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ORIGINAL ARTICLE

Late-onset disease is associated with a mild phenotype in children with familial Mediterranean fever

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Abstract Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterised by recurrent, self-limited attacks of fever with serositis. Recently, it was shown that patients with early disease onset during childhood period had more severe disease. The aim of this study was to describe the demographic, clinical and genetic features of FMF patients who had late-onset disease during childhood period and to compare them to those with earlier onset patients. Files of patients who had been seen in our department between January 2013 and January 2014 were retrospectively evaluated. Patients were divided into two groups according to age of disease onset (group I, ≤8 years; group II, >8 years), and clinical findings were compared between the two groups. The study group comprised 317 FMF patients. There were 267 patients in group I and 50 patients in Group II. Median attack frequency was 24/year in group I and 12/year in group II ($p < 0.05$). Fever and M694V homozygosity were less frequently detected in group II ($p = 0.003$ and $p = 0.022$). Median delay in diagnosis was 24 months in group I and 12 months in group II ($p = 0.002$). Disease severity scores and final colchicine dosages were lower in group II ($p < 0.001$ and $p = 0.003$). Only a small number of FMF patients had disease onset at older ages in childhood period. It seems that FMF patients with late-onset disease have milder illness. However, more readily expression of their clinical findings in older ages yields earlier diagnosis in this group.

Keywords Disease severity · Familial Mediterranean fever · Late onset · Paediatric

Introduction

Familial Mediterranean Fever (FMF) is the prototype and the most common autoinflammatory disease, with the main clinical features of recurrent attacks of fever and inflammation of the peritoneum, pleura, joints and skin [1–3]. The prevalence of FMF is 1/1000–1/250 among Jews, Turks, Armenians and Arabs [4, 5]. 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-1β). Although the FMF gene was identified more than a decade ago, the diagnosis is still based on clinical criteria.

The age of onset of FMF varies. In about 60 % of patients, the first attack occurs before the age of 10, in 90 % before reaching 20 years and in most of the rest before 40 [2]. On the other hand, Majeed and colleagues had shown that in 14 % of patients with FMF, the symptoms begin after the age of 10 years [6]. Recently, it was shown that patients with FMF with early disease onset during childhood had more severe disease and a significant delay in disease diagnosis [7, 8]. Further, Tamir et al. [9] showed that in adults, late-onset disease seems to be milder. The aim of this study was to describe the demographic, clinical and genetic features of FMF patients who had late-onset disease during childhood period and to compare them with early-onset patients. Our hypothesis is that

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late-onset FMF patients may have different clinical profiles and milder disease course.

Materials and methods

Files of patients who had been seen in our department (during routine follow-up visits) between January 2013 and January 2014 were retrospectively evaluated. An information form was completed about demographic data, family history, clinical features, laboratory tests and genetic analysis of MEFV mutations. The diagnosis of FMF was based on the presence of clinical criteria [10]. Disease severity was determined by the use of scoring systems determined by Pras et al. [11] (with relevant changes made according to children, i.e. in the age factor and also in the colchicine dosages) [12]. At least six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the *MEFV* gene were studied. 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 [4, 5]. Patients were divided into two groups according to age of disease onset: Group 1 included patients who had their first attack ≤8 years, and group 2 comprised patients who had their first attack >8 years of age. 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 mean ± SD, median (minimum-maximum) or proportion as appropriate. Categorical variables were evaluated with chi-square test. Comparison between two groups for the non-normally distributed continuous variables was assessed by the Mann-Whitney *U* test. A p value < 0.05 was considered significant. All of the analyses were performed using SPSS Version 22.

Results

The study group comprised 317 FMF patients (170 females, 147 males) with a mean age of 12.2 ± 5.7 years. Mutation analysis was performed in 299 of the 317 patients. Ninety-seven (32.4 %) patients had homozygous, 83 (27.8 %) had compound heterozygous and 83 (27.8 %) had heterozygous mutations. Thirty-six (12 %) patients had none of the screened mutations. The most frequent mutations were M694V/M694V (28.7 %), M694V/− (15.7 %), M694V/M680I (10.7 %) and M694V/V726A (5.6 %).

There were 267 (84.2 %) patients in group I and 50 (15.8 %) patients in group II. Comparisons between the two groups are shown in Table 1. Median delay in diagnosis and attack frequency before colchicine therapy were lower in group II ($p < 0.05$). Although the frequency of majority of the clinical features did not differ between the groups, fever was seen less frequently in group II patients. M694V mutation was also less frequently detected in group II patients. Median disease severity score and final colchicine dosages were lower in group II ($p < 0.05$). Attack and attack-free acute phase reactants did not differ between the two groups ($p > 0.05$).

Discussion

In this study, we found that only a small number of FMF patients had disease onset at older ages in childhood period (15.8 %). These late-onset patients had less fever during the attacks, lower M694V carriage, lower disease severity scores and colchicine dosages confirming mild disease phenotype. On the other hand, the diagnosis of FMF was not significantly delayed at late-onset patients.

It is known that fever and abdominal pain attacks are the most common symptoms, occurring in >90 % of patients with FMF [13]. Recently, in two studies, the clinical findings of patients with very early disease onset (≤2–3 years of age) during childhood period were evaluated [7, 8]. It was found that clinical manifestations were comparable in both early- and late-onset patients. However, Padeh et al. [8, 14] found that a subgroup of patients who were diagnosed at ≤2 years had the highest rate of attack of fever as their sole manifestation. Interestingly, in this study, we found that attack frequency was lower and fever was seen less frequently in those patients who had their first attack >8 years of age. The other major clinical findings did not differ between the groups. On the other hand, it was found that arthritis and erysipelas like erythema were significantly less frequent in patients with adult-onset FMF (≥20 years old) when compared to patients with disease onset before 20 years of age [15, 16]. Tamir et al. [9] also evaluated late-onset FMF during adulthood period including all patients experiencing their first FMF attack at age 40 years or more. All had abdominal attacks and in most, these were the only manifestation of their disease. None had chronic or prolonged manifestations of FMF, for example, amyloidosis or chronic arthritis.

