Familial Mediterranean Fever and Accompanying Inflammatory Diseases: Effects on the Disease Severity Score

Ailevi Akdeniz Ateşine Eşlik Eden İnflamatuar Hastalıklar ve Hastalık Ağırlık Skoruna Etkisinin Değerlendirilmesi

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) stands as the most prevalent autoinflammatory disorder in childhood. It is well-established that certain inflammatory conditions may accompanying with FMF. Within the scope of our research, we examined the inflammatory diseases accompanying FMF and their possible effects on the course of the disease in pediatric FMF patients.

Material and Methods: We retrospectively reviewed the medical records of 349 patients diagnosed with FMF based on the diagnostic criteria, who were followed between January 1, 2015, and December 31, 2020. The effect of inflammatory diseases associated with FMF on the Pras disease severity score was investigated.

Results: Among the patients included in the study, 45.85% exhibited mild disease, 42.98% had moderate disease, and 11.17% had severe disease. Among the study participants, 16% were found to have accompanying inflammatory diseases. Specifically, IgA vasculitis was present in 5.73% of cases, sacroiliitis in 3.72%, prolonged febrile myalgia in 2.00%, acute rheumatic fever in 1.71%, juvenile idiopathic arthritis in 0.85%, polyarteritis nodosa in 0.57%, inflammatory bowel diseases in 0.85%, Behçet's disease in 0.28%, recurrent optic neuritis in 0.28%. In some cases, more than one inflammatory disease has been observed in addition to FMF. It was observed that the disease severity score was higher in patients with accompanying inflammatory diseases (p=0.04). Additionally, the rate of severe disease was found to be increased in patients with accompanying inflammatory diseases (17.31%) (p=0.02).

Conclusion: Our study demonstrated that accompanying inflammatory diseases increase the disease severity score and the clinical severity of FMF. Furthermore, patients with accompanying inflammatory diseases showed higher erythrocyte sedimentation rate values during attack-free periods and an increased use of biological agents.

Key Words: Biological Agent, Disease Severity Score, Familial Mediterranean Fever, Inflammatory Diseases

ÖZ

Amaç: Ailevi Akdeniz ateşi (AAA), çocukluk döneminde en sık görülen otoinflamatuar hastalıktır. Bazı inflamatuar hastalıkların AAA'ya eşlik edebildiği bilinmektedir. Çalışmamızda AAA tanılı hastalarda eşlik eden inflamatuar hastalıkları ve hastalık seyrine etkilerini inceledik.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The research received approval from the Health Sciences University Ankara Children's Hematology and Oncology Training and Research Hospital Ethics Committee under the decision number 2019-069 dated March 25, 2019.

Contribution of the Authors / Yazarların katkısı*: *İNCE YE: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***KARAGÖL C:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***ÇELİKEL ACAR B:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Gereç ve Yöntemler: 1 Ocak 2015-31 Aralık 2020 tarihleri arasında klinik tanı kriterlerine göre AAA tanısı ile takip edilen 349 hastanın tıbbi kayıtları geriye dönük incelendi. AAA ile birliktelik gösteren inflamatuar hastalıkların Pras hastalık ağırlık skoruna etkisi araştırıldı.

Bulgular: Çalışmaya dâhil edilen hastaların %45.85'inde hafif, %42.98'sinde orta ve %11.17'inde ağır hastalık mevcuttu. Çalışmaya dâhil edilen hastaların %16'sında eşlik eden inflamatuar bir hastalık tespit edildi (%5.73 IgA vasküliti, %3.72 sakroileit, %2 uzamış febril miyalji, %1.71 akut romatizmal ateş, %0.85 juvenil idiyopatik artrit %0.57 poliarteritis nodosa, %0.85 inflamatuar barsak hastalıkları, %0.28 Behçet hastalığı, %0.28 tekrarlayan optik nörit). AAA'ya eşlik eden birden fazla inflamatuar hastalığın olduğu durumlar mevcuttu. Hastalık ağırlık skorunun, eşlik eden inflamatuar hastalığı olanlarda olmayanlara göre yüksek olduğu bulundu (p=0.040). Ek olarak eşlik eden inflamatuar hastalığı olan hastalarda ağır hastalık görülme oranının (%17.31) arttığı görüldü (p=0.020).

Sonuç: Çalışmamızda eşlik eden inflamatuar hastalıkların AAA hastalığı ağırlık skorunu yükselttiği, ağırlık şiddetini artırdığı, bu hastalarda ataksız dönemdeki eritrosit sedimentasyon hızı değerlerinin yüksek seyrettiği ve biyolojik ajan kullanımının arttığı gösterilmiştir.

