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Original Article

Parental knowledge about familial Mediterranean fever: a cross-sectional study

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ABSTRACT

Background. The life-long course, long-term complications, necessity for regular treatment, and potential side effects of the medications must be well understood by parents of pediatric familial Mediterranean fever (FMF) patients. The aim of this study was to assess parental knowledge and to investigate how parents obtained scientific information about FMF.

Methods. One hundred and seventy-one pediatric FMF patients and their parents were enrolled in this cross-sectional study. Three-part questionnaires, including forms on socio-demographics, knowledge and perceptions of FMF, and how to get information about FMF, were administered to parents.

Results. In the analysis of the knowledge questions, 90.1% of parents were aware of colchicine as an effective drug for FMF, but only 39.2% of them were aware that there is no vital risk during FMF attacks. Caregivers preferred to obtain information from physicians (98.8%), websites (47.9%), seminars (3.5%), and books (1.7%). The knowledge scores of parents were significantly higher among those whose children were using anti-interleukin-1 therapy in addition to colchicine relative to those on colchicine alone ($p = 0.04$). There was a positive correlation between knowledge level and parental educational status ($p = 0.0001$).

Conclusions. Knowledge scores among parents of pediatric FMF patients are unsatisfactory. The parents whose children have a severe disease course and a need for anti-interleukin-1 therapy are more knowledgeable. For parents, continuing education programs including books, seminars and web-sites giving information about the course, prognosis, complications and treatments of FMF should be employed immediately after the diagnosis and thereafter.

Key words: childhood, familial Mediterranean fever, pediatric rheumatology, parental knowledge.

Familial Mediterranean fever (FMF) is the most common monogenic, chronic auto-inflammatory disease characterized by recurrent attacks of fever, pleuritis, pericarditis, peritonitis and arthritis. The attacks are self-limiting and typically resolve within 24-72 hours.[1] Mediterranean fever *(MEFV)* gene mutation causes hyperactivity of inflammasomes which leads to an increase of interleukin-1β (IL-1β) and resultant severe inflammation.[2] The prevalence of FMF is changing among communities, and the disease is reported in approximately 1/1000 people in Turkey.[3] Colchicine is a cheap, well tolerated, and life-long treatment that prevents the development of amyloidosis and must be used daily by oral delivery.[4] The inflammatory attacks generally occur before 20 years of age in 90% of FMF patients, so patients are generally diagnosed with FMF in childhood.[5] As a result, parents take responsibility for their children to take regular colchicine every day and go to routine outpatient follow-up visits.[5] Therefore, having a life-long disease with long-term complications, the necessity for life-long regular treatment, and the side effects of the therapy must be well understood by parents of pediatric FMF patients. Treatment compliance

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of pediatric FMF patients might be affected by social and demographic factors, such as education, age, and social network of parents. Parental knowledge about chronic diseases, such as rheumatic diseases, epilepsy, thalassemia, neurofibromatosis, and hypospadias, has been investigated previously.[6-11] However, to date, no data has been reported about the parental knowledge of pediatric patients with FMF.

We, herein, aimed to evaluate parental knowledge and perceptions of FMF and to investigate how parents obtained scientific information about it.

Material and Methods

FMF patients aged 4-16 years who had been suffering from FMF for six months or more and their primary caregivers were asked to participate in this cross-sectional study by a pediatric rheumatologist and a social worker. All patients were being followed by the Pediatric Rheumatology Department at the Gazi University Faculty of Medicine between June 2018 and November 2018. Patients who had an additional chronic disease were excluded from the study. All patients were evaluated clinically according to the Tel Hashomer Criteria.[12] Demographic data of patients and parents were recorded. All patients were receiving colchicine treatment. Resistance to colchicine therapy was quantified as experiencing one or more attacks per month despite receiving the maximally tolerated dose of colchicine for ≥ 6 months. Partial response to colchicine therapy was accepted as a decrease in attack frequency. Complete response to colchicine was accepted as resolved inflammatory attacks and serum acute phase reactant levels.[13] FMF patients using maximum tolerated colchicine dose regularly in everyday without forgetting were accepted as good compliance, while FMF patients with missing colchicine doses were accepted as non-compliance to the therapy. Biologics targeting IL-1 were started with some FMF patients due to partial response, resistant, non-compliance or intolerance to colchicine, or secondary amyloidosis development.

