ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Do Pediatric Patients with Familial Mediterranean Fever who have Phenotypically Predominant Arthritis, Arthralgia, and Myalgia Reflect a More Serious Underlying Disease than Those with Phenotypically Predominant Abdominal Pain?

Tekrarlayan Artrit, Artralji, Miyalji Fenotipinin Ön Planda Olduğu Ailevi Akdeniz Ateşi Olan Çocuklar Peritoneal Fenotipin Ön Planda Olduğu Çocuklara Göre Farklı Özellikler Gösteriyor mu?

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ABSTRACT

Aim: *The study aimed to determine the presence of different demographic, familial, clinical, laboratory, and genotypic characteristics between children with Familial Mediterranean Fever (FMF) with recurrent arthritis, arthralgia, and myalgia phenotype and children with FMF with recurrent abdominal attacks phenotype.*

Material and Method: *The study included patients who were admitted to the Pediatric Rheumatology Outpatient Clinic of the Kafkas University Research Hospital before 2020, who were diagnosed with FMF and followed up for at least 1 year, and who were diagnosed with clinically recurrent arthritis, arthralgia, myalgia, and recurrent abdominal pain. Patients were divided into two groups: 151 patients with recurrent arthritis, arthralgia, and myalgia with FMF phenotypic features (Group 1) and 102 patients with recurrent diffuse, incomplete peritoneal involvement with predominant FMF phenotypic features (Group 2). The demographic and familial characteristics, age at diagnosis, and other clinical, laboratory, and genetic features of these 2 groups were compared, and the differences were statistically evaluated.*

Results: *While 60.6% of the patients in Group 1 and 39.4% in Group 2 were female, 58.7% of the patients in Group 1 and 41.3% in Group 2 were male. No significant statistical difference was found between the two groups. When the groups were compared regarding genetic mutations, M694V homozygotes were observed in 17.2% of Group 1 and 8.8% of Group 2. There was a statistically significant difference between Group 1 and Group 2 in M694V homozygotes ($p<0.05$)*

Conclusion: *Patients with FMF with predominant recurrent arthritis, arthralgia, and myalgia tended to be diagnosed at an older age and exhibited more frequent symptoms such as pallor and nausea compared to patients with FMF who predominantly had peritoneal involvement. Furthermore, pleural involvement was frequently observed, and the co-occurrence with the homozygous M694V mutation was genotypically high.*

Key words: *familial Mediterranean fever; arthritis; arthralgia; myalgia; involvement*

ÖZET

Amaç: *Tekrarlayan artrit, artralji, miyalji fenotipinin ön planda olduğu Ailevi Akdeniz Ateşi (AAA) olan çocuklar ile tekrarlayan yaygın ve inkomplet abdominal atakların ön planda olduğu AAA'li çocuklar arasında farklı demografik, ailesel, klinik, laboratuvar, genotipik özelliklerin olup olmadığını değerlendirmekti.*

Materyal ve Metod: *Kafkas Üniversitesi Araştırma Hastanesi Çocuk Romatoloji polikliniğine2020 yılından önce başvuran AAA tanısı alıp en az bir yıl takip ettiğimiz hastalarımız arasından klinik olarak tekrarlayan artrit, artralji, miyaljisinin ön planda olduğu hastalar ile tekrarlayan karın ağrısının ön planda olduğu hastalar çalışma kapsamına alındı. Hastalar tekrarlayan artrit, artralji, myalji tutulumun var olduğu AAA TİPİ fenotipik özelliği öncelikli gösteren 151 hasta (Grup1) ve tekrarlayan yaygın, inkomplet peritoneal tutulumun var olduğu AAA tipi fenotipik özelliğini baskın olarak gösteren 102 (Grup2) hasta olarak iki gruba ayrıldı. Bu 2 grubun demografik, ailesel özellikleri, tanıdaki gecikme yaşı diğer klinik, laboratuvar ve genetik özellikleri karşılaştırılarak farklar istatistiksel olarak değerlendirildi.*