Anahtar Sözcükler: Biyolojik Ajan, Hastalık Ağırlık Skoru, Ailevi Akdeniz Ateşi, İnflamatuar Hastalık

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease in childhood. It is characterized by recurrent attacks marked by fever, abdominal pain, joint pain, chest pain, and erysipelas-like erythema (ELE) (1).

The disease is caused by mutations in the MEFV gene, which encodes the pyrin protein involved in regulating inflammation (2). The most frequent mutations observed in our country are M694V, M680I, and V726A. It is known that M694V reflects the most severe clinical phenotype (3,4). Colchicine effectively controls the recurrent attacks of the disease. The use of colchicine has a dramatic impact on the course of the disease and prevents an increase in the number of patients with renal amyloidosis. In cases of colchicine resistance, biologic agents can be used (5-7).

It is well-established that certain inflammatory diseases can accompany with FMF. Investigating the possible accompanying diseases in FMF patients is essential to understand their clinical impact, determine if they share a common etiological pathway, and identify potential common treatment approaches. In particular, diseases such as IgA vasculitis, sacroiliitis, juvenile idiopathic arthritis (JIA), polyarteritis nodosa (PAN), inflammatory bowel diseases (IBD), prolonged febrile myalgia (PFM), acute rheumatic fever (ARF), and Behçet's disease can be seen alongside FMF (8). Accompanying diseases may adversely affect the quality of life of FMF patients and could be related to disease severity.

In our study, we aimed to evaluate the frequency of accompanying inflammatory diseases in FMF patients. We also evaluated the relationship between the presence of accompanying inflammatory diseases and the patients' mutations, disease severity, and colchicine resistance.

MATERIALS and MATERIALS

In this study, we retrospectively examined the medical records of 349 FMF patients according to the Yalçınkaya-Özen diagnostic criteria (5). The data were collected from January 2015 to December 2020 at the Pediatric Rheumatology Clinic of the Health Sciences University Ankara Children's Hematology and Oncology Training and Research Hospital. Patients who had not undergone mutation analysis, were followed up for less than 6 months, or had incomplete file data were excluded from the study. The research received approval from the Health Sciences University Ankara Children's Hematology and Oncology Training and Research Hospital Ethics Committee under the decision number 2019-069 dated March 25, 2019.

Patient characteristics including age at diagnosis and follow-up duration, family history, mutations, accompanying inflammatory diseases, time of onset of FMF in relation to the accompanying condition, colchicine dosage (mg/kg/day), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) during the attack-free period, yearly attack frequency before and after colchicine treatment, use of biologic agents in treatment, and treatments for accompanying inflammatory diseases were retrospectively reviewed. The Pras et al.(10) disease severity score was used to assess disease severity, and information related to disease onset age, monthly attack frequency, arthritis, ELE, amyloidosis, and colchicine dosage was analyzed (9).

The accompanying inflammatory diseases recorded in the study included IgA vasculitis, sacroiliitis, JIA, PAN, IBD [ulcerative colitis (UC), Crohn's disease (CD)], PFM, ARF, Behçet's disease, and ON.

Genetic mutations were grouped as M694V heterozygous, M694V homozygous, non-M694V homozygous, and non-M694V heterozygous, M694V compound heterozygous, as well as mutation-negative cases. This classification was designed with the aim of assessing the clinical implications of the M694V mutation, a mutation known to be associated with severe disease, in a subgroup-specific manner. The use of biologic agents for FMF treatment and the specific biologic agents used were queried.

The Pras et al. (10) disease severity score was categorized as mild (score 3-5), moderate (score 6-8), and severe (score 9 and above) (9) (Table I).

Statistical analysis was conducted using SPSS 23.00 software (IBM SPSS Statistics for Windows, Version 22.0, Armork, NY, USA). Descriptive statistics such as mean, standard deviation,

Table I: Severity score by Pras et al. (10) modified for children.

Parameter	Features	Score
Age of onset (years)	11-20	2
	6-10	3
	<6	4
Number of attacks per month	<1	1
	1-2	2
	>2	3
Arthritis	Acute	2
	Protracted	3
Erysipelas-like erythema		2
Amyloidosis		3
Dose of colchicine	Less than appropriate* dose	0
	Appropriate dose	1
	More than appropriate dose	2

minimum, maximum, percentage, and frequency were used for parametric and non-parametric data. The chi-square test was used for comparisons of categorical data. If significant results were observed in the chi-square test, the group responsible fort he difference was identified with a post-hoc multiple comparasion test. Independent sample t-tests were employed for binary group comparisons of parametric data, while ANOVA test was used for comparisons involving three or more groups. The critical significance level was set at 0.050 for all analyses.