Pras activity scores were used for evaluating disease severity in FMF patients.[14] The FMF severity score comprised of age at FMF onset, frequency of attacks, presence of arthritis, erysipelas-like erythema, amyloidosis, and the required dose of colchicine prophylaxis necessary to control FMF symptoms. Escalating scores indicate mild (score, 1-5), moderate (score, 6-9), and severe (score, >10) FMF activity.[15]

Three self-administered surveys which were developed by authors, were given to caregivers:

a. Caregivers' socio-demographics form: Caregivers (mother or father) were asked to provide personal demographic information, including age, gender, education status, and having FMF or not.

b. FMF parental knowledge and perceptions form: The knowledge section of the questionnaire contained 14 items. To evaluate the parents' knowledge level of FMF, we posed a set of 14 questions to all participants. This non-standardized questionnaire was generated by authors. These questions included whether FMF is a contagious or a genetic disease or a disease that should be followed-up regularly in a pediatric rheumatology department; whether or not children with FMF have a vital risk during attacks or have lower IQs than their peers; whether or not colchicine is an effective treatment agent; whether or not drugs for FMF are addictive or have side effects such as infertility; whether or not FMF resolves spontaneously over time or worsens with age; whether or not FMF patients can work actively and join sport activities; and whether or not FMF symptoms get worse or irreversible damage develops in internal organs, such as kidneys, when medication is not used regularly (Table II). Each item is rated on a 3-point scale (Yes, No, I don't know). Each correct answer was given 1 point. The total score of knowledge was graded between 0 (the lowest grade) and 14 (the highest grade) points.

c. Getting information about FMF form: Parents were asked to a respond to a total of four statements about where they obtain information about FMF, such as from physicians, books, symposia, or web sites.

This study was approved by the Gazi University Medical Faculty Ethics Board (11.06.2018/456) and was applied in accordance of the Declaration of Helsinki. Informed consents were obtained from each participants' caregivers.

Statistical analysis

Statistical analysis of the data was performed by Statistical Package for Social Sciences (SPSS) software version 15 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD). The differences between two independent groups were compared by using independent sample t-test for normally distributed variables or Mann-Whitney U test for non-normally distributed ones. Correlations between variables were evaluated by Pearson or Spearman correlation coefficients for variables. A p value of less than 0.05 was considered to be significant.

Results

One hundred and seventy-one pediatric FMF patients aged 4-16 years and their primary caregivers were enrolled in this study. Three parents refused to participate in the study. The caregivers' and patients' characteristics are summarized in Table I. Of the 171 study participants, 142 (83.0%) were mothers. The median paternal and maternal ages were 41 (27-56) and 39 (24-55) years, respectively. While half of the mothers had graduated from primary school (56.1%), a majority of the fathers had graduated from secondary/high school or university (64.3%). All patients were using oral colchicine, but 30 (17.5%) of them were nonadherent to this daily oral treatment and 16 patients (9.4%) were additionally receiving anti-IL-1 treatments, either anakinra or canakinumab. A total of 117 (68.4%) patients

Table I. The demographic data of caregivers and familial Mediterranean fever patients.

