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Investigation of factors associated with the diagnosis process and delayed diagnosis in Familial Mediterranean fever patients: a single-center experience

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ABSTRACT

Aims: Familial Mediterranean fever (FMF) is a common autoinflammatory disease in Türkiye and worldwide. Diagnosis may be delayed because it can present with diverse clinical phenotypes. This study aims to determine the initial symptoms of patients with FMF, the time from symptom onset to diagnosis, and factors associated with delayed diagnosis.

Methods: This cross-sectional study included patients with FMF who were under follow-up, receiving treatment, and who volunteered to participate. A face-to-face data collection form, including questions about the first symptoms of FMF, age at onset, and age at diagnosis, was administered to the patients.

Results: Of the 169 patients, 58% (n=98) were female, and the mean age was 34.31±10.96 years. The mean age at onset of symptoms was 17.26±11.43 years, and the mean age at diagnosis was 24.67±12.62 years. The diagnostic delay was 7.41±8.57 years. The most common initial symptom of FMF was abdominal pain (72.8%, n=123). Diagnostic delay was significantly longer in patients with joint pain than in patients without joint pain [6.00 (0-39) years vs. 3.00 (0-35) years; p=0.007]. Similarly, the diagnostic delay was significantly shorter in patients who had undergone surgery compared with those without a history of surgery [3.00 (0-39) years vs. 8.00 (0-37) years; p=0.002].

Conclusions: This study demonstrated that diagnostic delay remains a significant issue among patients with FMF, particularly those presenting with joint pain.

Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease. FMF is an autoinflammatory disease of ethnic origin and genetic inheritance that presents with recurrent and self-limiting attacks of fever, peritonitis, pleuritis, arthritic pain, or rash (1). It is common in populations of Eastern Mediterranean origin, particularly among Turks, Jews, Arabs, and Armenians. While the carrier rate in Türkiye is 1/5, the disease incidence is reported to be 1/1000 (2,3).

FMF disease is caused by mutations on chromosome 16 (16p13.3) encoding the pyrin protein of the Mediterranean fever gene, which is inherited in an autosomal recessive manner (4). Excessive activation of the pyrin inflammasome because of these mutations and the resulting inflammation causes the typical febrile attacks observed in FMF (5-7). The most common symptoms are abdominal pain, fever, arthritis, chest pain, and erysipelas-like erythema (2).

Diagnosis is based on clinical symptoms. However, the disease can present with different clinical phenotypes. The signs and symptoms of the disease are not specific, and the differential diagnosis includes many diseases. This can make diagnosis difficult and lead to significant delays in starting treatment. Several studies have reported that diagnosis may be missed or delayed even in countries such as Israel and Türkiye, which are considered endemic regions for FMF (8-9). Misdiagnosis can lead to unnecessary surgery. Delayed diagnosis may increase the risk of amyloidosis. Delayed diagnosis of FMF can significantly increase morbidity and contribute to increased mortality and healthcare costs (10).

The existing literature reveals a paucity of studies specifically addressing the reasons for diagnostic delay or misdiagnosis (8). In this context, our study aimed to assess the initial symptoms of patients with FMF, determine the time from symptom onset to diagnosis, and identify factors associated with diagnostic delay.

Methods

Study design and participants

The cross-sectional study was conducted using a face-to-face data collection form on 169 patients who had applied to the Rheumatology Department and affiliated outpatient clinics of a hospital providing tertiary healthcare services in Türkiye between 01.11.2021 and 30.10.2022, who were being followed up and treated with a diagnosis of FMF, and who volunteered to participate in the study. The diagnosis of FMF in all patients was made by rheumatologists based on the Tel-Hashomer diagnostic criteria (11), which are widely accepted and validated for clinical use.

Data collection

The study collected information on the sociodemographic characteristics of the participants, their initial complaints related to FMF, the age at which their initial complaints began, and the age at which the diagnosis was made, the frequency of attacks before and after diagnosis, any diseases other than FMF, the healthcare institutions and specialist doctors they consulted before receiving a diagnosis, and the diagnosis for their initial complaints. Before the diagnosis, the patient was asked about their surgical history, history of amyloidosis, genetic testing, and family history of FMF or other rheumatological diseases. The FMF patient data collection form, comprising 38 questions related to the diagnostic process, was administered to patients via face-to-face interviews after obtaining their consent. Data were collected using a structured data collection form specifically developed for this study.

