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Original Article

The impact of illness perception on medication adherence in pediatric patients with familial Mediterranean fever

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ABSTRACT

Objective: Poor adherence to medications is an important problem, especially in patients with chronic diseases such as familial Mediterranean fever (FMF). In this study, we aimed to evaluate medication adherence in pediatric FMF patients and investigate the relationship between disease perception and treatment compliance.

Method: Pediatric patients (<18 years old) with a diagnosis of FMF and at least six months of follow-up period participated in the study. Patient perceptions of illness and medication adherence were measured via a brief illness perception questionnaire (brief IPQ) and the Medication Adherence Scale in FMF Patients (MASIF), respectively.

Results: A total of 50 patients (46% girls, n:23) with a median age of 9.9 (IQR 5.9-15.8) years were included. The median age at diagnosis was 5.4 (IQR 3.2-10.1) years. Twenty-eight patients (56%) had good medication adherence (the MASIF score>60), while 44% of the patients were non-adherent to the treatment. Patients aged under 12 years of age were more adherent to colchicine treatment than those over 12 years of age (68.2% vs. 25.0%, p= 0.002). The comparison of the illness perception and medication adherence revealed higher brief IPQ total scores in patients who adhered to the treatment (median 48.5 vs 52.5, p=0.037). We found significant differences in timeline scores between patients who were adherent and those who were non-adherent to the treatment (p=0.01).

Conclusion: Non-adherence to medication is an important and widespread problem, particularly among adolescent patients. Perceptions of the illness and beliefs about the duration of the disease may affect adherence to treatment. Medication adherence should be routinely assessed at follow-up visits and educational interventions might improve adherence to the treatment.

Keywords: Familial Mediterranean fever, medication adherence, illness perception

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent febrile attacks and serositis (e.g., peritonitis, pericarditis, synovitis). The Mediterranean fever (*MEFV*) gene responsible for FMF encodes a protein called pyrin.[1] Mutated pyrin causes uncontrolled production of interleukin-1β and increased inflammatory response.[2,3] Attacks usually last for 12-72 hours.[4] The goal of the treatment is to prevent complications that occur as a result of chronic inflammation, such as amyloidosis, and to control attacks. Colchicine is the mainstay of FMF treatment. Some patients have an attack despite colchicine treatment. Although colchicine resistance may be observed in some of the FMF patients, non-adherence to

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colchicine treatment should be investigated first in these cases.[5] Melikoglu et al.[6] evaluated 108 FMF patients and found that 11% of patients identified as unresponsive to colchicine treatment actually had inadequate medication adherence. A Medication Adherence Scale for Familial Mediterranean Fever (MASIF) was developed in a cohort of Turkish children in 2015.[7] Sönmez et al.[8] evaluated drug compliance using the MASIF scale in 82 pediatric FMF patients and found that 33 patients were non-adherent with their medication. Meanwhile, they found that the number of attacks, hospitalization in the last six months, and admissions to the hospital and the emergency department were significantly higher in non-adherent patients.

There are many factors that influence adherence to treatment, such as socio-economic factors, health system-related factors, or patient-related factors. Illness perception is one of the most important factors in medication adherence. A brief illness perception questionnaire was developed to provide a quantitative assessment of illness perception.[9] It evaluates cognitive illness representations, emotional representations (concerns and emotions), and comprehension of illness. The relationship between illness perception and medication adherence has been investigated in many diseases. However, there is a lack of data in the literature on the illness perception of FMF patients.

In this study, we aimed to evaluate medication adherence in pediatric FMF patients and investigate the relationship between disease perception and treatment compliance.

MATERIAL AND METHODS

Study population

This is a cross-sectional study. Pediatric patients (<18 years old) who were followed up with the diagnosis of FMF between December 2021 and October 2022 in Aydın Obstetrics and Pediatrics Hospital, Department of Pediatric Rheumatology participated in the study. The clinical diagnosis of FMF was made according to the Yalçınkaya-Özen criteria.[10] Patients with at least six months of follow-up period were included in the study. There were 78 FMF patients who applied to the pediatric rheumatology outpatient clinic during the study period. Patients with a shorter follow-up period (<6 months) (n=19) and those who refused to participate in the study (n=9) were excluded from the study. The demographics (age, sex, age at diagnosis), *MEFV* gene analysis results, and clinical presentations of the patients were recorded. Afterward, the patient's medication adherence and disease perceptions were evaluated.