Bulgular: *Grup 1'de %60,6 oranında kız, Grup 2'de %39,4 oranında kız var iken; Grup 1'de %58,7 oranında erkek, Grup 2'de %41,3'ü erkek idi. iki grup arasında anlamlı bir istatistiksel fark saptanmadı. Genetik mutasyon açısından gruplar karşılaştırıldığında; . M694V homozigot Grup 1 %17,2 oranında görülmekteyken, Grup 2'de %8,8 oranında görülmekteydi. Grup 1 ve Grup 2 M694V homozigot istatistiksel olarak anlamlı farklılık göstermişti ($p<0,05$).*

Sonuç: *Tekrarlayan artrit, artralji, miyalji tutulumunun baskın olduğu AAAli hastalarda peritoneal tutulumun baskın olduğu AAAli hastalara göre tanı yaşında gecikme ile birlikte daha büyük tanı yaşı, solukluk, mide bulantısı gibi semptomların daha sık olduğu görüldü. Bu da fenotipik olarak artrit, artralji, myaljinin ağırlıklı olduğu AAA olan hastalar sanılanın aksine fenotipinde karın ağrısının ağırlıklı olduğu gruba göre altta yatan çok daha ciddi kliniği bize göstermekte idi.*

Anahtar Kelimeler: *ailevi Akdeniz ateşi; artrit; artralji; miyalji; tutulum*

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Introduction

Familial Mediterranean Fever (FMF) is a recurrent, autosomal recessive disease characterized by serous membrane inflammation. It results in abdominal, chest, and joint pain accompanied by fever. FMF is common in populations of Eastern Mediterranean origin, especially Jews, Turks, Armenians, and Arabs. The prevalence of the disease is 1/1000, and the carrier rate is as high as 1/5[1].

Two separate groups cloned the gene causing FMF in 1997. The International FMF Consortium and the French FMF Consortium showed that the gene encoding a 781-amino-acid protein called pyrin/marenostrin on the short arm of chromosome 16, 16p13.3, is associated with FMF[2].

The gene involved in the disease is called MEFV (MEditerraneaneanFeVer), identified in 1997, consisting of 10 exons, 3505 nucleotides, 785 amino acids, and encoding a protein called pyrin[3]. Pyrin is a component of the inflammatory complex that drives active interleukin-1β production within the cell. Pyrininmutant forms cause uncontrolled interleukin-1β production and increased inflammatory response[2]. Today, over 200 mutations have been identified in this gene[2]. The most common mutations are M694V, M680I, M694I, and V726A[4]. The most common mutations in Turkish FMF patients were reported as M694V and M680I[1].

M694V genotype exhibits the most severe disease course. Due to the autosomal recessive inheritance pattern of FMF, the disease is more common in individuals born of consanguineous marriages[5]. Although familial Mediterranean fever is diagnosed with elevated clinical and acute phase markers, the demonstration of genetic mutations is helpful in the definitive diagnosis. TellHashomer criteria, Livneh criteria, and, since 2009, the criteria set out by Yalcinkaya et al. have been widely used to diagnose the disease[6]. The disease is characterized by fever and pain attacks caused by inflammation in body parts, including the abdomen, chest, and joints.

Abdominal pain attacks are the most common clinical manifestation of Familial Mediterranean Fever after fever. The most common cardinal findings other than fever in FMF are presentation with abdominal pain and joint and muscle involvement. Attacks with recurrent abdominal pain (diffuse, incomplete peritoneal attacks) are intense, and FMF is the primary clinical diagnosis in the differential diagnosis of diseases with abdominal pain. However, in children with arthritis, arthralgia, and myalgia, the diagnosis of FMF is often delayed because FMF is not considered in the differential diagnosis.