Characteristics	Median (min.-max.)	n (%)
Parents		
Total		171 (100)
Mother		142 (83)
Father		29 (17)
Age of mothers (years)	39 (24-55)	
Age of fathers (years)	41 (27-56)	
Education status of mothers		
Primary school		96 (56.1)
Secondary - high school		59 (34.5)
University		16 (9.4)
Education status of fathers		
Primary school		61 (35.7)
Secondary - high school		76 (44.4)
University		34 (19.9)
Children		
Total		171 (100)
Male		75 (43.9)
Female		96 (56.1)
The feature of age groups		
Preschool age		38 (22.2)
School age		133 (77.8)
Age of present time (years)	12 (4-16)	
Family history of FMF		117 (68.4)
Attack frequency in a year		
≤2 attacks per year		138 (80.7)
>2 attacks per year		33 (19.3)
Frequency of emergency visits		
≤2 visits per year		157 (91.8)
>2 visits per year		14 (8.2)
FMF symptoms		
Abdominal pain		152 (88.9)
Fever		170 (99.4)
Arthralgia		113 (66.1)
Myalgia		37 (21.6)
Arthritis		66 (32.3)
Chest pain		41 (24.0)
Erysipelas-like erythema		28 (16.4)
Amyloidosis		3 (1.8)
Compliance of colchicine treatment		
Adherent		141 (82.5)
Nonadherent		30 (17.5)
Response of colchicine treatment		
Complete		152 (88.9)
Partial		12 (7)
Resistant		7 (4.1)
Response to anti-IL-1 treatment		
Complete		13 (81.2)
Partial		3 (18.8)
PRAS activity score*	6 (3-15)	
Mild course		54 (31.6)
Moderate course		86 (50.3)
Severe course		31 (18.1)

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FMF: familial Mediterranean fever, IL-1; interleukin-1.
*The Pras activity score evaluates the severity of the disease with scores of 2–5 for those having mild activity, 6–10 for moderate activity, and > 10 for severe activity.[15]

had a positive family history for FMF. The median Pras activity score was 6 (3-15).

All knowledge-related questions are presented in Table II. Of 171 parents, 154 (90.1%) knew that colchicine is an effective drug in FMF treatment. In contrast, only 67 (39.2%) knew that there is not a vital risk during attacks of FMF disease.

In evaluating parents' sources for gathering knowledge about FMF, we determined they preferred obtaining information from physicians (98.8%), web-sites (47.9%), seminars (3.5%), and books (1.7%) (Table III).

Parental knowledge scores and patients' Pras activity scores were compared by demographic findings and treatment responses (Table IV). There were no significant differences in knowledge scores of parents by either patients' or parents' age, gender, education status, or compliance with colchicine use ($p > 0.05$). However, the knowledge scores were significantly higher in parents whose children needed to use anti-IL-1 therapy in addition to colchicine ($p = 0.04$). There were no correlations between parental knowledge scores and Pras activity scores in mothers' ages, fathers' ages, patients' ages and colchicine compliance ($p > 0.05$) (Table V). There was, however, a positive correlation in knowledge level and parental educational status ($p = 0.0001$).

Table II. Percentage of correct answers to questions comprising the knowledge score of parents of children with familial Mediterranean fever.

Items	% of correct answers
FMF is a contagious disease	85.4
FMF is a hereditary genetic disease	71.3
There is a vital risk during attacks of FMF disease	39.2
Colchicine is the effective drug in FMF treatment	90.1
Drugs of FMF are addictive	49.7
FMF is a disease that affects intelligence	63.2
FMF is a disease that passes by itself over time	62.0
FMF gets worse with age	46.8
FMF patients cannot work actively	68.4
FMF patients cannot do any sports	74.3
FMF disease gets worse when colchicine is not used regularly	71.9
Medications of FMF have side effects such as infertility	61.4
Damage to internal organs such as kidneys can develop when colchicine is not taken regularly	83.6
FMF is a chronic disease that must be followed-up regularly by a pediatric rheumatologist and/or a pediatrician.	80.1

FMF: familial Mediterranean fever.

Table III. Parents' sources of information for familial Mediterranean fever.

Item	%
I have information about FMF from physicians	98.8
I have read a book about FMF	1.7
I have participated a seminar about FMF	3.5
I have followed a web-site about FMF	47.9

FMF: familial Mediterranean fever.