Statistical Analysis

The research data were analyzed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The research data were examined for normality using the Kolmogorov-Smirnov test. In the analysis, the Mann-Whitney U test compared two independent groups, and the Kruskal-Wallis test compared three or more independent groups. Median (minimum-maximum) values were reported in the analysis. Multiple-comparison tests were performed using the Bonferroni correction to determine which groups differed. The relationships between variables were evaluated using Spearman correlation tests. A value of $p<0.05$ was considered statistically significant in the analyses.

Ethical approval

The University of Health Sciences Türkiye, Gülhane Non-Interventional Research Ethics Committee approved the study at the board meeting held on 21.10.2021 with decision number 2021/369. It was accepted at the board meeting number 16 of the University of Health Sciences Türkiye, Gülhane SBU Health Application and Research Center Medical Specialization Education Board dated 24.09.2021 and numbered E-50687469-799.

Results

Socio-demographic and clinical characteristics

The mean age of the 169 participants was 34.31±10.96 years. The mean age at onset of symptoms was 17.26±11.43 years, while the mean age at diagnosis was 24.67±12.62 years. The mean diagnostic delay was 7.41±8.57 years. Among the patients who participated in the study, 58% (n=98) were female; 62.7% (n=106) were married; 46.7% (n=79) were university graduates; 46.2% (n=78) were employed; and 79.9% (n=135) lived in urban areas (Table 1).

The participants' initial complaints of FMF were abdominal pain (72.8%, n=123), joint pain (59.2%, n=100), and fever (51.5%, n=87) (Figure 1). Of those with other diseases, 57.1% (n=16) had ankylosing spondylitis; 10.7% (n=3) had inflammatory bowel disease; 7.14% (n=2) had rheumatoid arthritis; and 17.8% (n=5) had other rheumatological diseases.

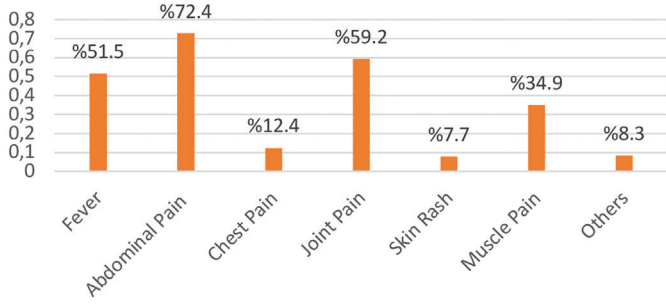

Figure 1. Distribution of initial complaints in patients with Familial Mediterranean fever
Others: Back pain (n: 5), weakness (n: 3), nausea (n: 3), syncope (n: 1), drowsiness (n: 1), bloody urine (n: 1)

The most common healthcare institutions to which patients in the study presented before diagnosis were public hospitals (57.4%) and training and research hospitals (56.8%); the most common specialties were internal medicine and rheumatology.

Following a thorough evaluation of participants' initial diagnoses, 92.9% (n=157) were found to have been misdiagnosed. In the present study, the subjects were diagnosed as follows: 33.7% (n=57) with gastrointestinal system diseases; 17.2% (n=29) with appendicitis; 12.4% (n=21) with arthritis; and 6.5% (n=11) with acute rheumatic fever (ARF) (Figure 2).

Table 1. Socio-demographic characteristics of patients with Familial Mediterranean fever (n=169)

Variables		n (%)
Gender	Male	71 (42)
	Female	98 (58)
Marital status	Married	106 (62.7)
	Single	63 (37.3)
Educational status	Primary school	26 (15.4)
	Middle school	12 (7.1)
	High school	52 (30.8)
	University	79 (46.7)
Working status	Employed	78 (46.2)
	Unemployed	91 (53.8)
Place of residence	Urban	34 (20.1)
	Rural	135 (79.9)
Physical activity	None	101(59.8)
	Irregular	46 (27.2)
	Regular	22 (13.0)
Smoking	No	116 (68.6)
	Yes	53 (31.4)
Alcohol use	No	158 (93.5)
	Yes	11 (6.5)