Chest pain in Familial Mediterranean Fever occurs due to pleuritis or pericarditis. During attacks, pleural effusion and atelectasis can rarely be observed on chest radiography. In patients homozygous for M694V, pleural involvement was reported to be more frequent than in patients with other mutations[7].

Regarding this objective, the differences between children with FMF with and without recurrent arthritis, arthralgia, and myalgia involvement (recurrent diffuse, incomplete abdominal attacks) were compared statistically.

Materials and Methods

The study was planned retrospectively on children with recurrent arthritis, arthralgia, and myalgia in phenotype I FMF and without recurrent arthritis, arthralgia, and myalgia in phenotype II FMF (with predominant recurrent abdominal pain) who were admitted to the Pediatric Outpatient Clinic and Pediatric Rheumatology Outpatient Clinic of the Kafkas University Research Hospital until 2020 and diagnosed with FMF based on Tel Hashomer or Yalcinkaya-Ozen criteria.

The inclusion criteria for this study are as follows:

1. Children aged 2–18 years diagnosed with FMF based on Tel-Hashomer or Yalcinkaya-Ozen criteria with well-recorded clinical records,
2. Children with FMF with recurrent arthritis, arthralgia, myalgia (at least 2 times in 1 year), and recurrent abdominal pain (at least 2 times in 1 year) who were diagnosed in our clinic,
3. Children with FMF were analyzed for genetic mutations,
4. Children with FMF without comorbidities such as chronic metabolic disease or malnutrition.

The ethical approval for our study was obtained from the Ethics Committee of Kafkas University Faculty of Medicine, with the number 80576354–050–99/276, concluding that it complied with the ethics committee guidelines. Patients in the Pediatric Rheumatology outpatient clinic were grouped as phenotype with recurrent arthritis, arthralgia, myalgia (PHENOTYPE I) and without (PHENOTYPE II) (with a predominant phenotype of recurrent abdominal pain), and these groups were evaluated by dividing them into specific forms. Demographic, familial, clinical, and laboratory characteristics and genetic mutation analyses were recorded in these forms.

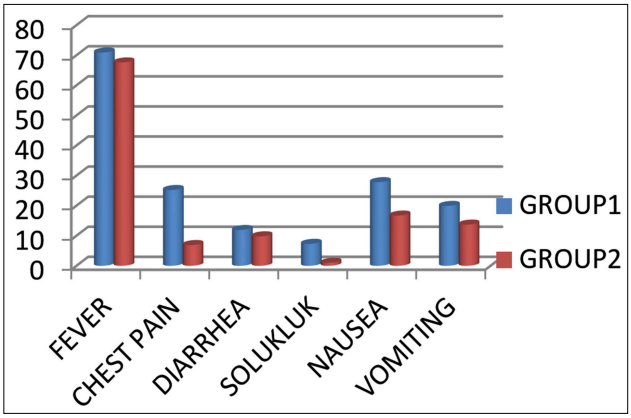

Figure 1. *Distribution of clinical results between groups (%)*

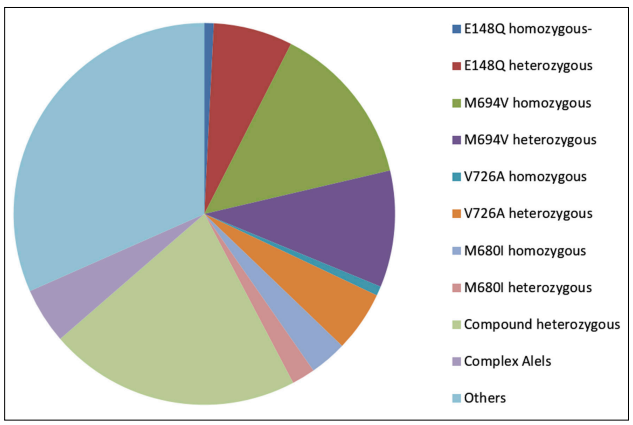

Figure 2. *Distribution of genetic mutations in patients (%)*

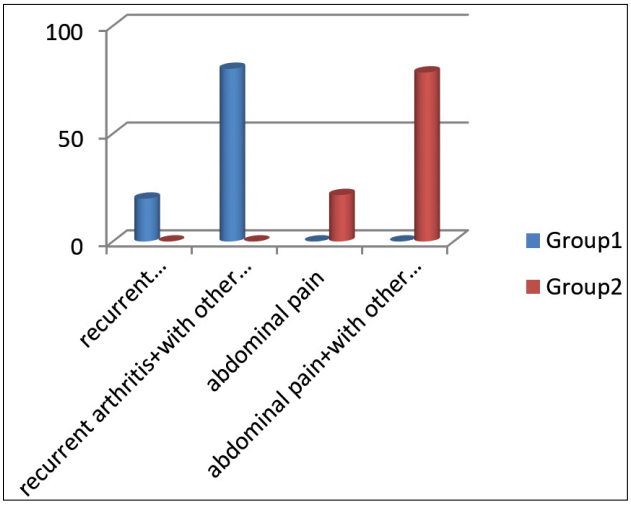

Figure 3. *Distribution of clinical findings between groups.*

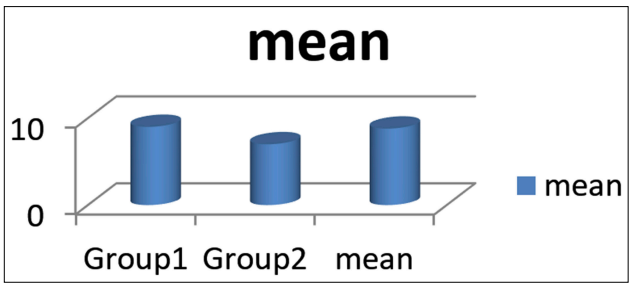

Figure 4. *Age distribution and mean values between groups.*

Statistical Analysis

Statistical analysis IBM Statistical Package for Social Sciences (SPSS) program version 20.0 software was used to evaluate the data, and the conformity of the variables to normal distribution was determined using the Kolmogorov-Smirnov test. In two independent groups, if the numerical variables met the normal distribution condition, the Student test was performed; if they did not meet the normal distribution condition, the Mann-Whitney U test was performed. The chi-square test was used to compare categorical variables between independent groups. The statistical significance level was accepted as $p<0.05$.

Results

The mean age of 253 patients in our study was 8.8±4.31 years. The mean age of the patients was 9±4.2 years in Group 1 and 7±4.16 years in Group 2. A statistically significant difference was observed between Group 1 and Group 2, with Group 1 having a higher mean age than Group 2 ($p<0.05$). 51.6% of our patients in Group 1 had a family history of FMF, and 59.7% in Group 2 had a family history of FMF ($p>0.05$). In Group 1, 73.5% of patients had 2 or more attacks per year, while 26.5% had 2 attacks per year ($p>0.05$). In Group 2, 65.7% of patients had 2 or more attacks per year, while 34.3% had 2 attacks per year ($p>0.05$). The most common complaint at presentation in our overall FMF patients was fever. This was followed by arthritis-arthralgia, myalgia (except febrile myalgia) (59.6%), abdominal pain (40.3%), nausea (23.3%), chest pain (17.7%), vomiting (17.3%), diarrhea (11.06%) and pallor (4.74%), respectively. While 70.9% of the patients in Group 1 presented with fever, this rate was 67.6% in Group 2 ($p>0.05$). In Group 1, 25.2% of the patients presented with chest pain (pleural involvement) compared to 6.9% of the patients in Group 2 ($p<0.05$). 7.3% of the patients in Group 1 and 1% in Group 2 presented with pallor ($p <0.05$). 27.8% of the patients in Group 1 and 16.7% in Group 2 presented with a complaint of nausea ($p <0.05$). 11.9% of patients

