Diagnosis delay in familial Mediterranean fever (FMF): Social and gender gaps disclosed

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Abstract

Objective

To characterize the factors contributing to a greater than 10 year delay in the diagnosis of familial Mediterranean fever (FMF)

Methods

50 patients, in whom diagnosis of FMF was delayed by more than 10 years, comprised the study population. The clinical, demographic and molecular genetic characteristics were compared to a control group of 50 FMF patients, in whom the diagnosis was made within a reasonable time period (less than 5 years from onset). Additional factors contributing to a delayed diagnosis in the study group, including physician-related factors, patient-related factors, disease-factors and other factors, were studied as well.

Results

Overall, attack sites, duration and severity were comparable among study and control groups. No differences in ethnic origin or family history of FMF were noted between the groups. There were significantly more females ($p = 0.009$), newly-arrived immigrants ($p = 0.005$) and carriers of unidentified MEFV mutations ($p = 0.04$) in the study group. Delayed diagnosis of FMF stemmed from misdiagnosis and physician negligence (70%), as well as from patient negligence (70%). The diagnosis was ultimately made mainly due to a change in disease pattern and other causes, such as diagnosis of FMF in a relative.

Conclusion

The study unveils unexpected causes behind a prolonged delay in the diagnosis of FMF such as social status (immigrant), female gender, physician negligence and lack of patient awareness. The possibility that the delay stems from a milder disease pattern was dismissed.

Key words

MEFV mutation, gender, colchicine, immigration, FMF, diagnosis.

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Introduction

Familial Mediterranean fever (FMF) is a genetic disease, characterized by recurrent episodes of fever and sterile peritonitis, arthritis, pleuritis and erysipelas-like skin eruption, usually lasting 24-72 hours and remitting spontaneously (1,2). In most patients, the disease begins before the age of 20 (2). The clinical expression of the disease is vast, ranging from complete absence of symptoms to debilitating, life threatening manifestations (2). While attacks are accompanied by an increase in acute phase reactants, namely fibrinogen, C reactive protein and serum amyloid A, these may not serve as diagnostic tests, as they are all nonspecific and usually revert to normal once the attack subsides.

Molecular analysis of the FMF gene, termed MEFV, identifies mutations in the majority of, but not in all, FMF patients (3-5). Moreover, population based studies, looking at the frequency of mutation carriers and at the actual number of individuals with 2 disease associated mutations, have shown that the prevalence of overt FMF is far below that expected, indicating that the majority of individuals, who fulfill the genetic criteria for FMF, remains unaffected (5-8).

Thus, limited by phenotypic variability, absence of pathognomonic laboratory tests, and a mutation analysis that is neither sensitive nor specific, the diagnosis of FMF is difficult to establish. This forms the basis for the diagnosis delay, documented in a significant number of patients. However, the concrete factors underlying a significant diagnosis delay were never thoroughly investigated. The present study sought to identify the clinical, demographic, genetic and social factors that predispose patients to a delayed diagnosis of FMF.

Materials and methods

Setting

The National Center for FMF (also called the FMF Clinic) at the Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, is the main facility for diagnosis and treatment of FMF patients in Israel. It serves patients referred by primary care physicians and specialists from all over the country. At the time of the study, the registry consisted of 7000 patients, half of whom are being followed-up annually, or more frequently if required. Most of the patients were diagnosed in our center, usually at first presentation based on their history, letter of referral and other documents. The diagnosis is purely clinical. Mutational analysis of the MEFVserves only as an ancillary tool.

Study group

The study population (cases) included 50 patients, enrolled at the FMF clinic of the Chaim Sheba Medical Center, Tel-Hashomer, in whom the diagnosis of FMF was made ≥ 10 years after disease onset. All patients fulfilled the clinical criteria for the diagnosis of FMF (9). Patients were recruited consecutively during their routine follow-up visits to the FMF clinic. All patients underwent a clinical interview and examination. The overall severity of their disease was estimated, using an accepted score accounting for the age of onset, frequency of attacks at any site, presence of arthritis and erysipeloid eruption, amyloidosis and colchicine dose (10). A site specific severity of the attack was estimated using a visual analogue scale (VAS) with 10 degrees of severity. MEFV genetic analysis for the 3 most common mutations in our population (M694V, V726A, E148Q) was performed, using published techniques (5).