78.7% (n=133) of the participants had not undergone surgery before diagnosis. The most common surgical procedure was appendectomy (76.9%, n=30), followed by hernia surgery (2.5%, n=1), and gallbladder surgery (8%, n=3). The study examined the genetic testing status of the participants. Of the participants who underwent genetic testing (n=161), 87.6% (n=148) tested positive for a genetic mutation. Among those who tested positive, 64.5% (n=109) knew their specific genetic mutation. Of the participants whose genetic mutation was known, 22.9% (n=25) were M694V homozygous; 13.8% (n=15) were M694V heterozygous; 10.1% (n=11) were M694V/V726A compound heterozygous; 9.2% (n=10) were M694V/M680I compound heterozygous; and 8.3% (n=9) were M694V/E148Q compound heterozygous.

73.4% of the participants had a family history of FMF; among these, 62.1% (n=105) had a history of FMF in 1st-degree relatives, 26.7% (n=45) in 2nd-degree relatives, and 30.8% (n=52) in other relatives.

Diagnostic delay and associated factors

Correlation analysis showed that the length of diagnostic delay was positively and significantly associated with patients' current age (r=0.360, p<0.001) and with their age at diagnosis (r=0.436, p<0.001). In contrast, there was no significant correlation between the length of diagnostic delay and the age at which symptoms first appeared.

The results for diagnostic delay times by participants' socio-demographic characteristics are shown in Table 2.

In the results for diagnosis delay times according to the participants' initial complaints, a significant difference was found between participants with and without joint pain complaints [3.00 (0-35) years vs. 6.00 (0-39) years; p=0.007]. The diagnosis delay time for those with joint pain was found to be higher than the diagnosis delay time for those without joint pain (Table 2).

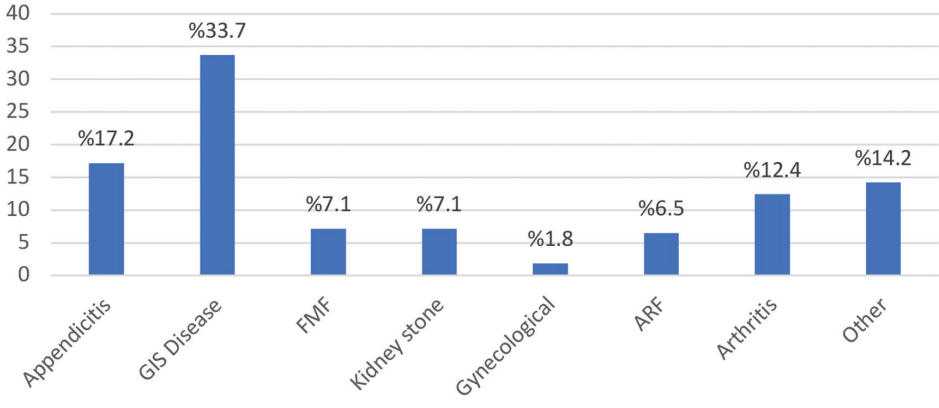

Figure 2. Distribution of initial diagnoses in patients with Familial Mediterranean fever
Others: Myalgia (n: 14), pericarditis (n: 4), Henoch-Schönlein Purpura (n: 2), cellulitis (n: 1), gout (n: 1), cholecystitis (n: 1)
FMF: Familial Mediterranean fever, ARF: Acute rheumatic fever, GIS: Gastrointestinal system

The results for diagnostic delay periods, stratified by the healthcare institutions patients visited before diagnosis, revealed a significant difference between participants who visited private hospitals and those who did not [3.50 (0-39) years vs. 6.00 (0-35) years; p=0.037]. The average diagnostic delay was found to be higher for participants who visited private hospitals than for those who did not. No significant difference was found in diagnostic delay for visits to other healthcare institutions.

The present study found no statistically significant correlation between diagnostic delay times and patients' initial diagnosis, genetic test status, genetic test result, gene mutation, and family history of FMF (p>0.05).

A significant difference in diagnostic delay time was found between participants who had undergone surgery and those who had not [3.00 (0-39) years vs. 8.00 (0-37) years; p=0.002]. Examination of the results revealed that diagnostic delay was longer in patients who underwent surgery than in those who did not.