RESULTS

Demographic characteristics:

Out of the 349 patients included in the study, 182 (52.14%) were female, and 167 (47.86%) were male. The mean age at diagnosis was 7.43±3.77 years, and the mean follow-up duration was 5.93±3.60 years. In 304 patients (87.11%), a clinically significant genetic mutation was detected in the MEFV gene, either homozygous, compound heterozygous, or heterozygous (Table II).

Disease severity and applied treatments:

The patients were grouped based on their disease severity scores, with 160 (45.85%) classified as having mild severity, 150 (42.98%) as moderate, and 39 (11.17%) as severe disease. The median ages for patients with mild, moderate, and severe disease were 8.63 years, 6.62 years, and 5.58 years, respectively. Patients with mild disease had a statistically significantly higher median age compared to those with moderate and severe disease (p=0.039).

All patients with FMF diagnosis were on colchicine treatment. Among them, 329 patients (94.26%) responded to colchicine, while 20 (5.74%) were colchicine-resistant and required the use of biologic agents alongside colchicine. It was observed that patients using biologic agents had significantly higher ESR levels (p=0.012), but there was no statistically significant difference in CRP values (p=0.532).

Association between accompanying inflammatory diseases and disease severity:

Out of the 349 patients, 52 (14.89%) had accompanying inflammatory diseases. The occurrence rates of accompanying inflammatory diseases are listed in Table III. IgA vasculitis was the most common accompanying disease with FMF, present in 20 patients (38.46%). Among these patients, 11 were diagnosed with IgA vasculitis before FMF, five were diagnosed with FMF before IgA vasculitis, and four were diagnosed simultaneously with both conditions.

Among the 20 patients with both IgA vasculitis and FMF, two had prolonged febrile myalgia, and one had sacroiliitis as accompanying diseases. One patient with accompanying FMF and ulcerative colitis also had sacroiliitis.

Upon analyzing disease severity scores, patients with accompanying inflammatory diseases had significantly higher scores (6.37±1.90) compared to those without accompanying inflammatory diseases (5.79±1.71) (p=0.038). Patients with accompanying inflammatory diseases had a higher proportion of severe disease (n=9, 17.30%), whereas patients without accompanying diseases had a higher proportion of mild disease (n=143, 48.14%) (p=0.019) (Table IV).

In patients with accompanying inflammatory diseases, 9 (17.30%) had an ESR value >20 mm/hour during the attack-free period, while this was observed in 17 patients (5.72%) without accompanying inflammatory diseases. The ESR levels during the attack-free period were significantly higher in patients with accompanying inflammatory diseases (p=0.011).

The average colchicine dose was 0.026±0.023 mg/kg in patients with accompanying inflammatory diseases and 0.029±0.011 mg/kg in patients without accompanying inflammatory diseases, with no statistically significant difference (p=0.310). The use of biologic agents was significantly higher in patients with accompanying inflammatory diseases (11.51%) (p=0.041).

Table II: Mutation Groups

Accompanying inflammatory diseases	None	M694V heterozygous	M694V homozygous	M694V compound heterozygous	non-M694V heterozygous	non-M694V homozygous	p
No*	41(13.80)	50 (16.83)	74 (24.91)	59 (19.86)	34 (11.44)	39 (13.13)	0.51†
Yes*	4 (7.69)	8 (15.38)	14 (26.92)	15 (28.84)	7 (13.46)	4 (7.69)	0.51†

** n(%), †Chi-square test was performed*

Table III: The occurrence rates of accompanying inflammatory diseases

Accompanying inflammatory diseases	of patients with accompanying inflammatory diseases*	of all patients*
IgA vasculitis	20 (38.46)	20 (5.73)
Sacroiliitis	13 (25.00)	13 (3.72)
Acute Rheumatic Fever	6 (11.53)	6 (1.71)
Prolonged Febrile Myalgia	7 (13.46)	7 (2.00)
Juvenile Idiopathic Arthritis	3 (5.76)	3 (0.85)
Poliarteritis Nodosa	2 (3.84)	3 (0.57)
Ulcerative Colitis	2 (3.84)	2 (0.57)
Crohn Disease	1 (1.92)	1 (0.28)
Behçet's Disease	1 (1.92)	1 (0.28)
Recurrent Optic Neuritis	1 (1.92)	1 (0.28)