Control group

The control group comprised 50 consecutive patients, arriving at the clinic for a routine follow-up visit, in whom the diagnosis of FMF was made within 5 years of symptom onset. Patients of the control group underwent clinical and genetic analysis similar to that of the study group. No attempt was made to clinically or demo-graphically match the 2 populations.

Study questionnaire

A questionnaire, probing detailed clinical and demographic information, was completed for each individual based on

patient history and examination, as well as on data abstracted from the clinical charts. The age of onset and of diagnosis were obtained from the charts, which always included these data and a detailed description of the manifestations, leading to the decision on these items. During the interview with the patients of the study group, potential causes leading to diagnosis delay were examined, discussed for each case, and those elucidated were allocated into one of 4 categories as follows:

I. Disease related-causes, such as mild or infrequent attacks, responding favorably to analgesic treatment with long remissions and atypical manifestations (e.g., absence of fever); II. Patient related causes, such as misinterpretation and avoidance of medical help; III. Physician related causes, such as misdiagnosis, very long work-up or denial of expert help; and IV. Other causes such as frequent substitution of family practitioners.

The parameters that eventually led to the correct diagnosis were also examined and allocated into one of the above mentioned categories.

Analysis of the data obtained by the questionnaire

Differences between categorical variables were analyzed using chi-square test or Fisher's exact test, according to the size of the cells examined. Student t test was used for comparison of continuous variables between the two study groups. All tests of significance were two-tailed; p-values of < 0.05 were considered statistically significant.

Multivariant logistic regression analysis was carried out to determine which factors were independently associated with the delay in the diagnosis of FMF, accounting for gender, place of birth (immigrant versus Israeli-born), age at disease onset, disease severity and genotype.

Results

The study and control populations comprised 50 patients each. Demographic and background data is summarized in Table I. Cases were significantly older than controls (mean age: 44.5 vs. 30 years, respectively, $p = 0.001$). The percentage of women among the cases was significantly higher than among the controls (66% vs. 38%, $p = 0.009$). A greater majority of patients of the control group were Israeli-born (90% vs. 60% of the study patients, $p = 0.001$). North African and Iraqi Jewish descent predominated among both cases and controls. Family history of FMF was equally prevalent in both groups, as was age of disease onset (≤ 20 years). Age of disease diagnosis differed significantly between the groups; while the diagnosis was made in most patients of the control group before the age of 20, the cases were only diagnosed at a mean age of 31 years. Part of the difference in the age of diagnosis was determined by the requirement of a minimum of 10 years delay in diagnosis for inclusion in the study group. Finally, both groups were diagnosed around the same calendar year (Table I). Therefore, one may not speculate that improved diagnostic abilities underlied earlier diagnosis.

Abdominal attack characteristics were comparable between the groups with regard to frequency, severity, duration and need for analgesic relief (Table II). Of note is the increased frequency of "classical", diffuse abdominal attacks among control group patients. No significant differences in joint attack and chest attack characteristics were reported between the groups (Table II). No differences were reported in the incidence of pericarditis, erysipelas-like erythema, fever, scrotal attacks and myalgia (Table II).

Similar rates were reported for chronic or protracted manifestations including chronic arthritis or exertional leg pain, proteinuria, anemia, hematuria and renal insufficiency (Table III). More cases underwent an appendectomy, suggesting a role for misdiagnosis and diagnostic delay in excess of this operation (Table III). Alternatively, more aggressive attacks, with higher rates of referrals to the emergency department,

Table I. Demographic and background data.

Parameter		Cases n = 50	Control Group n = 50	p value
Current age (years)		44.5 ± 15.8	30.4 ± 15.8	0.001
Women		33 (66)*	19 (38)	0.009
Country of birth	Israel	30 (60)	44 (88)	0.001
	Asia and North Africa	18 (36)	4 (8)	
Ethnic origin	North Africa and Iraq	40 (80)	32 (64)	NS
One or more relatives with FMF		34 (68)	36 (72)	NS
Age at onset ≤ 20 years**		35 (70)	34 (68)	NS
Age at diagnosis (years)	≤ 20	7 (14)	34 (68)	0.001
	21-30	22 (44)	13 (26)	
	≥ 31	21 (42)	3 (6)	
Calendar year at:	Onset	1971 ± 13.1yrs	1985.7 ± 11.4yrs	—-
	Diagnosis	1987.8 ± 11.3yrs	1987.6 ± 11yrs	—-
Diagnostic delay (years)		15.7 ±13.8	1.8 ± 1.5	0.001

*Numbers in parentheses denote % of patients; **the age of onset and at diagnosis were abstracted from the charts; NS: not significant.

Table II. Attack characteristics.

Site of attacks	Parameter		Cases n = 50	Control group n = 50	p value
Abdominal	Prevalence		48 (96)	48 (96)	NS
	Type	Diffuse	41 (85)	30 (62)	0.02
	Frequency	Once a month	27 (56)	34 (70)	NS
		1 in 3 months	13 (27)	13 (27)	
	Fever	≥ 38°C	40 (83)	40 (83)	NS
	Duration (hours)	> 24	43 (90)	39 (82)	NS
	Severity (VAS)	6-8	18 (38)	19 (40)	NS
		9-10	30 (62)	26 (54)	
	Analgesics use		41 (85)	36 (75)	NS
Joint	Prevalence		32 (64)	32 (64)	NS
	Type	Arthritis	18 (56)	21 (65)	NS
	Extremity	Lower	19 (60)	24 (75)	NS
	Frequency	Once a month	19 (59)	15 (47)	NS
		1 in 3 months	8 (25)	11 (34)	
	Fever	≥ 38°C	17 (53)	17 (53)	NS
	Duration (hours)	> 24	23 (72)	24 (75)	NS
	Severity (VAS)	6-8	9 (28)	5 (16)	NS
		9-10	20 (63)	20 (63)	
	Analgesics use		25 (78)	22 (69)	NS
Chest	Prevalence		20 (40)	23 (46)	NS
	Type	Unilateral	9 (45)	16 (69)	NS
	Frequency	≥ 1 in 3 months	13 (65)	18 (70)	NS
	Fever	≥ 38°C	13 (65)	15 (65)	NS
	Duration (hours)	> 24	12 (60)	20 (86)	NS
	Severity (VAS)	9-10	14 (70)	20 (87)	NS
	Analgesics use		12 (60)	20 (87)	NS
Pericard	Prevalence		2 (4)	1 (2)	NS
Muscles	Prevalence		15 (30)	9 (18)	NS
Scrotum	Prevalence		1 (6)	6 (19)	NS
ELE	Prevalence		9 (18)	12 (24)	NS
Fever alone	Prevalence		8 (16)	11 (22)	NS

Parentheses include % of patients.
NS: not significant; ELE: erysipelas-like erythema; VAS: visual analogue scale.

Table III. Chronic clinical manifestations, laboratory findings and other diseases.

Chronic affection	Parameter	Cases n = 50	Control group n = 50	p value
Clinical	Calf pain	37 (74)	30 (60)	NS
	Chronic arthritis	3 (6)	3 (6)	NS
Laboratory	Proteinuria (≥ 0.5 g/24 hr)	5 (10)	5 (10)	NS
	Renal failure (S Cr ≥1.5 mg/ dcl)	-	1 (2)	NS
	Hematuria	5 (10)	8 (16)	NS
	Anemia (hemoglobin ≤ 11 g/dcl)	8 (16)	8 (16)	NS
Other diseases	Hypertension	7 (14)	2 (4)	NS
	Appendectomy	25 (50)	14 (28)	0.04
	Diabetes mellitus	3 (6)	1 (2)	NS
	Asthma	5 (10)	2 (4)	NS
	Esophageal reflux	6 (12)	1 (2)	NS

Parentheses include % of patients. NS: Not significant; S Cr: serum creatinine.

can explain this discrepancy. Other associated diseases were reportedly the same.

Compliance with colchicine intake was fair among both groups (Table IV). A daily dose of 1 mg colchicine sufficed to prevent attacks in more control patients than cases (54% vs. 32%, p = 0.04). Disease severity was moderate in both groups (Table IV).

Significant, albeit mild, differences in the MEFV genetic characteristics were found: more patients of the control group carried two mutated MEFV alleles, while more cases had no identifiable mutations (Table V). The overall frequency of the 3 screened mutations was similiar between the 2 groups (Table VI), yet a greater number of M694V mutation carriers was discerned among control group patients with joint attacks (p = 0.03).

The multivariant regression analysis of the factors, possibly associated with a delayed diagnosis, revealed that a birthplace outside Israel (an immigrant) is the only significant factor leading to a delay in the diagnosis of FMF (Table VII). However, female patients and carriers of any disease associated alleles, other than the M694V/M694V genotype, showed a

Table IV. Colchicine treatment and disease severity.

