Familial Mediterranean fever in small children in Turkey

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ABSTRACT

Objectives. *Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterised by recurrent, self limited attacks of fever with serositis. The aim of our study was to describe the demographic, clinical and genetic features of FMF patients who had early disease onset and to compare them with late onset patients. Our second aim was to investigate the factors associated with delay in diagnosis.*

Methods. *The study group consisted of recently diagnosed FMF patients who came to routine follow-up visits between January and July 2009. Patients were divided into two groups according to age of disease onset (Group I: ≤3 years of age; Group II: >3 years of age). In the second part, patients were analysed according to the duration of delay in diagnosis.*

Results. *There were 83 patients in group I and 73 patients in Group II. Median delay in diagnosis was 4 years in Group I and 2 years in Group II ($p<0.001$). The presence of M694V mutation was more frequent in Group I (81%) as compared to Group II (65%), ($p=0.034$). Mean attack Hb was lower ($p<0.01$) and mean attack leukocyte count was higher ($p=0.017$) in Group I. Final colchicine dosages were higher in Group I as compared to Group II. There was a statistically significant negative correlation between the age at disease onset and period of delay in diagnosis ($p<0.001$).*

Conclusion. *This study suggests that FMF patients with early disease onset have more severe disease. Moreover, the smaller the age of disease onset, the more likely their diagnoses are delayed.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease of childhood characterised by recurrent attacks of fever and inflammation in the peritoneum, synovium, or pleura, accompanied by pain (1-3).

The gene responsible for FMF, designated as *MEFV*, encodes pyrin expressed primarily in the myeloid cell lineage that affects the inflammatory response by regulating the processing of interleukin-1β (IL-1 β). Although the FMF gene was identified more than a decade ago, the diagnosis is still based on clinical criteria (4, 5). Despite high carrier frequencies in our and other severely affected populations, the prevalence of FMF is less than expected; indicating that the disease is under diagnosed. In a multicentre study, representing the largest series of FMF that includes all age groups, it was shown that the prevalence of amyloidosis, the most severe manifestation of the disease is still alarmingly high (13%) (6). This might be a reflection of the delay in diagnosis and/or misdiagnosis. In fact, in the same study, the patients who developed amyloidosis were younger at disease onset, and the delay in diagnosis was significantly longer. Although most of the patients have symptoms in younger ages even in very early days of their lives, there is very little information about the clinical features of FMF in small children.

The aim of our study was to describe the demographic, clinical and genetic features of FMF patients who had early disease onset and to compare them with late onset patients. Because of the fact that early diagnosis and daily colchicine treatment have a key role in preventing FMF attacks and the development of amyloidosis, our second aim was to characterise the factors associated with delay in diagnosis.

Methods

The Paediatric Nephrology Department of Ankara University is one of the major paediatric nephrology centres in

Turkey and serves as a referral centre for the diagnosis, treatment and follow up of the patients with FMF since 1990. More than 500 children were actively on follow up with updated patient files in our clinic. The study group consisted of FMF patients (diagnosed within the last 10 years) that came to routine follow-up visits to our outpatient clinic between the dates of January 2009 and July 2009. All patients who came to control visits during the study period were included. Parents of the patients were interviewed by one of the authors about the onset and clinical features of the disease. In addition, files of patients were carefully evaluated retrospectively about the demographic data, clinical and laboratory features (complete blood count, erythrocyte sedimentation rate, C-reactive protein, fibrinogen levels of the attack and attack free period) of the disease and genetic analysis of *MEFV* mutations. The diagnosis of FMF was based on the previously described diagnostic criteria (7, 8). Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the *MEFV* gene were studied in most of the patients. Exon 10 of the *MEFV* gene was screened using direct sequencing of the PCR amplified fragments. The p.E148Q mutation was analysed with a previously reported PCR restriction fragment length polymorphism (RFLP) protocol (9, 10).

In the first part of the study the patients were divided into two groups according to age of disease onset: Group I includes the patients who presented their first attack before or equal to 3 years of age; Group II includes the patients who presented their first attack after 3 years of age. We think that at three years of age children can express themselves better (for example describe abdominal pain more easily), thus we choose age 3 as a cut-off level. In the second part, the study group was categorised into three groups and analysed according to the duration of delay in diagnosis. Group A includes the patients in whom the diagnosis was made 1–12 months after the disease onset whereas Group B encloses the patients 13–59 months and Group C ≥60 months diagnostic delay. Informed consent was obtained from the parents of each patient and the study was approved by the institutional ethics committee.