Assessment of the medication adherence

The MASIF scale was used to evaluate medication adherence (Supplementary Table S1).[7] The scale consists of 18 questions and the questions are classified into 4 groups: knowledge about the medication (1st, 10th, 13th, and 16th questions), adherence to the treatment (2nd, 5th, 6th, 8th, 15th, and 17th questions), barriers to drug use (4th, 7th, 12th, 14th, and 18th questions), and the factors that may increase adherence (3rd, 9th, and 11th questions). Each item was scored ranging from 1 to 5 (1=strongly agree, 2=agree, 3=no idea, 4=disagree, 5=strongly disagree). A total score above 60 points was considered "good medication adherence" while a score below 60 points was considered "poor drug compliance". For patients under the age of 7, only the parents answered the questions, whereas the patients over the age of 7 answered the questions together with their parents. In addition, we investigated whether there was a difference in drug compliance rates in patients over 12 years of age, which corresponds to the adolescence period, compared to those under 12 years of age.

Assessment of the illness perception

The brief illness perception questionnaire (brief IPQ) which was developed by Broadbent et al.[9] in 2006 was used for the evaluation. It consists of eight items plus the causal questions: assessment of consequences (item 1), timeline (item 2), personal control (item 3), treatment control (item 4), identity (item 5), concern (item 6), illness comprehensibility (item 7), and emotional response (item 8) (Supplementary Table S2). Causal representation was evaluated with an open-ended question asking patients to write down the three most important causal factors in their illness. (Item 9). All questions except one open-ended question (item 9) were scored on a numerical rating scale from 0 to 10. The eight-item brief IPQ was also used in the study.

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee (Approval number: 2022/186) and was conducted according to the guidelines of the Declaration of Helsinki.

Statistical analyses

The SPSS version 20.0 (Armonk, NY: IBM Corp) package program was used in the statistical analyses. Descriptive statistics were presented as frequencies (n (%)) for categorical data and median (interquartile range [IQR]) for numerical data. Visual (histograms and probability plots) and analytical methods (the Kolmogorov-Smirnov and Shapiro-Wilk tests) were used to decide whether

a variable had a normal distribution. The Chi-square test or Fisher's exact test (when the values observed in cells did not meet the assumptions of the Chi-square test) was used for the comparison of categorical variables. With regard to distribution characteristics, the Student's t-test was used for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters in the intergroup comparison. The associations between the MASIF score and brief IPQ, which were non-normally distributed, were calculated using the Spearman test. A p-value of less than 0.05 was used to define statistical significance.

RESULTS

A total of 50 patients, 23 of whom were girls (46%) were included in the study. The median age of the patients was 9.9 (IQR 5.9-15.8) years and the median age at diagnosis was 5.4 (IQR 3.2-10.1) years. 28 patients (56.0%) were under the age of 12. The median follow-up time was 2.2 (IQR 1.1-6.7) years. The clinical presentations of the patients were as follows in decreasing order: fever (n=45, 90%), abdominal pain (n=40, 80%), arthralgia (n=27, 54%), chest pain (n=14, 28%), arthritis (n=10, 20%), and erysipelas-like erythema (n=4, 8%). Six patients had an additional disease: five had asthma and one had a diagnosis of epilepsy. However, none of them were taking oral medication regularly for these diagnoses. Fifteen (30%) of the patients were homozygous, 25 (50%) were heterozygous, and 10 (20%) were compound heterozygous. The allele frequencies of the *MEFV* mutations were M694V (53.3%), E148Q (16.0%), M680I (13.3%), V726A (12.0%), R761H (4.0%), and P369S (1.3%). Colchicine was used on a twice-daily dosage schema in 47 patients, and a once-daily dosage schema in three patients. Patients were using colchicine at a median dose of 1 mg (range 0.5 mg to 2 mg).

Evaluation of the medication adherence

The median scores of the items of the MASIF were shown in Table 1. Twenty-eight patients (56%) had good medication adherence (the MASIF score>60), while 44% of the patients were non-adherent to the treatment. The median age of patients with good medication adherence was lower compared to those of non-adherent patients (15.3 (IQR 9.3-17.0) vs 7.5