After the discovery of *MEFV* gene, genotyping has shown that the disease is associated with a wide variety of symptoms. However, genotype-phenotype relationship is not well established. In general, it was suggested that adult-onset autoinflammatory diseases present with mild forms of the disease and they seem to be associated with the presence of low-penetrance mutations [17]. Some of the previous studies showed that M694V homozygosity was related with a more severe disease. Lidar et al. [18] found that M694V homozygotes had earlier age at diagnosis, more frequent attacks prior

Table 1 Comparison of the patients according to age at disease onset

	Group I $n = 267$ (%) Median (range)	Group II $n = 50$ (%) Median (Range)	p
Age	12.6 (1.5–22)	18.5 (10–23)	*0.000*
Sex			
Male	127 (48)	20 (40)	0.325
Female	140 (52)	30 (60)	
Consanguinity	67 (25)	9 (18)	0.281
Family history of FMF	158 (59)	25 (50)	0.228
Age at disease onset (years)	2.5 (0–7.5)	10 (8–20)	*0.000*
Age at colchicine onset (years)	5 (0.5–20)	12 (8.5–22)	*0.000*
Delay in diagnosis (months)	24 (0–187)	12 (0–78)	*0.002*
Attack frequency before colchicine (year)	24 (2–100)	12 (1–96)	*0.049*
Attack duration before colchicine (hours)	72 (1–168)	72 (2–168)	0.766
Clinical findings at onset			
Fever	245 (92)	39 (78)	*0.003*
Abdominal pain	235 (88)	41 (82)	0.245
Chest pain	69 (26)	16 (32)	0.367
Arthritis	46 (17)	10 (20)	0.637
Arthralgia	107 (40)	27 (54)	0.071
ELE	8 (3)	2 (4)	0.661
Leg pain	117 (44)	19 (38)	0.445
Heel pain	98 (37)	15 (30)	0.364
PA	6 (2)	1 (2)	1.000
PFM	5 (2)	0 (0)	1.000
Vasculitis	7 (3)	3 (6)	0.198
Presence of two mutations[a]	154 (61)	26 (55)	0.712
M694V positivity[a]	179 (71)	26 (55)	*0.033*
M694V homozygosity[a]	79 (31)	7 (15)	*0.022*
Duration of colchicine therapy (months)	41 (1–240)	38 (1–132)	0.845
Final colchicine dosage (mg/day)	1 (0.37–3)	1.5 (1–2)	*0.000*
Final colchicine dosage (mg/kg/day)	0.03 (0.008–0.33)	0.02 (0.01–0.04)	*0.000*
Final colchicine dosage (mg/m^2/day)	1 (0.42–2.3)	0.83 (0.5–1.49)	*0.003*
Elevated attack free AFRs	41 (16)	4 (9)	0.199
Pras score	7 (4–16)	5 (3–11)	*0.000*
Pras			
Mild	70 (26)	32 (64)	*0.000*
Moderate	144 (54)	14 (28)	
Severe	53 (20)	4 (8)	
Pras[1] score	3 (0–13)	2 (1–6)	*0.040*

Statistically significant p values are highlighted in bold

Pras[1] score total Pras score without age of onset score, *FMF* familial Mediterranean fever, *ELE* erysipelas-like erythema, *PA* protracted arthritis, *PFM* protracted febrile myalgia, *AFR* acute phase reactant

[a] Mutation analysis was performed in 299 of the 317 patients

to treatment and more frequent arthritis attacks. Further, those patients required higher doses of colchicine and were much less responsive to colchicine. It was also shown that FMF patients with very early disease onset had more M694V carriage and more severe disease during childhood period. In this current study, we found that patients who had their first attack >8 years of age had less M694V homozygosity (15 %) and M694V carriage (55 %). Thus, our results further support the result of previous ones. Median disease severity scores and colchicine dosages were also lower in late-onset group. Whereas, studies done in small children showed the need for high colchicine dosages in order to control the attacks [7].

Overall, all these findings indicate that late-onset FMF during the childhood period had mild disease course. Tamir et al. [9] also suggested milder disease phenotype in adult late-onset patients. Their patients' response to treatment was good despite using low colchicine dose; overall severity score indicated a mild disease and mutational analysis revealed the absence of M694V homozygosity in that population.

Padeh et al. [8] reported that delay of diagnosis was longer in patients with very early presentation; 3.2 ± 3.2 years vs 1.9 ± 2.7 years in ≤2 years of age and 2–16 years of age, respectively. Yalçınkaya et al. [7] also showed 4 years delay in diagnosis in patients ≤3 years of age. In contrast, we found that late presentation is associated with shorter delay in diagnosis (median 12 months). We thought that although these children had milder illness, more readily expression of the clinical findings at older ages could promote early diagnosis.

The retrospective nature of the study and relatively low number of patients with late-onset disease could be the limitations of our study.

As a conclusion, although late-onset FMF during childhood is rarely encountered, it is associated with a milder disease course and earlier disease diagnosis. Age of onset is an important prognostic factor while following these patients. Clinicians dealing with FMF can feel better regarding the prognosis of the disease when they meet late-onset FMF patients during childhood period.

Compliance with ethical standards

Disclosures None.

Ethics approval Informed consent was obtained from the parents of each patient and the study was approved by the institutional ethics committee.

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