Statistical analysis

Results are given as a mean ± standard deviation or proportion as appropriate. Categorical variables were evaluated by Chi-square test or Fisher's exact test, where applicable. Comparison between two groups for the non-normally distributed continuous variables was assessed by Mann Whitney U-test. Difference among three groups for the non-normally distributed continuous variables was evaluated by Kruskal-Wallis variance analysis. When the *p*-value from the Kruskal-Wallis test statistics is statistically significant, multiple comparison test was used to know which group differs from which others (11). Degree of association between non-normally distributed continuous variables was calculated by Spearman's correlation coefficient.

Results

The study group consisted of 156 FMF (80 female, 76 male; mean age 12.67±5.5 years) patients. Mean follow up period was 58.4±45.0 months. Demographic features and clinical findings of the study group are shown in Table I. Mutation analysis was performed in 137 of the 156 patients. Forty one (30%) patients had homozygous, 46 (34%) had compound heterozygous and 36 (26%) had heterozygous mutations. Fourteen patients (10%) had none of the screened mutations. The most frequent mutations are M694V/M694V (24%), M694V/- (16%), M694V/M680I (15%) and M694V/V726A (7%). Overall 101 of the 137 patients (74%) had at least one M694V mutation. Erysipelas-like erythema (ELE) was described in 8% of the patients and we have only 6 patients (4%) with attacks of fever alone. Vasculitis, protracted arthritis, protracted febrile myalgia occurred in 7%, 4% and 4.5% of the patients, respectively. Colchicine response was evaluated in 145 patients (the rest were newly diagnosed patients). Attacks completely disappeared in 67%, frequency and duration decreased in 31% and colchicine resistance was seen in 2% of the patients. Attack-free acute phase response was high in 17% and colchicine side effects were observed in 5% of the patients.

There were 83 patients who presented their first attack at or before three years of age (Group I) and 73 patients who presented their first attack after three years of age (Group II). Comparisons of the two groups are shown in Table I. Median delay in diagnosis was longer and the presence of M694V mutation was more frequent in Group I. Mean attack and attack free Hb was lower and mean attack leukocyte count was higher in Group I ($p<0.05$). Colchicine dosages were similar between groups at the beginning. However, final colchicine dosages were higher in Group I as compared to Group II. Interestingly 32.5% of the families in group I and 17.8% of the families in group II describe their child as fussy about trifles ($p=0.036$). On the other hand, clinical features, attack frequency, attack duration, consanguinity, appendectomy history, family history of FMF, family history of renal disease and colchicine response were similar between the groups (Table I).

The second part of the study that includes three groups according to the duration of the delay in diagnosis revealed the following results. There were 48, 57 and 51 patients in Groups A (1–12 months delay), B (13–59 months delay) and C (≥60 months delay), respectively. Sixty nine percent of the patients in Group C had disease onset ≤3 years of age and conversely 67% of the patients in Group A had disease onset >3 years of age ($p=0.002$). Family history of FMF was more frequent in Group C as compared to Group B (52% in Group A, 37% in Group B and 61% in Group C) ($p=0.013$). Clinical findings, attack frequency, attack duration, consanguinity and laboratory results were similar among all groups. There was a statistically significant negative correlation between the age at disease onset and period of delay in diagnosis ($p<0.001$).

Discussion

In this study we showed that in Turkey the main clinical characteristics of FMF

Table I. Comparison of demographic features and clinical findings of Group I and II.