Table IV. Demographic findings and treatment responses by parental knowledge and by patients' Pras activity scores.[12]

Factor	Knowledge	p value	Pras activity score*	p value
Parents				
Mother	8.9±2.9	0.36	7.14±2.4	0.20
Father	9.5±2.1		6.69±2.3	
Mother's age				
30-50 years	8.9±2.7	0.18	7.05±2.4	
51-70 years	10.1±3.1		7.19±2.3	
Father's age				
30-50 years	8.8±2.8	0.17	7.08±2.5	0.89
51-70 years	9.6±2.6		7.02±2.3	
Mother's education status				
Primary school	8.9±2.7	0.43	6.54±1.9	0.04
Secondary/high school/university	9.3 ±2.8		7.33±2.6	
Father's education status				
Primary school	8.9±2.9	0.53	6.62±2.1	0.012
Secondary/high school/university	9.1 ±2.7		7.53±2.6	
Patients with FMF				
Age				
4-7 years	8.7±3.1	0.49	6.74±1.7	0.33
8-16 years	9.1 ±2.6		7.17±2.6	
Age at diagnosis				
< 10 years	8.8±2.9	0.22	7.27±2.4	0.03
> 10 years	9.5 ±2.2		6.45±2.3	
Compliance of colchicine use				
Regular	8.9±2.8	0.53	7.18±2.5	0.43
Not regular	9.3±2.4		6.63±2.0	
Response to colchicine				
Complete response	8.8±2.4	0.04	6.73±2.3	0.001
Incomplete response	10.1±2.8		9.94±1.5	
Anti-IL-1 therapy				
Not users	8.9±2.4	0.04	6.73±2.2	0.001
Users	10.1±2.7		10.38±1.9	

FMF: familial Mediterranean fever, anti-IL-1: anti-interleukin-1.
*The Pras activity score evaluates the severity of the disease with scores of 2–5 for those having mild activity, 6–10 for moderate activity, and > 10 for severe activity.[15]

Discussion

This study has evaluated parental knowledge, perceptions, and the ways parents access scientific information about FMF. This study showed that parents of FMF children did not have adequate knowledge about FMF, and they mostly tried to get information from their physicians and web-sites. Furthermore, we found that the parents whose children had a severe disease course and needed to use anti-IL-1 therapy in addition to colchicine were more knowledgeable than the others about FMF disease. Also, the level of educational status of parents was positively correlated with knowledge about FMF disease. Surprisingly, the knowledge level of parents was insufficient

Table V. Correlation between parental knowledge and patients' Pras activity scores

Factor	Knowledge		Pras activity score*	
	r value	p value	r value	p value
Child age	0.12	0.09	0.04	0.55
Mother age	0.13	0.09	0.01	0.87
Father age	0.11	0.10	0.06	0.43
Age of onset symptoms	0.13	0.09	-0.38	0.0001
Attack frequency in a year	0.28	0.0001	0.44	0.0001
Mother education	0.35	0.0001	-0.16	0.03
Father education	0.33	0.0001	-0.20	0.008
Response of colchicine treatment	-0.14	0.04	0.40	0.0001
Use of anti-IL-1 treatment	-0.07	0.36	0.29	0.0001
Compliance to colchicine treatment	0.04	0.58	-0.09	0.24

Anti-IL-1: anti-interleukin-1.
*The Pras activity score evaluates the severity of the disease with scores of 2–5 for those having mild activity, 6–10 for moderate activity, and > 10 for severe activity.[15]

even though Turkey is one of countries where FMF is most commonly seen.