Table 2. Comparison of diagnostic delay times by socio-demographic characteristics and patients' initial complaints

Characteristics		n	Diagnostic delay (years) Median (min-max)	Test statistic	p
Gender	Male	71	3.00 (0-29)	Z=-1.16	0.242[a]
	Female	98	5.00 (0-39)		
Marital status	Married	106	6.00 (0-39)	Z=-3.97	**<0.001**[a]
	Single	63	1.00 (0-37)		
Educational status	Primary school	26	9.50 (0-35)	X^2=15.49	**0.001**[b]
	Middle school	12	1.50 (0-39)		
	High school	52	2.00 (0-29)		
	University	79	6.00 (0-37)		
Working status	Employed	78	5.00 (0-30)	Z=-0.51	0.605[a]
	Unemployed	91	4.00 (0-39)		
Place of residence	Urban	34	5.50 (0-27)	Z=-0.04	0.962[a]
	Rural	135	4.00 (0-39)		
Physical activity	None	101	3.00 (0-35)	X^2=2.12	0.345[b]
	Irregular	46	5.50 (0-39)		
	Regular	22	3.50 (0-37)		
Smoking	No	116	3.50 (0-37)	Z=-1.16	0.246[a]
	Yes	53	7.00 (0-39)		
Alcohol use	No	158	4.00 (0-39)	Z=-0.04	0.962[a]
	Yes	11	4.00 (0-18)		
Fever	No	82	4.50 (0-39)	Z=-0.29	0.772[a]
	Yes	87	4.00 (0-37)		
Stomachache	No	46	5.00 (0-39)	Z=-0.24	0.806[a]
	Yes	123	4.00 (0-35)		
Chest pain	No	148	4.00 (0-39)	Z=-1.17	0.238[a]
	Yes	21	8.00 (0-18)		
Joint pain	No	69	3.00 (0-35)	Z=-2.69	**0.007**[a]
	Yes	100	6.00 (0-39)		
Skin rash	No	156	4.00 (0-39)	Z=-0.51	0.610[a]
	Yes	13	6.00 (0-17)		
Muscle pain	No	110	3.00 (0-35)	Z=-1.17	0.241[a]
	Yes	59	5.00 (0-39)		
Other	No	155	5.00 (0-39)	Z=-1.77	0.077[a]
	Yes	14	1.00 (0-28)		

[a]: Mann-Whitney U test, [b]: Kruskal-Wallis test
min-max: Minimum-maximum

Discussion

The diagnostic delay for patients included in the study was approximately 7.5 years. Diagnostic delay time increased with both patient age and age at diagnosis; it was significantly longer in married than in single patients, in patients whose first complaint was joint pain than in those without joint pain, and in patients who underwent surgery than in those who did not.

In the literature, the diagnostic delay time was reported to be approximately 7 years in the study of 2838 FMF patients in Türkiye, approximately 10 years in the multicentre study by Yaşar Bilge et al. (10), and approximately 8 years in the study by Hageman et al. (12), where it was known that the majority of the patients included were of Türk origin (2). It has been reported that the delay in diagnosis is longer outside the Mediterranean countries, with an average of 15 years in a study conducted in Germany, approximately 18 years in another study conducted in Italy, and an average time to diagnosis of approximately 9 years in another study conducted by Migita et al. (13) in Japan (14,15). The delay in diagnosis observed in our study is consistent with previous studies of patients of Turkish origin. It shows that, even in countries like Türkiye, where FMF is endemic and the disease is common, diagnostic delay remains a problem, and awareness of the disease needs to be increased.

The most common initial complaint in FMF was abdominal pain, followed by joint pain and fever. In a study of 197 FMF patients in Türkiye, abdominal pain was reported by 65%, fever by 47%, and joint symptoms by 43% when the first complaints were investigated (8). In the study by Samuels et al. (16), arthritis was reported as the third most common cause of clinical presentation after fever and abdominal pain, with a rate of 45%. Although the data obtained in our study are consistent with prevailing opinion, the second most common complaint—joint pain—appears to result from patients' inability to distinguish arthritis from arthralgia; consequently, they interpret all joint complaints as joint pain.