Table 1. *Distribution of age groups and comparison of mean values between groups*

Age Groups (years)		n	%	Mean± Std. deviation	P value
Under 4 years old	Group 1	15	9.9	2.93±1.09	p>0.05
	Group 2	29	28.4	2.86±1.15	
5-9 years old	Group 1	63	41.7	7.09±1.31	
	Group 2	45	44.1	6.91±1.44	
10-14 years old	Group 1	48	31.8	12.2±1.42	
	Group 2	19	18.6	11.4±1.57	
15 years old and above	Group 1	25	16.6	15.8±15.7	
	Group 2	9	8.8	15.7±0.83	

in Group 1 and 9.8% in Group 2 presented with diarrhea (p>0.05). Nephritic/nephrotic proteinuria was observed in 4.74% of our FMF patients. This rate was 5.3% in Group 1 and 3.9% in Group 2 (p>0.05).

The distribution of children according to age groups is as follows: Under 4 years old, 9.9% in Group 1 and 28.4% in Group 2; 5–9 years old, 41.7% in Group 1 and 44.1% in Group 2; 10–14 years old, 31.8% in Group 1 and 18.6% in Group 2; 15 years old and above, 16.6% in Group 1 and 8.8% in Group 2.

Regarding genetic mutations, E148Q homozygote was observed in 1.3% of Group 1, and M694V homozygote was observed in 17.2% of Group 1 and 8.8% of Group 2. When patients without mutation were compared, this rate was 10.5% in Group 1 and 15.6% in Group 2.

Genetic mutations were not statistically significant when compared for either group (p>0.05).

Of the patients included in our study, 13.8% were M694V homozygous, 9.8% were M694V heterozygous, 3.1% were M680I homozygous, 1.97%were M680I heterozygous, 0.79% were V726A homozygous, 5.1% were V726A heterozygous, and 12.6% were mutation negative.

Discussion

The distribution of the children included in our study according to age groups was as follows: 18.5% under the age of 5, 41.5% between the ages of 5 and 10, 26.4% between the ages of 10 and 15, and 13.4% aged 15 years and older. The distribution of children according to age groups is as follows: Under 4 years old, 9.9% in Group 1 and 28.4% in Group 2; 5–9 years old, 41.7% in Group 1 and 44.1% in Group 2; 10–14 years old, 31.8% in Group 1 and 18.6% in Group 2; 15 years old and above, 16.6% in Group 1 and 8.8% in Group 2. The average age at diagnosis in the literature is between 12 and 13 years, which is almost identical in both groups in our study and consistent with the literature. Presentation with recurrent abdominal pain is more common in the younger age group, especially patients under 4 years of age. Joint and muscle involvement is less common in this age group than in the 10–14 age group and children older than 15. However, the inability of young children to adequately express arthralgia and myalgia should be taken into account.

The female-to-male ratio in the study conducted by the Turkish FMF study group 1 was 1:1.4, while in the study conducted by Majeed et al., in 47 pediatric patients with FMF of Arab origin, it was 1.1:1[8].

In the Sonmezgoz et al.[9] study, the female-to-male ratio was 1:1.07, while in the study conducted by Çağlar et al., it was 1:1.31 5. In the study conducted by Soylemezoglu et al., the female-to-male ratio was found to be 1.16:1 [10]. In our study, this ratio was 1:1.21, whereas it was 1.04:1 for Group 1 and 1:1.04 for Group 2.

Erguven et al. found that the age of delay in diagnosis was 3.5 years in their series of 120 pediatric patients[11]. In the study conducted by Sonmezgoz et al.[9], similarly, this period was found to be 3.5 years. The time until diagnosis was 30.4±29.2 months in the patients included in our study. The time to diagnosis in Group 1 and Group 2 was 24±31.3 months and 12±24.14 months, respectively. There was a statistically significant difference between Group 1 and Group 2; duration time was higher in Group 1 than in Group 2 (p<0.05). Patients in Group 1 were diagnosed later than patients in Group 2 because they presented with complaints of arthritis and arthralgia rather than abdominal pain at the time of diagnosis. This shows that many physicians may miss the diagnosis of FMF and delay the diagnosis

when patients present with joint symptoms. They are likely to be diagnosed with different rheumatic diseases. It suggests that physicians lack knowledge and experience about joint involvement in patients with FMF.

