Familial Mediterranean fever: misdiagnosis and diagnostic delay in Turkey

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ABSTRACT

Objective. *The diagnosis of familial Mediterranean fever (FMF) can be missed or delayed even in countries where FMF prevalence is high. In this study we investigated the presentation pattern, the frequency of misdiagnosis and the duration of diagnostic delay and its underlying causes in a large cohort followed by a single tertiary centre in Turkey.*

Methods. *We studied 197 (118 F, 79 M) consecutive patients with FMF (median age: 34 years [IQR: 27-44]). The median registry year of the patients was 2006 [IQR: 2001-2011]. A standardised questionnaire was used to assess age at first symptom, date at diagnosis, previous diagnosis and treatments before the FMF diagnosis.*

Results. *A total of 167 (84%) patients were misdiagnosed and 56 (28%) underwent surgical operations before FMF diagnosis. The most common misdiagnoses were appendicitis (55%) and acute rheumatic fever (ARF) (45%). The median duration of diagnostic delay was 11 years. Joint attacks were observed to start at a significantly younger age (median age: 3 years) than abdominal attacks (median age: 12 years). Early onset with solo joint attacks, without usual peritonitis attacks and being a carrier of M694V were found to be significantly associated with ARF misdiagnosis.*

Conclusion. *Misdiagnosis frequency is still significantly high and diagnostic delay is long even in a cohort of patients registered after year 2000 in Turkey. Atypical presentation with solo joint attacks, especially among patients with early onset, seems to play a significant role in misdiagnosis and delay in diagnosis.*

Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease. It is characterised by recurrent episodes of fever and sterile peritonitis, arthritis, pleuritis and erysipelas-like skin eruption (ELE) (1-3). The prevalence of FMF is 1/1000-1/250 among Jews, Turks, Armenians and Arabs (1-5). The disease usually begins before 20 years of age. There is no pathognomonic laboratory test. The gene that is thought to be strongly associated with FMF, termed MEFV, can be found in the majority of patients, but not all of them (6). The diagnosis is based on clinical symptoms but the disease may present with different clinical phenotypes (7). Several studies reported that its diagnosis can be missed or delayed even in countries considered as endemic regions for FMF, such as Israel and Turkey (6). However, studies specifically investigating the causes of diagnostic delay or misdiagnosis are limited.

In this survey we investigated the presentation pattern, the frequency of misdiagnosis and the duration of diagnostic delay and its possible causes in a large cohort followed by a single tertiary centre in Turkey.

Methods

We studied 197 (118 F, 79 M) patients with FMF seen consecutively at the Rheumatology Outpatient Clinic of Cerrahpaşa Medical Faculty between January and April 2017. All patients were of Turkish origin, fulfilled the Tel-Hashomer criteria (8) and were using colchicine. Patients with associated another inflammatory condition were not included in the study. A standardised questionnaire was prepared to assess the level of formal education, current age, age at disease onset or age at initial symptom, description of the initial and cumulative symptoms (at disease onset and later on until the patient was diagnosed as FMF), previous misdiagnosis and previous medical or surgical treatments received before FMF diagnosis and date at FMF diagnosis

or date at starting using colchicine. For joint involvement especially, in case patients could not remember or define what has happened, a picture of a swollen and red ankle that can be described as erysipelas-like erythema (ELE) was shown. The questionnaire also sought whether there were any relatives or friends with FMF who inspired the patient for FMF investigation and whether MEFV gene testing was done to avoid misdiagnosis. The questionnaire was distributed to all patients to be completed while waiting to be seen, and then a physician (M.E.) went over the filled form with each patient. Clinical characteristics related to FMF and MEFV gene results were taken from the patient's charts.

We defined demographic and clinical variables that could affect delay in diagnosis or misdiagnosis and investigated whether there were any associations between them. These variables were: a. gender; b. lower level of education; c. carrying M694V in at least one allele; d. being <16 years of age at initial symptom; e. disease onset before year 2000; f. diagnosis before or after year 2000; g. initial symptoms (abdominal pain, fever episodes, pleuritic pain or joint involvement).

The study protocol was approved by the Local Ethics Committee of Cerrahpasa School of Medicine of the University of Istanbul-Cerrahpaşa (no: 17/03/2017-106199).

Statistics

Comparisons of continuous variables between groups were made using the Student's *t*-test. The categorical variables were compared by the chi-square test or the Fisher exact test. Continuous variables with non-normal distributions were compared by using Mann-Whitney U. All tests were performed using SPSS for Windows, v. 18.0, software (SPSS Inc, Chicago, IL, USA).

Results

Demographic and clinical characteristics and educational status of the patients are shown in Table I. The median current age of the patients was 34 years [IQR: 27-44]. MEFV mutations were available in 163 (118 F/45 M) patients. These were most commonly exon 10 (n=138) and rarely exon 2 or 3 mutations (n=18). Eight patients (6%) did not carry any mutation. The median registry year to the outpatient clinic of the patients was 2006 [IQR: 2001–2011]. Information on education was available on 186 patients (94%) and among them those who received primary education or less were 29%.

Table I. Demographic and clinical characteristics.

Total, n (M/F)	197 (79/118)
Current age, median [IQR] years	34 [27 - 44]
MEFV mutations	n=163 (%)
M694V Heterozygous	56 (34)
M694V Homozygous	48 (29)
M680I Homozygous	11 (7)
M726A Homozygous	0
Other Exon 10	23 (14)
Exon 2	17 (10)
Exon 3	1 (1)
No mutation identified	8 (5)
Level of education	n =186 (%)
Primary school or less	53 (29)
High school or more	133 (71)
Initial attacks	n= 192 (%)
Peritonitis	125 (65)
Fever	90 (47)
Joint involvement (arthritis or ELE)	83 (43)
Pleuritis	14 (7)
Cumulative frequency of attacks before diagnosis	n= 197
Peritonitis	174 (88)
Fever	154 (78)
Joint involvement (arthritis or ELE)	129 (66)
Pleuritis	55 (28)

Initial attack

Information related to the initial attack was available in 192 patients. The initial symptom was abdominal attacks (n=98, 51%) in the majority followed by joint attacks or ELE (n=56, 29%), both abdominal and joint attacks or ELE (n=27, 14%) and pleuritic pain (n=14, 7%). A total of 88 patients (46%) reported that fever episodes were concomitantly present in these attacks while only 2 (1%) reported having solo fever attacks.

Cumulative frequency of attacks before diagnosis

The majority reported having had abdominal attacks (n=174, 88%) followed by joint attacks or ELE (n=129, 66%) and pleuritic pain (n=55, 28%) before being officially diagnosed as FMF. These attacks were associated with fever episodes in 154 patients (78%). Additionally, 23 patients (16 F/7 M) complained of having episodic attacks of nausea, vomiting, diarrhoea, constipation, headache and arthralgia (Table I).

Age at initial attack and age at diagnosis

As seen in Table II, the median age [IQR] at initial attack was 8 [5–15] years, while that at diagnosis was median 24 [IQR: 14–33] years. The median duration of delay in diagnosis was calculated as 11 [IQR: 4–18] years. Patients reported having joint attacks at a considerably younger age (median age: 3 [IQR: 1–6] years) than that at abdominal (median age: 12 [IQR: 6-19] years), pleuritic (median age: 11[IQR: 8-20] years) and fever attacks (median age: 11 [IQR: 5–17] years). Figure 1 shows 95% confidence intervals of the mean age of the patients when they experienced their initial attack. Additionally, the median diagnostic delay was significantly longer among 149 patients whose disease onset was < 16 years of age compared to 48 patients with dis-

Table II. Age at first symptom, delay in diagnosis, misdiagnosis and medical or surgical treatment before FMF diagnosis.

