathophysiology of Familial Mediterranean Fever (FMF) indicate that the disease primarily affects the innate immune system.[8] The adaptive immune system is a part of the immune system that develops specific responses to antigens and possesses memory. It typically develops after infection and functions through specific antibodies and T cells. Research on the impact of FMF on the adaptive immune system has yet to yield definitive results. Therefore, understanding the role of the

adaptive immune system in FMF pathogenesis can be more thoroughly elucidated through future research.[9] This will contribute to a better understanding of the disease and the development of effective treatment methods. In this study, we aimed to investigate changes in the adaptive immune system in FMF by measuring the levels of peripheral blood lymphocyte subsets using flow cytometry.

In comparison to healthy control references, we observed significant changes in T cell and B cell subsets.[5] In our study, we found decreased levels of CD3, CD4, CD19, CD16+56+, CD3CD4CD45RACD31, CD4+CD45RA+, CD8+CD45RA+, CD19+CD27+IgD+IgM+, CD19+CD27+IgD-IgM-, and CD19+CD38+CD21 cells, while CD8, CD19+CD27-IgD+, and CD3/CD8/TCRGD cell levels were higher compared to healthy controls. Additionally, in the study by Musabak et al., it was found that CD3, CD4, and CD8 levels were increased in FMF patients compared to the control group.[10] T-cell subsets and interleukin (IL)-1 and IL-2 production were examined in 39 patients and 14 controls. The study results showed no change in total T-cell and B-cell counts in FMF patients, but a significant decrease in suppressor T-cell and helper T-cell counts, and an increase in NK cells were observed.[11]

Naive T cells (T lymphocytes) are T cells that have not yet encountered and been activated by an antigen. Naive T cells reside in lymphoid organs and enter the activation process upon encountering an antigen. They are divided into two main subsets: Naive T4 (CD4+) and Naive T8 (CD8+) cells.[12] In our study, Naive T4 was found to be low in 36% of patients, while Naive T8 was low in 34% of patients. However, no data could be found in the literature regarding the effects of these cells on FMF pathophysiology, and their roles remain not fully understood. Current research on T cells and their subsets, especially focusing on Regulatory T Cells (T-regs) in FMF, has gained emphasis.[13] A study indicating the critical importance of these cells in maintaining immune tolerance and their potential association with FMF pathogenesis suggests a potential impact of regulatory T cells in controlling inflammatory responses. Additionally, the percentage of T-reg cells and Foxp3 expression have been evaluated in FMF patients, comparing the results with those of healthy controls, FMF remission status, and the onset and progression of attacks. An increase in regulatory T cell numbers after FMF attacks has been observed, peaking 7 days after the onset of attacks. These findings suggest a potential role of T-reg cells in terminating attacks in FMF patients.[14]

Another study indicates that peripheral T cell populations are differently affected in FMF, chronic granulomatous disease, and gout patients.[15] In this study, the distribution of various T cell subsets (e.g., CD3+, CD4+, CD8+ cells) and activation markers (e.g., CD38, CD69) were examined, emphasizing the role of these changes in the pathophysiology of the disease. Additionally, another study focusing on the polarization of Th17 cells in FMF patients has suggested that these cells may play a significant role in the pathophysiology of FMF. Evidence has been presented regarding the involvement of Th17 cell polarization in the inflammatory process of FMF.[16]

FMF is a disease characterized by attacks, and inflammatory markers in blood tests become prominent during these periods. However, even during periods without attacks, abnormal activations in activation markers such as CD25 and CD69 on CD3+ T cells have been detected in FMF patients. This suggests that the T cell system remains abnormally active during both attack and non-attack periods in these patients. Furthermore, the low levels of IL-10 in these patients may contribute to a tendency for continuous low-level immune activation. This study suggests that FMF is not limited to attack periods alone and may be associated with a continuous state of immune activation.[10] Although we could not examine lymphocyte activation tests in our patients, we believe this issue should be addressed in future studies.

In our study, NK cell levels were found to be low. Natural Killer (NK) cells are known to be cytotoxic lymphocytes involved in innate immunity. In addition to their cytotoxic responses, these cells produce cytokines to support adaptive immune responses. While Kholoussi and colleagues found that CD3, CD4, and CD8 were statistically increased in the patient group compared to the normal control group, CD16 was statistically decreased.[17] Some medications used in the treatment of FMF (e.g., colchicine) may affect NK cell functions. Treatment may modulate inflammatory responses by influencing NK cell activation and cytokine production.[18] All of our patients in the study were taking colchicine. Therefore, the cause of NK cell deficiency was considered to be both the disease itself and the medication they were taking.

In FMF patients, an increase in proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α) and their potential to exacerbate inflammatory responses are well known. In one study, it was found that even during non-attack periods in Familial Mediterranean Fever (FMF) patients, the mRNA levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8) were elevated. These cytokines were found to be higher in circulating leukocytes and showed a significant difference compared to controls. These results suggest the presence of continuous low-grade inflammation even during inter-attack periods in FMF patients.[19] However, due to our limitations, we were unable to conduct cytokine tests.

In our study, among the treatment protocols for patients, in addition to colchicine, some were receiving steroids and IVIG. In the group using steroids, it was observed that CD3 values were low, as expected. In the group receiving IVIG, CD3 and CD19 values were found to be low compared to normal references, which is associated with immunodeficiencies. Moreover, a statistically significant difference was found between the groups receiving IVIG and those not receiving it ($p=0.0001$). This may be due to the referral of patients with a history of frequent infections and suspected immunodeficiency to our clinic. Additionally, some of our patients had concomitant immunodeficiency-related diseases.

This research indicates that FMF patients may not only have disorders in the innate immune system but also significant changes in T and B lymphocyte subsets associated with the adaptive immune system. With the use of targeted therapies in autoinflammatory diseases, a more in-depth evaluation of the pathophysiology of the disease could lead to the development of new personalized treatment options. This study also emphasizes that the immunological disorders present in these patients may be associated with other underlying immune system conditions.

Authors Contrıbutıon

SİKK: conceptualized and designed the study. FE, ZGG: conducted data collection and analysis. AY: supervised the study and provided critical revisions. All authors contributed to the writing of the manuscript, interpreted the results, and gave final approval. All authors are responsible for the accuracy and integrity of the work.

Conflıct of Interest

The authors declare no conflict of interest.

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