Table 1. Evaluation of the medication adherence of the patients

The item of the medication adherence scale in FMF patients (MASIF) (min-max score)	The median scores of patients (IQR)
I know about my illness and I am aware that my treatment will continue for a long time (0-5)	1 (1-2)
I sometimes forget to take my medication (0-5)	2 (2-4)
I rely on the treatment prescribed for my disease (0-5)	1 (1-2)
I refrain from others when taking drugs (0-5)	4 (4-5)
Continuous drug usage affects my daily life (0-5)	4 (3-4)
When I am out of home, I forget to take my drugs	2 (2-4)
I wish this disease had a treatment without drugs (0-5)	2 (1-3)
I sometimes do not take my drugs on time because of my daily routine (0-5)	2 (1-4)
I think my illness will get better, if I use my drug regularly (0-5)	2 (1-3)
I know the adverse effects of the drug (0-5)	3 (2-3)
I need to be convinced to use my medication regularly, for a long time (0-5)	4 (2-4)
I'm afraid that continuous drug use may lead to other diseases (0-5)	3 (2-4)
If I leave my drug, my disease may worsen (0-5)	2 (1-3)
I could not get used to using my drug regularly (0-5)	4 (2-4)
When I realise that I forgot to take my medication, I take my drug even it is de-layed, I do not skip doses (0-5)	2 (1-2)
When I disrupt my drug my complaints may increase (0-5)	2 (1-2)
I am tired of continuous drug use (0-5)	3 (2-4)
I think it is quite difficult to use medicine in multiple doses during a day (0-5)	3 (2-4)

FMF: familial Mediterranean fever; IQR: interquartile range.

(IQR 5.1-12.2), p=0.002). The patients aged under 12 years of age were also more adherent to colchicine treatment than those over 12 years of age (68.2% vs 25.0%, p= 0.002). There was no significant difference between the genders in terms of adherence to treatment. The routine daily dose of colchicine was higher in non-adherent patients compared to adherent patients (p=0.003).

Evaluation of the illness perception

The median brief IPQ score was 50.0 (IQR 45.0-55.2). The score of the brief IPQ scale showed no significant difference between genders (p=0.296). There was no significant correlation between the MASIF score and the brief IPQ score (p=0.109, r=0.230). However, the comparison of the illness perception and medication adherence revealed higher brief IPQ total scores in patients who adhered to treatment (median 48.5 vs 52.5, p=0.037). The median scores of the items of the brief IPQ and the median scores of the items of the brief IPQ according to drug compliance are summarized in Table 2 and Table 3, respectively. We found significant differences in timeline scores between patients with poor medication adherence and good medication adherence (p=0.01). In addition, the brief IPQ scores did not differ significantly between the homozygous, heterozygous, and compound heterozygous groups (p=0.111).

Table 2. Assessment of the illness perception of the patients

The item of the brief IPQ (min-max score)	The median scores of patients (IQR)
Consequences (0-10)	4 (2.7-6.0)
Timeline (0-10)	9 (5.0-10.0)
Personal control (0-10)	6.5 (4.0-9.0)
Treatment control (0-10)	8.5 (7.0-10.0)
Identity (0-10)	6.0 (3.0-8.0)
Concern (0-10)	5.0 (4.0-8.0)
Illness comprehensibility (0-10)	9.0 (6.0-10.0)
Emotional response (0-10)	5.0 (1.7-7.2)

IPQ: illness perception questionnaire; IQR: interquartile range.

DISCUSSION

Our study indicates that poor adherence to treatment, which was observed in 44% of patients, is a significant problem in FMF patients. We found that those with a greater perception of illness had better medication adherence.

The brief IPQ was used in many different diseases to examine patients' perception of illness and its relationship with medication adherence was investigated.[11-13] Tolu et al.[14] reported that a greater perception of illness was significantly associated with better medication adherence in patients with ankylosing spondylitis. Similarly, Hughes et al.[15] found that some IPQ domains were associated with medication adherence in patients with rheumatoid arthritis. In our study, medication adherence was better in patients with higher brief IPQ total scores. Also, the association between the timeline domain of brief IPQ and medication adherence was positive, indicating that those who did not believe that FMF is a long-lasting disease were experiencing poor adherence to medications. Since FMF is a life-long illness, they might have felt compelled to take the drug,

Table 3. Evaluation of the items of the brief IPQ according to treatment adherence

The item of the brief IPQ	Patients' treatment adherence according to the MASIF		p value
	Adherent patients median (IQR) (n=28)	Non-adherent patients median (IQR) (n=22)	
Consequences	4 (1-6)	5 (3-6.2)	0.490
Timeline	10 (8-10)	7 (5-10)	**0.01**
Personal control	7 (5-9.7)	6 (3.7-8)	0.08
Treatment control	9 (8-10)	8 (4-10)	0.166
Identity	5.5 (3-8)	6 (4.7-7.2)	0.615
Concern	5 (4-8)	5 (3-7)	0.269
Illness comprehensibility	9 (8-10)	9 (6-10)	0.443
Emotional response	5 (2-7.7)	5 (2-6.2)	0.664

IPQ: illness perception questionnaire; IQR: interquartile range; MASIF: medication adherence scale in FMF patients.

which can have numerous consequences if they do not adhere to the treatment. It seems plausible that receiving information about the disease, especially the duration of the disease, might improve drug compliance.