	Total, n=197
Age at first symptom, median [IQR] years	8 [5-15]
Age at diagnosis, median [IQR] years	24 [14-33]
Duration of delay in diagnosis, median [IQR]	11 [4-18]
Consulted a physician after someone in the entourage has been diagnosed with FMF, n (%)	86 (44)
MEFV gene testing performed before diagnosis, n (%)	87 (44)
Misdiagnosed patients, n (%)	165 (84)
Appendicitis	90 (55)
Acute rheumatic fever	75 (45)
Gastrointestinal diseases	47 (28)
Inflammatory arthritis	25 (15)
Kidney stones	20 (12)
Gynaecological diseases	16 (10)
Others	18 (11)
Medical treatment other than Colchicine, n (%)	107 (54)
Penicillin treatment	53 (50)
Other drugs	54 (50)
Surgical operation before diagnosis, n (%)	56 (28)
Appendectomy	51 (91)
Other (gastrointestinal or gynaecological surgeries)	5 (9)

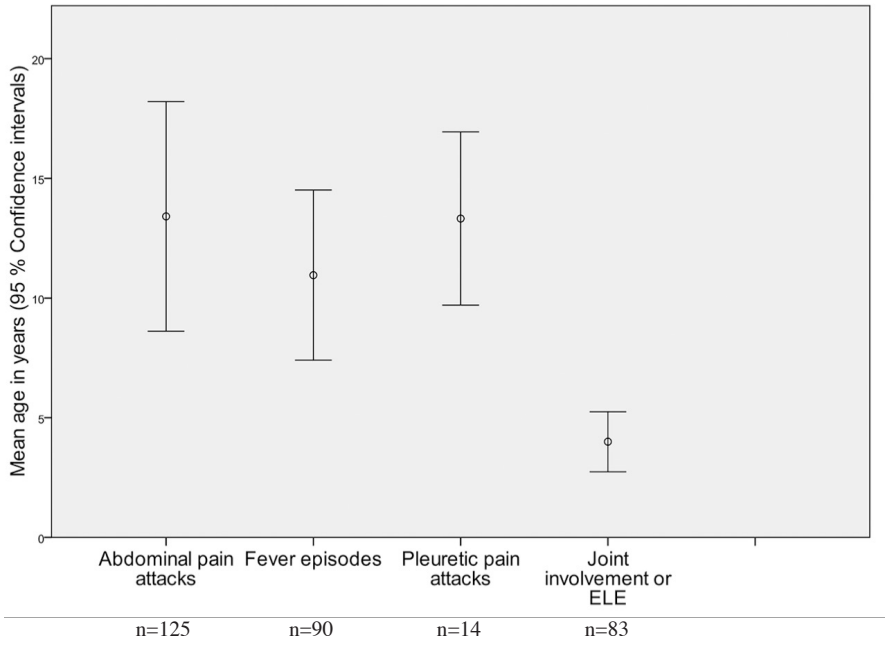

Fig. 1. Mean age at first symptom.

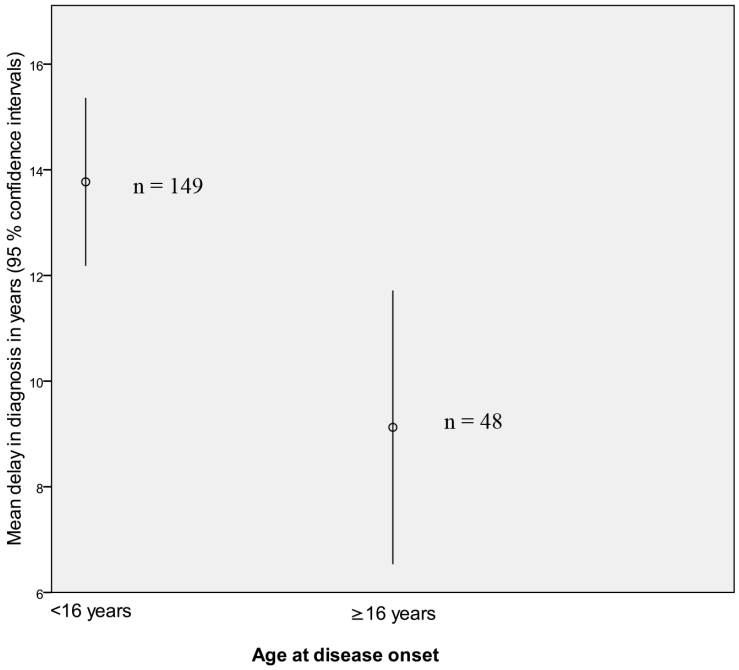

Fig. 2. Duration of diagnostic delay according to age at disease onset.

ease onset ≥16 years of age (13 [IQR: 6–20] years *vs*. 5 [IQR: 2-12] years, *p*=0.004). Figure 2 depicts the mean and 95% confidence intervals of the delay between these 2 groups.