**n (%)*

Table IV: The Relationship Between the Presence of Accompanying Inflammatory Disease and Disease Severity

FMF with Accompanying Inflamatory Disease	Disease Severity			p
	Mild	Moderate	Severe	
No*	143 (48.14.9	125 (42.08)	29 (9.76)	0.020†
Yes*	17 (32.69)	26 (50.00)	9 (17.31)	0.020†

**n (%), †Chi-square test was performed*

DISCUSSION

In this study, it was demonstrated that approximately 16% of FMF patients had an accompanying inflammatory disease, with IgA vasculitis being the most frequent among them. In FMF patients with accompanying inflammatory diseases, it was observed that there were higher ESR levels during the attack-free period and a higher of severe illness.

Familial Mediterranean fever is considered the prototype of autoinflammatory diseases resulting from dysregulations in the innate immune system. Identifying accompanying inflammatory diseases associated with this condition will enable the implementation of the most appropriate patient care by evaluating common points in their pathogenesis and treatment options. This study revealed a significant occurrence rate of approximately 16% for accompanying inflammatory diseases. In another study conducted in our country with 686 patients, the rate of accompanying inflammatory disease was found to be 18.9% (8). Yet another study from our country reported this rate as 12.8% (11). In both studies, vasculitis, IBD, sacroiliitis, and JIA were prominent. Among the diseases identified in association with FMF in our study, IgA vasculitis was the most common. In cases where the course of IgA vasculitis is more severe than expected, the possibility of accompanying FMF should be considered. Detailed anamnesis for diagnosis and MEFV gene analysis in suspected cases direct towards FMF diagnosis. In a study published in 1997 with 207 FMF patients, the frequency of IgA vasculitis was reported as 7% (12). IgA vasculitis is the most common initial diagnosis in over half of the patients. Cattan et al. (12), in 2004, reported that IgA vasculitis is frequently the initial diagnosis in the accompanying of both diseases and suggested that MEFV mutation analysis should be performed on patients diagnosed with IgA vasculitis in regions where FMF is common (13). Although the clinical manifestations of FMF start earlier, the more dramatic course of IgA vasculitis necessitates an earlier diagnosis. If IgA vasculitis presents with more severe symptoms than expected or if symptoms like rash and abdominal pain persist for an extended period, the possibility of accompanying FMF should be considered. In our study, three FMF patients were found to have other inflammatory diseases, and among them, IgA vasculitis was the most common. PFM was observed in association with IgA vasculitis in two patients, and sacroiliitis was seen in one patient on the background of FMF.

Poliarteritis nodosa is another vasculitis that can be accompanying with FMF. The prevalence of PAN is 9 per 1.000.000 adults. Several studies have highlighted the importance of variations in the MEFV gene as a significant susceptibility factor for PAN. In a study conducted by Tunca et al. (3) in 2005 with 2.838 patients, this rate was found to be 0.9%, and in another study by Barut et al. (1), it was 0.3%. Our study and other studies in the literature demonstrate an increased frequency of PAN in FMF patients (14). FMF and PAN can present with similar clinical manifestations, such as fever and abdominal pain. Therefore, diagnosing PAN in FMF patients can be challenging, and clinicians should have a high awareness of PAN in cases of fever and severe abdominal pain that exceed the typical attack duration for FMF. Vasculitis such as IgA vasculitis and PAN may be associated with inadequately controlled inflammation due to FMF. Although prolonged febrile myalgia is defined as a condition seen in FMF, it is more often considered as a vasculitic syndrome accompanying FMF (15). In a study on diseases associated with FMF, PFM was reported in 1.4% of patients (16). In our current study, PFM was observed in 2.00% of FMF patients.

Behçet's disease was another disease investigated in association with FMF. In a study by Schwartz et al. (17) involving 4,000 FMF patients, this rate was 0.9%, and another study reported a rate of 0.14% for Behçet's disease among 686 FMF patients (9). Behçet's disease is seen in our country at a rate of 1-3 per 10,000 individuals (17). The relationship between Behçet's disease and FMF is not as clearly understood as in other vasculitides, and further studies are needed in this regard (18).