In Group I, only cases with 3 or more musculoskeletal involvement per year were included in the study, primarily in cases with recurrent arthritis, arthralgia, and myalgia. Due to the nature of our case selection, the number of Group I cases with arthritis, arthralgia, and myalgia may not be compatible with the literature, as our study plan included all phenotype I and phenotype II FMF cases with 2 or more attacks in 1 year. These cases were on colchicine treatment. In addition, only arthritis and arthralgia were evaluated in most literature studies. Since arthritis, arthralgia, and myalgia (except febrile myalgia) were assessed together in our study, the number and percentage of arthritis, arthralgia, and myalgia cases were higher than in the literature. Also, due to the nature of the group selection, the exact percentage of other clinical signs and symptoms in all FMF cases may differ from the literature.

Regarding the distribution of the number of attacks in each group, 73.5% of the patients in Group 1 had 2 or more attacks per year, while 26.5% had 2 attacks per year. In group 2, 65.7% of patients had 2 or more attacks per year, while 34.3% had 2 attacks per year. No statistically significant relationship was observed when both groups were compared regarding the number of attacks ($p>0.05$).

Regarding the clinical findings, 70.9% of the patients in Group 1 and 67.6% in Group 2 presented with fever; no statistical significance was determined in fever complaints ($p>0.05$). Regarding presentation with chest pain (pleural and pericardial involvement), 25.2% of patients in Group 1 and 6.9% of patients in Group 2 presented with chest pain, which was statistically significant ($p<0.05$). This is further complicated because pleural involvement is more common in arthritis, arthralgia, and myalgia than abdominal pain. We could not find this relationship in the literature. It should be studied with a larger number of patients.

Regarding the complaint of pallor, 7.3% of the patients in Group 1 and 1% in Group 2 presented with pallor, which was found to be statistically significant ($p<0.05$). When it was investigated, it was found that the pallor was not due to any underlying chronic additional disease or anemia, and it was considered to be due to pleural and pericardial involvement and nausea, which were significantly detected in patients in Group 1. This suggests that patients with arthritis, arthralgia, and myalgia are more severely affected clinically, contrary to what is assumed. 27.8% of patients in Group 1 and 16.7% in Group 2 presented with nausea, which was statistically significant ($p<0.05$). This shows that patients with predominant arthritis, arthralgia, and myalgia also had mild gastrointestinal involvement, albeit not very severe.

Of the patients, 13.8% were M694V homozygous, 9.8% were M694V heterozygous, 3.1% were M680I homozygous, 1.97% were M680I heterozygous, 0.79% were V726A homozygous, 5.1% were V726A heterozygous, and 12.6% were mutation negative. When the groups were compared regarding genetic mutations, E148Q homozygote was observed in 1.3% and E148Q heterozygote in 5.2% in Group 1, while these rates were 0% and 8.8% in Group 2, respectively. M694V homozygotes were observed in 17.2% in Group 1 and 8.8% in Group 2.

In the literature, M694V mutation was correlated with a higher incidence of arthritis and erysipelas-like erythema[12]. In the study of Berdeli et al., M694V mutation was associated with the development of amyloidosis, febrile attacks, and joint findings[13]. Similarly, in our study, M694V was more common in patients with arthritis.

In conclusion, the late diagnosis of patients with arthritis, arthralgia, myalgia, and myalgia, as well as the fact that pleural involvement and M694 homozygous mutation are more common in these patients, indicate a more severe disease course compared to cases with predominant peritoneal involvement.

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