Our study found a significant difference in diagnostic delay time in those with joint pain compared to those without, and it was observed that the diagnostic delay time was longer in those with joint pain. A study by Erdogan et al. (8), stated that joint attacks play an important role in diagnosis delay and misdiagnosis, and it was reported that patients were less likely to have abdominal pain at the onset of FMF, while they were more likely to have joint involvement. A study by Barut et al. (17), reported that patients with symptoms of arthritis/arthralgia had longer diagnostic delays than those with symptoms of fever and serositis. The data obtained in our study are similar to those reported in the literature. Given the available data, it should be noted that complaints of joint pain may not initially be attributed to FMF; other diagnoses may be considered, and patients with FMF may present with isolated joint symptoms. This information should be considered when establishing the differential diagnosis of FMF.

We observed that the majority of patients (92.9%) were misdiagnosed. These were in order of frequency: gastrointestinal diseases, acute appendicitis, and arthritis. A study by Erdogan et al. (8) in 2019 reported that 84% of participants were misdiagnosed before diagnosis of FMF. It was reported that the two most common diagnoses in misdiagnosed patients were acute appendicitis and ARF. In another study of 143 patients in Türkiye, the misdiagnosis rate was 73%, and it was reported that appendicitis was the most common diagnosis, followed by gastrointestinal disease (18). In our study, the frequent occurrence of gastrointestinal disease as the first diagnosis may be explained by the fact that abdominal pain was the most common complaint: patients most often presented to emergency services with abdominal pain and were discharged without a clear diagnosis. The study did not find a significant association between the patients' initial diagnosis and the delay in diagnosis.

The results indicated that approximately one-fifth (21.3%) of the patients underwent surgical intervention; the most common intervention was appendectomy. In the study by Erdogan et al. (8), the surgical operation rate was 28%, and the most common operation was appendectomy in 91%. In a single-center retrospective study conducted in Amsterdam in 2019, appendectomy was the most common surgical operation (12). In the study by Kaşifoğlu et al. (19) to investigate the frequency of surgical operations in FMF patients, the surgical operation rate was reported to be 29.1% and the appendectomy rate was 91.8%. In our study, the surgical operation rate and the history of appendectomy were consistent with the literature. The heterogeneous and variable clinical course of FMF attacks, which can be mistaken for an acute abdomen, may lead to high rates of surgical intervention, including appendectomy, because of the disease's rarity and low awareness.

It was observed that those who underwent surgery had a longer delay in diagnosis than those who did not, suggesting that undergoing surgery may cause a diagnostic delay. In the literature, the study by Lidar et al. (9) found that surgery played an important role in misdiagnosis and delayed diagnosis. Increasing physicians' knowledge and awareness of FMF may contribute to the early diagnosis of FMF and to avoiding unnecessary surgery. A detailed medical history is important for a definitive diagnosis of FMF and other abdominal pathologies.

Study Limitations

Our study has several limitations. First, since it was conducted in a hospital providing tertiary health care in Türkiye, the results may be limited in that they are not generalizable to patients living in rural areas or to patients from other ethnic groups. Second, because the results are based on face-to-face patient responses, they may lack objectivity in this context. Third,

given the prevalence of this disease in Türkiye, our sample size could have been larger. Fourth, certain clinically important characteristics of FMF, such as attack severity, frequency, or multi-site attacks, were not evaluated.

Conclusion

The study found that patients waited a long time for a diagnosis, and this was longer for those with joint symptoms. This should always be considered when a patient presents with joint symptoms.

In light of these findings, it is challenging to pinpoint the causes of diagnostic delays. However, to prevent FMF complications, physicians need to be better informed.

Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, Gülhane Non-Interventional Research Ethics Committee approved the study at the board meeting held on 21.10.2021 with decision number 2021/369.

Informed Consent: All patients participating in the study provided informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ö., Concept: M.Ö., Y.Ç.D., S.Y., Design: M.Ö., Y.Ç.D., Ü.A., S.Y., Data Collection or Processing: M.Ö., Analysis or Interpretation: M.Ö., Y.Ç.D., Literature Search: M.Ö., Y.Ç.D., Writing: M.Ö., Y.Ç.D., Ü.A., S.Y.

Declaration of Interests: One authors of this article, Ümit Aydoğan, are a members of the Editorial Board of the Gulhane Medical Journal. However, they did not involved in any stage of the editorial decision of the manuscript.

Conflict of Interest: The authors declare that there is no conflict of interest.

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