It is known that the frequency of sacroiliitis increases in FMF. However, in some cases, it is challenging to distinguish whether sacroiliitis develops secondary to FMF or if it is part of enthesitis-related arthritis. The age of disease onset, clinical presentation,

ocular findings, and HLA B27 or MEFV gene analysis can be helpful in making this distinction. All sacroiliitis patients included in our study were distinguished from FMF-related sacroiliitis by the presence of HLA-B27 positivity, enthesitis, or uveitis. In our study, sacroiliitis was the second most common accompanying inflammatory disease. Additionally, one patient was diagnosed with sacroiliitis in association with IgA vasculitis, and another patient was diagnosed with sacroiliitis in association with ulcerative colitis (UC). In a study involving 392 patients, the rate of sacroiliitis in FMF patients was found to be 1.7% (19).

Inflammatory bowel diseases are another inflammatory disease that can accompanying with FMF (20). In our study, one of the patients with FMF had CD, and two had UC. One patient diagnosed with UC also had sacroiliitis. In a study presenting accompanying diseases, the rate of IBD in FMF patients was found to be 0.8% (21). Similar studies have reported the incidence of IBD-FMF accompanying as 1.45% and 1.16% (9). A study focusing on the frequency of IBD in FMF patients reported that the accompanying disease rate was higher than the prevalence of the individual diseases (20).

It is known that ARF can also accompanying with FMF . In a study conducted by Balcı-Peynircioğlu et al. (21) in 2015, this accompanying rate was found to be approximately 0.8%. The prevalence of ARF in our country was reported as 21 per 100,000 individuals in the most comprehensive study conducted between 2000 and 2009 (16). It should be noted that the Modified Jones criteria were revised in 2015, and the current prevalence may be higher. As arthritis is prominent in both diseases, correct diagnostic approaches for both conditions are crucial to demonstrate their accompanying and to avoid diagnostic challenges.

In some FMF patients, multiple inflammatory diseases were observed to co-occur. The presence of FMF-IgA vasculitis-sacroiliitis, FMF-sacroiliitis-UC and FMF-IgA vasculitis-PFM indicates the presence of more than one disease with FMF on the basis of inflammation.

In our study, there was no significant relationship between patients' mutations and the development of accompanying inflammatory diseases. However, the presence of at least one M694V mutation in patients with accompanying inflammatory disease is similar to the data in the literature. Ayaz NA. et al. (16) reported a rate of 72% in a study with 1687 patients.

Patients with accompanying inflammatory diseases had significantly higher disease severity scores compared to the group without accompanying diseases. When evaluating disease severity, the rate of severe disease was higher in patients with accompanying inflammatory disease and statistically significantly lower in patients without accompanying disease. Recently, a study with 1687 patients also indicated that accompanying conditions may be associated with disease severity (16). This relationship will guide clinicians in the clinical follow-up and treatment of FMF patients with accompanying inflammatory diseases. In cases of severe FMF grouped as severe disease, consideration should be given to possible accompanying inflammatory diseases that may develop and not conform to the course of FMF. Additionally, patients with accompanying inflammatory diseases during the attack-free period had significantly higher ESR levels. These parameters routinely used in the diagnosis and follow-up of FMF also provide insight into subclinical inflammation (22). Investigating the possible presence of other diseases that may cause subclinical inflammation in these patients can prevent unnecessary escalation of colchicine dosage.

In our study, no significant relationship was found between the presence of accompanying inflammatory diseases and the dosage of colchicine in FMF patients. However, patients with accompanying inflammatory diseases showed significantly higher rates of using biological agents. The response to colchicine dosage was not associated with the presence of accompanying inflammatory diseases in patients responding to colchicine. However, colchicine-resistant patients are at risk for the development of other inflammatory diseases. We believe that patients using biological agents, i.e., colchicine-resistant patients, need to be monitored for other inflammatory diseases.

The main limitation of this study is its retrospective and single-center design. Nevertheless, this study is important in drawing attention to the possible presence of accompanying inflammatory diseases in patients with FMF, the most common autoinflammatory disease in our country, where severe disease and high ESR during the attack-free period were observed.

In conclusion, various inflammatory diseases, including IgA vasculitis, sacroiliitis, and PFM, can accompanying in FMF patients. Accompanying inflammatory diseases can increase the disease severity score and severity of FMF, leading to higher ESR values during the attack-free period in these patients. The presence of an additional inflammatory disease alongside FMF may contribute to the severity of the disease, and the use of biological agents may be considered during follow-up.

The clinicians should be aware of the possibility of accompanying inflammatory diseases and the potential impact on disease severity in FMF patients. Close monitoring of FMF patients for potential inflammatory diseases, especially those using biological agents or resistant to colchicine, is crucial to provide appropriate management and ensure better patient outcomes.

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