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Is age associated with disease severity and compliance to treatment in children with familial Mediterranean fever?

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Abstract

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease in the world. The disease characteristics may vary in different age groups. In this study, we aimed to compare disease characteristics and treatment compliance according to the age of pediatric FMF patients. This is a single-center, cross-sectional study. Between August and October 2016, patients who were diagnosed with FMF, participated to the study. 378 pediatric FMF patients were enrolled in the study. Among those, age at symptom onset was ≤ 5 years in 69%, 6–11 years in 26% and ≥ 12 years in 5%. Patients older than 12 years old at symptom onset, had significantly less frequent fever attacks than the patients from other age groups. Patients younger than 5 years old at symptom onset had significantly higher international severity scoring system for FMF (ISSF) than other patients. And M694V homozygosity was significantly more frequent in patients with younger age at symptom onset. Patients younger than 5 years old were using their drugs more regularly than the other age groups ($p = 0.002$). Drug compliance was 90.5% in patients ≤ 5 years, 64.4% in patients 6–11 years, 58.3% in patients ≥ 12 years. The disease characteristics of FMF may differ between patients with different age at symptom onset. Younger age at disease onset seems to be related with more severe course; thus these patients should be followed-up more closely. In addition, treatment compliance which is critical for prevention of amyloidosis in FMF should be questioned especially in adolescent patients.

Keywords Familial Mediterranean fever · Adherence to colchicine · Severity

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic inherited autoinflammatory disease, manifesting with recurrent, unprovoked, self-limited febrile attacks and polyserositis [1, 2]. It is caused by mutations in *Mediterranean Fever (MEFV)* gene located on chromosome 16p13.3 [1, 2]. FMF attacks last between 12 h and 3 days. Most of the patients appear clinically well during attack-free periods, however, elevated inflammatory markers may be seen in-between the attacks. The attack frequency is not regular and the first febrile attack usually manifests during childhood. Approximately, 90% of patients have the first clinical episode by age 20 years [3]. However, the clinical presentation and severity of the disease may vary according to different age groups. For instance, FMF patients with early disease onset present more severe course and diagnostic delay is more common at younger ages [4]. The mainstay of treatment is colchicine [5]. However, up to 5% of patients do not respond to colchicine despite maximum tolerable dose. Lack of compliance to the treatment play role in the resistance to colchicine [5]. Poor drug adherence may result in poor disease control and disease-related complications both of which will reduce the quality of life. Studies on drug compliance in FMF are scarce. Most recently, Corsia et al have demonstrated that adherence to colchicine was 73% in adults and 96% in children [6]. However, there is no gold

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standard method to measure drug adherence. Usually, indirect methods, such as patient diaries, and pill counts are used to assess drug compliance. In 2015, a group of experts have developed a validated and reliable adherence scale for FMF patients, called medication adherence scale for FMF (MASIF) [7]. However, until now, there is no study evaluating drug adherence using standard methods such as MASIF or compare the drug adherence status of patients according to their age. In this study, we aimed to examine the disease severity and drug adherence in FMF patients according to their age at disease-related symptom onset and current age, respectively. We also compared the clinical characteristics of FMF patients according to their age at symptom onset.

Materials and methods

In this cross-sectional study, we evaluated FMF patients who were referred to the Pediatric Rheumatology Outpatient Clinic of Hacettepe University between August 2016 and October 2016. Totally 378 patients were enrolled in the study. The patients were evaluated in three groups according to their age at symptom onset as follows; 0–5, 6–11, 12–18 years old. Patients were classified as having FMF according to previously described criteria [8]. Demographic data, clinical manifestations, laboratory findings (C-reactive protein [CRP; mg/dl, normal value ≤ 0.5], erythrocyte sedimentation rate [ESR; mm/h, normal range 0–20]), treatments and *MEFV* variant analysis were documented from electronic records.

Disease activity and severity were evaluated with autoinflammatory disease activity index (AIDAI) and international severity scoring system for FMF (ISSF), respectively [9, 10]. The AIDAI consists of 13 items, including fever, overall symptoms, abdominal pain, nausea/vomiting, diarrhea, headaches, chest pain, painful nodes, arthralgia or myalgia, and joint problems especially swelling, ocular manifestations, rashes, and pain relief. Each item is scored daily as present (1 point) or absent (0 points) during 1 month [9, 10]. ISSF consists of nine items including clinical manifestations and laboratory findings. Patients were classified as having severe disease in presence of ISSF ≥ 6 [9].

Patients were classified as being colchicine-unresponsive in presence of one or more episodes per month despite the use of colchicine at the maximum dose for at least 6 months and/or presence of amyloidosis [11]. Compliance to treatment was assessed by face-to-face interview in 199 patients. It was assessed with MASIF. The MASIF includes 18 items, divided into four categories: knowledge about the medication, adherence to the treatment, barriers to drug use and factors that may increase compliance [7].

The subjects' written consents were obtained according to the Declaration of Helsinki (1964) and the study was approved by the ethics committee of Hacettepe University (GO-16/187 – 48; approval date, 10th May 2016).

Statistical analyses

Statistical analyses were performed using the SPSS software version 21. Continuous data were described as mean and standard deviation (SD) or median and minimum–maximum where appropriate. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov) to determine whether or not they were normally distributed. Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate. The Mann–Whitney U test was used to compare the non-normally distributed continuous data between two groups. Kruskal–Wallis test was used to compare multiple groups. The Mann–Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. A p value of less than 0.05 was considered to show a statistically significant result.

Results

378 pediatric FMF patients participated in the study. The clinical characteristics and disease severity were examined in this whole group ($n = 378$) and these parameters were compared among patient groups according to the age at disease-related symptom onset. Drug compliance was evaluated in 199 patients with MASIF and compared according to the current ages of these 199 patients.

The mean ± SD age at symptom onset, at the diagnosis, and current age was 4.59 ± 3.56, 5.67 ± 3.54 and 11.28 ± 4.02 years, respectively. 55.3% ($n = 209$) of patients were male. Among 378 patients, age at symptom onset was ≤ 5 years in 69% ($n = 261$), 6–11 years in 26% ($n = 98$) and ≥ 12 years in 5% ($n = 19$). 81.5% ($n = 308$) of patients had fever, 77.5% ($n = 293$) had abdominal pain, 53.2% ($n = 201$) arthralgia, 20.6% ($n = 78$) arthritis, 14% ($n = 53$) chest pain, and 5.3% ($n = 20$) had erysipelas-like erythema. The median (minimum–maximum) AIDAI score was 0 (0–14). The median (minimum–maximum) attack frequency at the last 6 months and duration was 2 (1–19) and 2 (0–7) days, respectively. 36.5% ($n = 138$) of the patients were homozygous for M694V mutation in *MEFV* gene. 64.4% ($n = 128/199$) of the patients used their medication regularly.

When we compared the patients according to the age at symptom onset, patients who were older than 12 years old at symptom onset had significantly less frequent fever attacks than the other age groups ($p = 0.002$). There were no significant differences in terms of gender, AIDAI, attack frequency at the last 6 months, white blood cell count, ESR,

and CRP ($p > 0.05$). However, hemoglobin values were lower and platelet counts were higher in patients who were younger at symptom onset ($p < 0.05$) (Table 1). ISSF was significantly higher in patients younger than 5 years old at symptom onset than other patients ($p = 0.02$). However, there was no significant difference with regard to AIDAI scores in different age groups. The M694V homozygote patients were significantly younger at symptom onset than those who were not homozygous for M694V (median age, 3 vs 4 years, respectively; $p = 0.02$).

Three patients (0.8%) were classified as being colchicine-unresponsive. Two of them were treated with anakinra and one patient received canakinumab. These three patients were younger than 5 years old at FMF-related symptom onset. For the other patients with higher ISSF, colchicine dose was increased. Since they were not receiving colchicine at the highest tolerable dose, these patients had not been classified as being colchicine-resistant. Interestingly, four patients (1%) had sacroiliitis and they were treated with anti-tumor necrosis factor alpha drugs (two with adalimumab and two with etanercept).

When we compared the drug adherences according to the current ages of the patients, we observed that patients younger than 5 years old were using their drugs more regularly than the other age groups ($p = 0.002$). Drug compliance was 90.5% in patients ≤ 5 years, 64.4% in patients 6–11 years, 58.3% in patients ≥ 12 years. The parents of all patients who were ≤ 5 years were administering their drugs to their children, while most of the patients ≥ 12 years (85%) were receiving their drugs by themselves. Approximately one-third of the patients (37.6%) between 6 and 11 years old were using their drugs by themselves. Colchicine side effects such as diarrhea and dyspepsia were more frequent in non-compliant than compliant patients ($n = 19$ out of 128, 14.7% vs $n = 2$ out of 71, 0.03%, respectively; $p = < 0.001$). There was no difference with regards to the education level of parents between compliant and non-compliant patients.

Table 1 The characteristics of familial Mediterranean fever (FMF) patients according to the age at symptom onset