Al-Eid et al.[7] reported that the majority of parents have insufficient knowledge regarding rheumatic diseases, and proposed to increase health education programs to enhance awareness of pediatric rheumatic diseases in parents. Wickwar et al.[6] recommended a questionnaire to evaluate the knowledge level of parents about methotrexate therapy in pediatric rheumatic diseases. Although FMF is a chronic, life-long, and hereditary disease[4], there is still misinformation and a lack of knowledge about FMF. For example, 28.7% of parents were not aware that FMF is a hereditary disease, 60.8% of parents were not aware that FMF attacks do not pose a vital risk to patients, 50.3% of parents were not aware that FMF drugs are not addictive, and 53.2% of parents were not aware that FMF does not get worse as time goes on. Incorrect beliefs might occur due to the lack of education of parents. Higher education may provide easier access to information about healthier lifestyles and illnesses. In this study most of the mothers had graduated from primary school (56.1%), while most of fathers had graduated from secondary or high school (44.4%). We found a positive correlation between education status and the knowledge level of parents. We concluded that mothers adapt well to the idea of having a chronic disease like FMF in their children and can gain knowledge about FMF even if they have lower education status. This follows from the fact that many questions were answered correctly by the majority of the responders; for example 90.1% of parents think that colchicine is an effective drug in treating FMF, 85.4% think that FMF is not a contagious disease, 83.6% think that FMF may progress to chronic kidney disease without regular colchicine usage, and 80.1% think that FMF must be followed by a pediatric rheumatologist and/or a pediatrician.

One of the most important attitude problems in parents is not using the therapy on time for their children with FMF. Parents' ideas about addiction and side effects of treatments and children's fears of the subcutaneous needle treatments may lead to irregular use of treatments. In the present study, half of the parents thought that FMF drugs are addictive, and 38.6% thought that FMF drugs cause infertility over time. Delayed treatment due to late diagnosis may cause the development of complications, such as amyloidosis, and enhance morbidity and mortality in patients as well as bring severe economic and psychologic burden to families and communities.[16] In a society, the training of patients with chronic diseases and their caregivers could improve the

course of these diseases and the quality of life of patients and family members.[17] Patient and caregiver education aims to develop a sense of responsibility and improved health by building positive habits, such as healthy diet, regular prescription drug use, and regular follow-up to keep the chronic disease under control. Parents' correct perceptions and adequate knowledge about chronic diseases have an important effect on the successful management of the disease course. Programs about raising the knowledge and awareness of FMF could ensure the process of parents' acceptance of their children's disease and provide compliance with the treatments. Compliance is often a marker of patients' and parents' understanding and adaptation to a chronic disease, such as FMF. Poor compliance with colchicine use may increase attack rates of FMF.[4] The 82.5% of our patients found to be compliant represent a good compliance rate for colchicine, and we did not find any significant differences in parental knowledge scores between patients with poor and good compliance with colchicine usage. Poor colchicine response and higher disease severity with attacks cause parents to be more motivated to cope with FMF. This situation causes patients' relatives to take a more effective attitude towards obtaining information about FMF. There is a significant relationship between anti-IL-1 use and the knowledge scores about FMF; therefore, using anti-IL-1 therapy as an add-on therapy in FMF might encourage parents to read and know more about FMF to take care of their children properly and to make their lives better. Kinkar et al.[18] demonstrated that the parents of children who had been earlier diagnosed with epilepsy, had more knowledge about epilepsy as a chronic disease, but in our study, interestingly, there were no significant differences in evaluation of knowledge scores between ages of parents and children's age of diagnosis. Furthermore, we did not find any correlations between parental age, patients' age, patients' age at disease onset, and parental knowledge. Therefore, we concluded that the parents' efforts to learn more information about the disease did not show any difference by the age of the patients at diagnosis or by parental age.

The main limitations of this study were the small sample size from a single centre and the lack of a control group. Another limitation of this study was the questionnaire used, which is not validated and based on a previously published/validated pediatric scale.

In conclusion, having a good level of knowledge about FMF is important to increase patient compliance with treatment and, therefore, to prevent not only acute attacks but also long-term complications. However, in our study population, the knowledge about FMF among parents was unsatisfactory. The parents whose children have a severe disease course and, therefore, require anti-IL-1 add-on therapy were more knowledgeable. Educational tools, including books, on-line or live seminars, and websites giving information about FMF disease course, treatments, prognosis, and complications should be provided immediately after diagnosis and should be continuous.

Ethical approval

This study was approved by the Gazi University Medical Faculty Ethics Board (11.06.2018/456).

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Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DGY, SAB, SSA, NB; data collection: DGY; analysis and interpretation of results: DGY, SAB, SSA; draft manuscript preparation: DGY, SAB, SSA, NB. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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