	Study group n=156 (%) Mean ± SD;	Group I n=83 (%) Median (min-max)	Group II (n=73) (%) Median (min-max)	*p*-value
Sex Male	76 (49)	41 (49)	35 (48)	0.856
Female	80 (51)	42 (51)	38 (52)	
Age at disease onset (years)	4.3 ± 3.6	2 (0.1–3)	6 (3.5–17)	**<0.001**
Age at onset of therapy (years)	8.0 ± 4.1	6 (1.5–15)	9 (4–24)	**<0.001**
Delay in diagnosis (years)	3.7 ± 3.2	4 (0–13.5)	2 (0–15)	**<0.001**
Clinical features				
Abdominal pain	135 (87)	75 (90)	60 (82)	0.13
Fever	142 (91)	78 (94)	64 (88)	0.16
Chest pain	54 (35)	26 (31)	28 (39)	0.35
Arthritis	28 (18)	12 (15)	16 (22)	0.22
Arthralgia	50 (32)	23 (28)	27 (37)	0.21
Heel pain	25 (16)	17 (21)	8 (11)	0.10
Leg pain	46 (30)	28 (34)	18 (25)	0.21
Fussy about trifles	40 (26)	27 (33)	13 (18)	**0.03**
Attack frequency (attacks/year)	17.0 ± 13.0	12 (0–48)	12 (0–48)	0.53
Attack duration (hours)	52.0 ± 27.5	48 (0–120)	48 (0–168)	0.27
Appendectomy history	17 (11)	7 (8)	10 (14)	0.29
Consanguinity	31 (20)	16 (19)	15 (21)	0.84
Family history of FMF	77 (49)	44 (53)	33 (45)	0.33
Family history of renal disease	45 (29)	24 (29)	21 (29)	0.98
Presence of M694V mutation*	101 (74)	60 (81)	41 (65)	**0.034**
Attack Hb (g/dl)	12.1 ± 1.2	11.6 (7.8–14)	12.7 (9.1–15.8)	**0.001**
leukocyte count (/mm^3)	12823.5 ± 5402.5	13000 (6900–29700)	10500 (4800–25600)	**0.017**
ESR (mm/h)	54.2 ± 26.4	52 (8–122)	44 (14–122)	0.12
C-reactive protein (mg/dl)	11.2 ± 15.2	9.5 (0.6–80)	6.7 (0.5–126)	0.16
Fibrinogen (mg/dl)	481.9 ± 127.2	464 (252–888)	442 (243–914)	0.08
Attack free Hb (g/dl)	12.3 ± 1.3	12.0 (7.1–16.7)	12.5 (10.1–15.0)	**0.001**
Initial colchicine dosage				
mg/kg/day	0.05 ± 0.07	0.038 (0.01–0.3)	0.035 (0.01–0.66)	0.11
mg/m^2/day	0.99 ± 0.31	1.0 (0.29–2)	0.95 (0.52–2)	0.25
Final colchicine dosage				
mg/kg/day	0.03 ± 0.03	0.033 (0.02–0.33)	0.025 (0.01–0.06)	**<0.001**
mg/m^2/day	0.95 ± 0.30	0.96 (0.37–1.92)	0.86 (0.07–.57)	**0.038**

*Mutation analysis was performed in 137 of the 156 patients.

attacks in small children were similar to those in late onset. However, some striking differences were recognised. FMF patients with early onset had more M694V carriage, more severe attacks with higher acute phase response (though statistically insignificant) and needed more final colchicine dosage in order to control the attacks. These data suggest that FMF patients with early disease onset have more severe disease. Two recent studies from Israel emphasised the importance of early diagnosis of FMF in small children (12, 13). Although their study group differs in age range from ours, they found that in up to a third of their patients clinical manifestations begin ≤2 years of age, with attacks of fever alone as the sole manifestation in 13%. In contrast, we have only 6 patients (4%) with attacks of fever alone. Consistent with our results, clinical manifestations were comparable in both early and late onset groups in their cohort, and the delay of diagnosis was longer, M694V carriage was concurrently higher in the patients whose clinical manifestations begin ≤2 years of age.

In this current study we think that two findings are extremely important and worth to mention. One is the fact that there was a significant negative correlation between the age at disease onset and duration of delay in diagnosis. Therefore, the smaller the age of disease onset, the more likely their diagnoses are delayed. Similar results were reported by Padeh *et al*. (12) and he showed that diagnostic delay was more common in patients with disease onset ≤2 years of age. The second point is that family history of FMF was more frequent in patients who had the longest delay in diagnosis. This paradoxical result shows us that physicians do not pay attention to family history and question their patients carefully. Clinicians should consider 'family history of FMF' extremely important and it should be asked for the diagnosis of FMF especially to the patients with early disease onset. The importance of 'family history of FMF' is also proved during establishment of new diagnostic criteria set and constituted one of the 5 criteria (8).

Diagnosis of FMF in early childhood requires an awareness of the clinical findings of the disease in small children. Although physicians are familiar with the disease, patients under the age of three are sometimes misdiagnosed as having infectious diseases, fever of unknown origin or "surgical" emergency. Unfortunately, some of them later present with amyloidosis in our country. Lack of parents' awareness is another important factor in the diagnostic delay in small children with FMF. It seems necessary to make the population aware of the early presentation of FMF in order to prevent a delay in diagnosis and development of amyloidosis. In addition, as the clinical features of FMF in the early years of life become familiar throughout the world, well-documented patient groups might be reported from the populations in which the disease is rare.

In conclusion, this study unveils interesting results about the clinical features of FMF in small children. The possibility of delay in diagnosis due to milder disease course in small children was rejected because of the findings that Turkish FMF patients with early onset had more M694V carriage and needed more final colchicine dosage in order to control the attacks. We suggest that improvement in the awareness of parents and diagnostic capabilities of the physicians will provide earlier diagnosis in small children with FMF. Accumulation of the knowledge about the early-onset disease may lead to a higher perception for the early diagnosis of FMF throughout the world.

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