Chronic affection	Parameter		Cases n = 50	Control group n = 50	p value
Colchicine treatment	Duration of colchicine therapy (years)		11.68 ± 9.1	12.54 ± 9.2	NS
	Colchicine dose (mg/day)	1	16 (32)	27 (54)	0.04
		1.5	13 (26)	8 (16)	
		≥ 2	21 (42)	15 (30)	
	Good compliance*		39 (78)	33 (66)	NS
Overall disease severity	2-5		13 (26)	19 (38)	NS
	6-8		22 (44)	21 (42)	
	9-14		15 (30)	10 (20)	

Parentheses include % of patients;
NS -Not significant;
* Estimated by omission of less than 2 doses during the month preceded patient examination.

Table V. MEFVmutation analysis.

Mutation	Cases (n = 50)	Control group (n = 50)	p value
+/+	27 (54)	35 (70)	0.04
+/?	13 (26)	13 (26)	
?/?	10 (20)	2 (4)	

Parentheses include % of patients.
MEFV: MEditerranean FeVer gene.
+/+ Homozygous or compound heterozygous patient.
?/? None of the studied mutations were found.
+/? Heterozygous patient carrying one of the studied mutations.

Table VI. MEFV mutations and disease characteristics*.

Mutations	All manifestations			Joint attacks		
	Cases (100)**	Controls (100)	Pvalue	Cases (64)	Controls (64)	p value
E148Q	9	11	NS	4	5	NS
V726A	17	18	NS	8	11	NS
M694V	41	55	NS	28	40	< 0.03
Untested mutations	33	16	NS	24	8	—

*The distribution of mutations in cases with abdominal and chest attacks (not shown) is comparable to that of controls with these manifestations, respectively.
**Parentheses include the number of studied chromosomes (equals to 2x the number of cases or controls with the indicated manifestation).
NS: Not significant, MEFV: MEditerranean FeVer gene.

trend for late diagnosis of FMF. The age of onset and the severity score of the disease could not be linked to a diagnosis delay (Table VII).

The identified causes possibly underlying the diagnosis delay, as per the discussion between cases and the examining physician, varied and were multiple in the individual patients (Fig. 1). In most cases the delay in diagnosis resulted from a combination of physician and patient-related causes (Fig. 1). Of note is that a mild disease or an unusual disease course contributed to the diagnosis delay only infrequently. The ultimate diagnosis was usually made not due to physican or patient-related causes, but rather due to a change in disease manifestations or a coincident diagnosis of FMF in an acquaintance or a family member, designated as other causes (Fig. 2).

Discussion

The study points out that delayed diagnosis occurs more commonly in immigrant, female patients who carry rare MEFV mutations. Though cases, unexpectedly, experienced a somewhat more vigorous disease, reflected by an increased frequency of diffuse abdominal attacks, a larger number of appendectomies and a higher colchicine dose to suppress disease activity, other disease manifestations, including frequency and severity of attacks in each site, were quite similar in both cases and patients of the control group (Table II). Hence, the concurrent finding that the delayed diagnosis resulted from physician and patient related causes rather than a milder disease or other disease characteristics (Fig. 1), as would be expected, was complementary and corroborative. In most cases, the diagnosis was ultimately made due to a change in the disease course itself or as a result of auxiliary reasons such as a diagnosis of a contact (Fig. 2).

The minor genetic variation between the cases and the control group (Tables V and VI), including a higher prevalence in cases of unidentifiable MEFV alleles and a lower prevalence of the M694V allele, may imply a milder disease in cases (11). Still, we assume that this slight molecular difference is inconsequential, as the comprehensive description of disease manifestations obtained from cases, as well as their site specific VAS and our overall calculated severity score (Table II), imply a disease of equal severity between the two groups of patients. Additionally, the similar age of onset, ethnic origin and frequency of family history of FMF in both groups, indicate a comparable genetic background (Table I).

The disproportionate number of women among cases is an issue of major concern. Gender issues have received increased attention in social and medical science and there is a growing body of literature on “gender discrepancies” in the management of female patients (12). It has been established that women with cardiovascular disease are often subjected to incorrect diagnosis and treatment (13). Studies on gender differences in FMF are scarce. The 3:2 male:female ratio in FMF is unexplained by its autosomal recessive inheritance. Furthermore, this “male

Table VII. Factors associated with a delay in the diagnosis of FMF (by multivariant analysis).