Characteristics of the patients	≤ 5 years ($n = 261$)	6–11 years ($n = 98$)	≥ 12 years ($n = 19$)	*P* value
Current age, years, median (min–max)	10 (2–18)	13 (7–18)	17 (14–18)	< 0.001
Gender, female, *n* (%)	118 (45.2)	42 (42.9)	9 (47.4)	0.897
Disease duration, years, median (min–max)	7 (0–17)	5.5 (1–12)	3 (1–14)	< 0.001*
Presence of attacks at the last 6 months, *n* (%)	100 (38.3)	29 (29.6)	8 (42.1)	0.237
Frequency of attacks at the last 6 months, median (min–max)	2 (1–19)	2 (1–6)	1.5 (1–3)	0.226
ISSF, median (min–max)	2 (0–6)	0 (0–4)	1 (0–4)	0.02*
AIDAI, median (min–max)	1 (0–6)	1 (0–5)	1 (0–4)	0.103
Fever, *n* (%)	223 (85.4)	74 (75.5)	11 (57.9)	0.002*
Abdominal pain, *n* (%)	207 (79.3)	72 (73.5)	14 (73.7)	0.458
Arthralgia, *n* (%)	141 (54.0)	50 (51.0)	10 (52.6)	0.878
Arthritis, *n* (%)	46 (17.6)	27 (27.6)	5 (26.3)	0.096
Chest pain, *n* (%)	38 (14.6)	12 (12.2)	3 (15.8)	0.832
Skin eruption, *n* (%)	12 (4.6)	8 (8.2)	0	0.232
Nausea and vomiting, *n* (%)	13 (5.0)	4 (4.1)	1 (5.3)	0.933
Diarrhea, *n* (%)	11 (4.2)	4 (4.1)	0	0.660
Constipation, *n* (%)	2 (0.8)	1 (1.0)	0	0.897
Oral ulcers, *n* (%)	8 (3.1)	4 (4.1)	0	0.639
Headache, *n* (%)	2 (0.8)	4 (4.1)	0	0.069
Hemoglobin, g/dL, median (min–max)	12.4 (8.6–15.9)	13.0 (8.5–16.9)	13.2 (10.9–17.2)	0.001*
White blood cell count, $\times 10^3/mm^3$, median (min–max)	6.8 (3.5–16.5)	6.8 (4.3–13.2)	6.6 (4.3–9.0)	0.527
Platelet count, $\times 10^3/mm^3$, median (min–max)	284 (140–642)	269.5 (129–721)	226 (186–328)	0.001*
ESR, mm/h, median (min–max)	8 (1–79)	6.5 (1–75)	3 (2–21)	0.162
CRP, mg/L, median (min–max)	0.28 (0.01–25)	0.25 (0.01–9.55)	0.43 (0.10–2.49)	0.960

*Statistically significant differences with $p < 0.05$

AIDAI autoinflammatory disease activity index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ISSF* international severity scoring system for familial Mediterranean fever

Discussion

In this study, we demonstrated that FMF had a more severe course if the disease symptoms started at an early age. We have also shown that drug compliance decreased with age in pediatric FMF patients.

Previous studies demonstrated that FMF course may vary according to age at disease-related symptom onset. Patients with early onset tend to have a more severe course and a need for higher final colchicine dosages [4]. The presence of M694V mutation is more common in patients with early symptom onset and diagnostic delay was longer in these patients [4, 12, 13]. Compatible with previous studies, we demonstrated that patients with early onset had more severe course with a high frequency of M694V mutation. Thus, the risk of more severe disease with younger age at onset is probably confounded by the higher frequency of M694V among these patients.

A study from Israel showed that FMF in young children may just present with attacks of fever without overt serositis [12, 13]. This was the case in 3% of our patients as well. In the presented study, our patients who were older than 12 years old at symptom onset had significantly less fever when compared to the other age groups. This may be due to the duration of colchicine use. The clinical findings other than fever did not differ significantly among the age groups consistent with the results of previous studies.

Successful treatment mainly depends on full adherence to colchicine in FMF. However, especially in adolescents, it is not always easy to achieve full adherence. Non-adherence may depend on several factors such as parental problems, lower socioeconomic status, and refusing medication by the adolescent to avoid side-effects. Studies have shown that adolescents frequently tend to be non-compliant [14, 15]. Therapies are administered by parents to the patients at prepubertal age while adolescents mostly self-administer their drugs [16]. This situation, along with the psychological challenges of adolescence period, could cause decrease in drug adherence in adolescents. In our study, the drug compliance was significantly higher in the patients aged ≤ 5 years old. This is probably because the parents give the medication to the patients at younger ages, before adolescence.

The main strengths of our study are assessing drug compliance with a standard method as MASIF and comparing the compliance status according to the age groups of patients in pediatric FMF. To our knowledge, after the validation of MASIF, this is the first study using MASIF for assessment of colchicine compliance in FMF.

Our study is limited by retrospective design of the study and the drug compliance data was not available for all patients. Another limitation is that we compared the clinical characteristics of FMF patients under colchicine treatment which probably modified the disease course. However, it was difficult to gather information in all patients about the period before colchicine initiation since most of these patients were on colchicine for many years. Moreover, this would cause more recall bias as we would be questioning a specific period of time in the past.

Conclusion

Our results emphasized the effect of age at symptom onset on disease severity and the effect of the current age of patients on drug compliance in FMF. Since the disease has a more severe course in patients with early symptom onset, these patients should be followed-up more closely. In addition, drug compliance should be questioned routinely in outpatient clinics especially in adolescent FMF patients since failure of adequate treatment is a risk for ongoing inflammation and FMF-related complications such as amyloidosis.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Ethical approval The study was approved by the ethics committee of Hacettepe University (GO-16/187−48; approval date, 10th May 2016).

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