MEFV gene testing had been performed in 87 patients (44%) before the diagnosis. A total of 86 patients (44%) consulted a physician only after it was found out someone else in the family or a friend had a similar diagnosis.

Misdiagnosis

A total of 165 (98 F/67 M) patients (84%) were misdiagnosed before being officially diagnosed with FMF (Table II). The most common misdiagnoses were appendicitis (55%) and acute rheumatic fever (45%), followed by gastro-intestinal diseases (28%), inflammatory arthritis (15%), kidney stones (12%), gynaecological diseases (10%) and miscellaneous other diagnoses (11%). A total of 107 patients (54%) received long-term treatments, mainly monthly penicillin (n=53), prior to colchicine. There were 65 surgical interventions in 56 patients (28%), before the diagnosis of FMF, the most common being appendectomy in 51. Other less common types of surgeries were gastrointestinal (gastrectomy: n=2, cholecystectomy n=2, intestinal herniation: n=2) in 6, gynaecological in 1, and others in 2 patients.

Differences between males and females

While the median age at diagnosis was similar among females and males (23 [IQR: 13–33] *vs*. 25 [IQR: 14–33]), the median age at first symptom was more likely to be smaller (7 [IQR: 5–13] *vs*. 10 [IQR: 7–19], respectively, *p*=0.004) and the median duration of delay was longer among women (12 [IQR: 6–20] *vs*. 9 [IQR: 3–16], respectively, *p*=0.016). Besides that all demographic and clinical characteristics and the frequency of misdiagnosis were similar among females and males.

Factors associated with misdiagnosis

As expected, patients who had been misdiagnosed had significantly longer diagnostic delay than those who were correctly diagnosed as FMF (Table III). Additionally, they were more likely to have joint involvement whereas less likely to have abdominal pain at the beginning of their disease (Table III).

Factors associated with acute rheumatic fever diagnosis prior to FMF

As shown in Table IV, patients who were diagnosed as acute rheumatic fever (ARF) were significantly younger at disease onset and were more likely to carry M694V in at least one allele, than those who were not diagnosed as ARF. Additionally, similarly to those who were wrongly diagnosed, they were in general more likely to have joint attacks rather than abdominal attacks at disease onset. On the other hand, duration of diagnostic delay was similar between those who were and were not diagnosed as ARF.

Table III. Variables associated with misdiagnosis.

	Misdiagnosed, n=165	Correctly diagnosed, n=32	*p*
Females, n (%)	98 (59)	20 (63)	0.743
Current age, med [IQR]	**35 [28-44]**	**28 [23-35]**	**0.005**
Age at first symptom, med [IQR]	9 [5-16]	8 [6-14]	0.888
Duration of delay, med [IQR]	**12 [6-18]**	**6 [1-20]**	**0.034**
M694V in at least one allele, n (%)	91/139 (66 %)	14/24 (58 %)	0.500
Primary school or less, n (%)	48/156 (31 %)	5/30 (17 %)	0.129
<16 years of age at initial symptom, n (%)	123 (75 %)	26 (81 %)	0.419
Diagnosis before year 2000, n (%)	39 (24)	6 (19)	0.547
Abdominal pain as first attack, n (%)	**99/161 (62)**	**26/31 (84)**	**0.017**
Fever episode as first attack, n (%)	76 (47)	14 (45)	0.835
Joint involvement as first attack, n (%)	**75/161 (47)**	**8/31 (26)**	**0.032**
Pleuretic pain as first attack, n (%)	11/161 (7)	3/31 (10)	0.577
Consulted a physician after someone in the entourage has been diagnosed with FMF, n (%)	70 (42)	16 (50)	0.429
MEFV gene testing performed before diagnosis, n (%)	70 (42)	17 (53)	0.265

Table IV. Variables associated with having acute rheumatic fever (ARF) diagnosis prior to FMF.

	Dx as ARF (+), n=75	Non- Dx as ARF, n=122	*p*
Females, n (%)	49 (65)	69 (57)	0.222
Current age, med [IQR]	34 [26-42]	35 [28-44]	0.259
Age at disease onset, med [IQR]	**6 [4-12]**	**10 [6-17]**	**<0.001**
Duration of delay, med [IQR]	12 [7-18]	11 [3-20]	0.379
M694V in at least one allele, n (%)	**53/67 (79 %)**	**52/96 (54 %)**	**0.001**
Primary school or less, n (%)	23/71 (32 %)	30/115 (26 %)	0.355
Abdominal pain as first attack, n (%)	**37/74 (50)**	**88/118 (75)**	**0.001**
Fever episode as first attack, n (%)	39/74 (53)	51/118 (43)	0.200
Joint involvement as first attack, n (%)	**44/74 (59)**	**39/118 (33)**	**<0.001**
Pleuretic pain as first attack, n (%)	5/74 (8)	9/118 (8)	0.821
Consulted a physician after someone in the entourage has been diagnosed with FMF, n (%)	36 (48)	50 (41)	0.335
MEFV gene testing performed before diagnosis, n (%)	31 (41)	56 (46)	0.531

Factors associated with being diagnosed before or after year 2000

Duration of diagnostic delay was significantly shorter among those who had been diagnosed as FMF after the year 2000 (15 [9–22] years *vs*. 4 [1–9] years, respectively for before and after the year 2000, $p<0.001$). The frequency of overall misdiagnosis was similar (86% *vs*. 78%, respectively for before and after year 2000, $p=0.135$). This was also true for appendicitis and appendectomies (data not shown). However, patients who had been diagnosed with ARF were significantly less after the year 2000 (43% *vs*. 27%, respectively for before and after the year 2000, $p=0.038$).

Discussion

In this study we observed that 84% of FMF patients were misdiagnosed before being officially diagnosed as FMF. The most common misdiagnoses were appendicitis (55%) and acute rheumatic fever (45%). Twenty-eight percent underwent unnecessary surgical operations before diagnosis. The median duration of delay in diagnosis was 11 years. Females had a significantly longer delay (median: 12 *vs*. median: 9). Joint attacks were observed to start at a significantly younger age (median age: 3 years) than abdominal (median age: 12 years) or pleuritic attacks (median age: 11 years) and this seems to play a significant role in the misdiagnosis and long diagnostic delay. The duration of delay and the frequency of overall misdiagnosis did not differ among those who carry M694V and who do not. On the other hand, being carrier of M694V was found to be significantly associated with ARF diagnosis. Finally, although overall frequency of misdiagnosis did not change, duration of diagnostic delay was found to be shortened significantly after year 2000.

Lidar *et al*. investigated factors underlying diagnostic delay among 50 FMF patients in whom the diagnosis was made ≥10 years after disease onset and 50 patients in whom the diagnosis was made within 5 years of symptom onset (6). Although patients with longer delay experienced a somewhat more vigorous disease, reflected by a higher frequency of abdominal attacks, appendectomies and a higher colchicine dose, most of the disease manifestations were found to be quite similar in both longer and shorter delay group. There were significantly more females and immigrants among patients with longer delay. Additionally, they observed a lower prevalence of the M694V carriers in the longer delay group which is contradictory to what we and others have found.

In a similar design, Tezcan *et al*. studied diagnostic procedures that could affect early *versus* late diagnosis (9). Median diagnostic delay found in their study was quiet similar to ours: 11 [IQR: 3-18] years. Disease characteristics and the M694V carriers were found to be similar between early (n=67) and late diagnosed cases (n=76). While all medical tests, diagnostic procedures and referrals were performed less often, genetic testing was done more frequently among the early diagnosed patients.

We showed that patients with early disease onset were more likely to have a longer delay and to be diagnosed erroneously as ARF. Several studies have shown that patients with FMF with early disease onset during childhood had more severe disease, higher frequency of M694V carriers and a significant delay in disease diagnosis (1, 10-14). On the other hand, the age of onset of FMF varies considerably and the definition of early *versus* late onset is unclear. Early onset was defined as <8, <18, <20 or <40 years (1, 10, 11, 13). Paediatricians may even define as early onset children who are <2 or <3 years of age at initial attack (15, 16). Although early onset patients evolve over the course of illness to manifest a

severe clinical phenotype, they present usually with atypical forms (10, 15, 16). Joint attacks (arthritis/arthralgia or ELE) or fever episodes could be the sole manifestations in these patients and the smaller the age of disease onset, the more likely their diagnoses are delayed (15). The proportion of patients with arthritis and/or ELE as the first symptom in our study was found considerably higher than that reported in a paediatric cohort survey (n= 708) by Barut *et al*. (29% *vs*. 5.5%) (17). Barut *et al*. observed that 39 patients (5.5%) were diagnosed with FMF solely after recurrent arthritis attacks without any fever and serositis (17). Overall the frequencies of ELE (30%) and arthritis (41%), separately, in the paediatric cohort were also lower than that found in our study (cumulative rate for arthritis and/or ELE: 66%). It has to be noted that direct comparison of a paediatric and adult cohort would not be justified due to the obvious referral patterns and methodological differences. Interestingly, we observed that most patients do not report arthritis and/or ELE as a part of FMF unless we insist asking in detail, because they do not realise the joint problem could be related to their disease. Both patient's and physician's negligence could be responsible for this misinformation. A major concern in misdiagnosis with ARF is that patients receive penicillin treatment for years, which not only delays initiation of colchicine treatment, but also prevents further diagnostic investigation. In this setting, as some authors have suggested, MEFV gene investigation could be crucial in a patient who presents with recurrent attacks of arthritis/arthralgia or ELE (7, 9, 18).

Association of FMF with ARF could be another vague possibility, as noted in a large Turkish nationwide survey including 2838 patients. The frequency of ARF associated with FMF was reported to be 5% (1). While the authors thought these patients had been diagnosed erroneously as having ARF, increased frequency of MEFV gene mutations has been reported among patients with rheumatic heart disease indicating a possible association of these two diseases (19).

Yet, early disease onset, which was shown to be associated with ARF diagnosis, does not explain the high frequency of misdiagnosis with appendicitis (46%) or other gastrointestinal disorders (24%). In line with what was found in other studies, we could not find any variable that could be associated with misdiagnosis other than ARF. While it is quite difficult to establish the underlying causes of misdiagnosis/diagnostic delay, it could be due to merely patients' or physicians' negligence as suggested by Lidar *et al*. (6).

This study has several limitations. Females are over-presented most probably because male patients are usually employed and might be unwilling for the routine outpatient control during working hours. All patients were of Turkish ethnicity and followed up in a tertiary rheumatology centre. Therefore our results may not be extrapolated to patients from different ethnic background or other Turkish patients living in rural area. Since we did not include patients with another disease as a control group, we could not be certain about the specificity of our results. Also because the study is retrospective, there are missing data such as MEFV genes or education level. Finally, the methodology of our study which is based on self-assessment questionnaire may be subject to recall bias. However, as suggested by Lidar *et al*., there could be no way to prospectively investigate diagnosis delay (6). Recall bias may have also interfered when patients had difficulty in differentiating arthritis from ELE. Therefore we defined all these joint related symptoms as joint involvement. Also, as the education level of the majority of the patients was high (71%), we presume that the recall bias would be minimum. We assumed that roughly after the year 2000, FMF would be better recognised, with less delay in diagnosis and a lower rate of misdiagnosis. While this was found to be true for the duration of delay, the frequency of misdiagnosis remained almost the same. Considering that most patients in our study have been registered after year 2000, we think that our current healthcare system should take different measures to avoid misdiagnosis.

In conclusion, misdiagnosis frequency is still significantly high and diagnostic delay is long even in a cohort of patients registered after the year 2000 in Turkey. Atypical presentation with solo joint attacks especially among patients with early onset seems to play significant role in misdiagnosis and delay in diagnosis.

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