Parameter	OR	95% CI	p value
Female versus male	2.45	0.97 – 6.21	0.06
Immigrant versus Israeli-born	5.51	1.69 – 17.95	0.005
Age of onset	1.01	0.94 – 1.07	0.9
Disease severity score	1.16	0.93 – 1.43	0.2
M694V/M694Vversus others	0.26	0.07 – 1.04	0.06
M694V/V726Aversus others	0.33	0.07 – 1.46	0.14
V726A/V726Aversus others	0.49	0.33 – 18.48	0.4
E148Q/V726Aor M694Vversus others	0.41	0.1 – 1.61	0.2

OR: Odds ratio; CI: Confidence interval.

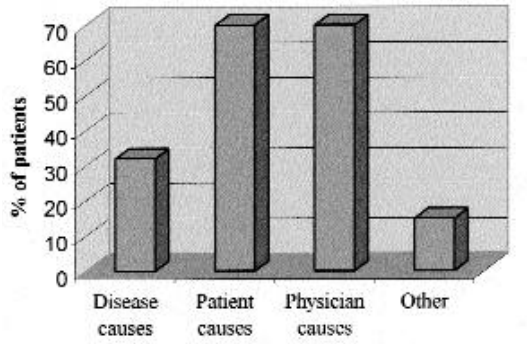

Fig. 1. Distribution of factors causing delayed diagnosis.

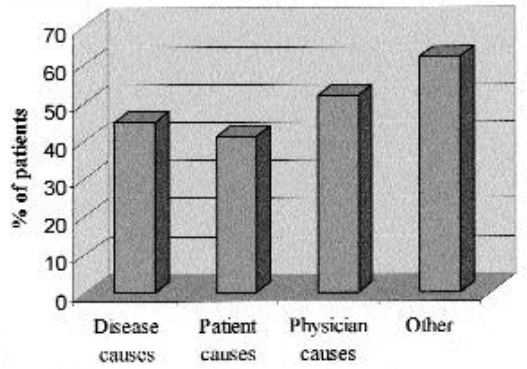

Fig. 2. Distribution of factors eventually leading to diagnosis after prolonged delay.

preponderance" first becomes evident only after sexual maturation, as the disease is equally prevalent in children of both sexes (2). The general assumption is that the gender discrepancy in FMF results from hormonal factors or associated, modifying genes which generate a disease of milder severity in females, which is hence diagnosed at a later stage. Our findings challenge these views by dismissing the role of lower disease severity as a key factor in delayed diagnosis, thus bringing forward the possibility that socioeconomic factors may contribute to a delay in the diagnosis of FMF in females, and in the meantime, falsely skew the disease sex ratio in favor of males. In addition, it has previously been shown that in female FMF patients, dolorimeter thresholds of fibrositic and control point sites were significantly lower than in male patients with FMF (14). Associated fibromyalgia may therefore contribute to misdiagnosis and delayed diagnosis in female FMF patients. Whether the gender difference in diagnosis delay translates into differences in patient outcomes is a concern which remains to be ascertained.

The preponderance of immigrants among the study group patients points to additional factors such as language barriers, adjustment difficulties and socioeconomic inferiority, which may play a part in the diagnostic delay. Immigration of families seeking work opportunities from countries highly affected by FMF to central and northern Europe, as well as to North America, turns FMF, once limited to the Mediterranean basin alone, to a true worldwide diagnostic concern in cases of episodic febrile disease. The pattern of diagnostic neglect in women immigrants may just repeat itself in the new homelands of these individuals.

Seventy percent of cases implicated physician-related factors in their delayed diagnosis (Fig.1). This is particularly surprising considering the high disease prevalence and carrier frequency in Israel, ranging from 1:3 (in Iraqi Jews) to 1:10 (in Ashkenazi Jews) (7). Considering the mortality associated with the disease, the need to spread current knowledge among colleagues and medical students is obvious.

The main limitations of the study are its retrospective nature and its localization to a certain country, which has a rather specific demographic structure. Yet, there is no way to prospectively investigate diagnosis delay, and the extraterritorial implications of our findings were discussed earlier. Another limitation may arise from disregarding personality traits, pain threshold, education level and other variables, some of which may underlie diagnostic delay. Yet, these factors may change only slightly the findings in Figure 1, and thus not disrupt our main findings and conclusions, that factors which mostly contribute to a 10 or more year delay in the diagnosis of FMF are gender gap, immigrant status and physician and patient ignorance.

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