Colchicine prevents the development of amyloidosis by reducing the frequency and severity of febrile attacks and improves the patient's quality of life.[16] Adherence to colchicine treatment has a direct impact on patient outcomes. The frequency of non-adherent patients to colchicine treatment according to MASIF was similarly reported as 40.2% in pediatric FMF patients.[8] In another study evaluating 171 pediatric FMF patients, 17.5% of the patients were reported to be non-adherent. However, a questionnaire was not used to assess drug compliance in this study.[17] Tekgöz et al.[18] also reported that when patients were asked whether they were regular colchicine users, 66.5% of adult FMF patients said that they were regular colchicine users. However, when adherence was evaluated using the Compliance Questionnaire on Rheumatology (CQR) scale, the rate of non-adherent patients was 83.8%. Poor medication adherence is a significant issue for physicians to be aware of. The use of scales may also be more appropriate for an accurate assessment of medication adherence.

In our study, non-adherence to medication was more frequent in patients over 12 years of age. Similarly, a study of 378 pediatric FMF patients investigated medication adherence according to age. Medication adherence was reported to be 90.5% in patients ≤ 5 years, 64.4% in patients 6–11 years, and 58.3% in patients≥12 years.[19] Poor adherence to medication in adolescents has been reported not only in FMF patients but also in other chronic diseases.[20,21] In children under 12 years of age, drugs are usually administered by parents, whereas children over 12 years of age generally take their own medication and take responsibility. Physicians should be attentive to poor adherence to treatment during the adolescent years.

Study limitations

There are some limitations of our study. First, other factors that may influence medication adherence, such as patient-related factors, financial barriers, and sociocultural factors, were not evaluated. The second limitation is the retrospective nature of the study and the single-center design. Multicenter studies with large numbers of patients are needed to accurately determine the impact of illness perceptions on medication adherence. Despite these limitations, to our knowledge, this is the first study evaluating the brief IPQ in pediatric FMF patients and examining the association between medication adherence and patients' perception of illness.

CONCLUSION

The patient's perception of the illness is important and affects medication adherence. Non-adherence to medication was found more often in patients over 12 years of age. Physicians should routinely assess medication adherence, especially in the adolescent period, and informing patients about their disease (especially the duration of the disease) might improve drug compliance.

Ethical approval

This study has been approved by the Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee (approval date 10/11/2022, number 2022/186). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: UKA, HO; Concept: UKA, HO, SB; Design: UKA, HO; Data Collection or Processing: UKA, HO, SB; Analysis or Interpretation: UKA, HO; Literature Search: UKA, HO, SB; Writing: UKA, HO. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Supplementary Table S1. Medication Adherence Scale in FMF Patients (MASIF) (Likert scale is used as 1=strongly agree, 2 = agree, 3 = no idea, 4 = disagree, and 5 = strongly disagree. A total score above 60 points was considered "good medication adherence" while a score below 60 points was accepted as "poor drug compliance")

No	Items	Strongly agree	Agree	No idea	Disagree	Strongly disagree
1.	I know about my illness and I am aware that my treatment will continue for a long time.					
2.	I sometimes forget to take my medication.					
3.	I rely on the treatment prescribed for my disease.					
4.	I refrain from others when taking drugs					
5.	Continuous drug usage affects my daily life.					
6.	When I am out of home (on vacations, travels, etc.) I forget to take my drugs.					
7.	I wish this disease had a treatment without drugs.					
8.	I sometimes do not take my drugs on time because of my daily routine.					
9.	I think my illness will get better, if I use my drug regularly.					
10.	I know the adverse effects of the drug.					
11.	I need to be convinced to use my medication regularly, for a long time.					
12.	I'm afraid that continuous drug use may lead to other diseases.					
13.	If I leave my drug, my disease may worsen.					
14.	I could not get used to using my drug regularly.					
15.	When I realise that I forgot to take my medication, I take my drug even it is delayed, I do not skip doses.					
16.	When I disrupt my drug my complaints may increase.					
17.	I am tired of continuous drug use.					
18.	I think it is quite difficult to use medicine in multiple doses during a day.					

Supplementary Table S2. The brief illness perception questionnaire (brief IPQ)										
How much does your illness affect your life?										
0	1	2	3	4	5	6	7	8	9	10
no affect at all										severely affects my life
How long do you think your illness will continue?										
0	1	2	3	4	5	6	7	8	9	10
a very short time										forever
How much control do you feel you have over your illness?										
0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme amount of control
How much do you think your treatment can help your illness?										
0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful
How much do you experience symptoms from your illness?										
0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms
How concerned are you about your illness?										
0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned
How well do you feel you understand your illness?										
0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly
How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)										
0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally