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Original Article

Factors Affecting Colchicine Adherence in Pediatric Familial Mediterranean Fever

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ABSTRACT

Aim: Familial Mediterranean Fever (FMF) is the most frequent monogenetic autoinflammatory disorder. It is characterized by fever and serositis. The first line treatment of FMF is colchicine. Adherence to colchicine is one of the main factors affecting colchicine response. In this study, we aimed to evaluate drug adherence in children with FMF using the medication adherence scale in FMF (MASIF). We also assessed the clinical characteristics of drug-adherent patients and factors affecting drug adherence.

Materials and Methods: Eighty-two children with FMF under colchicine therapy were included in this cross-sectional observational study. The patients were divided into two groups according to medication adherence and compared according to their demographic and clinical data.

Results: According to MASIF, 31 (38%) patients had non-adherence to colchicine. There was a significant difference between the colchicine-adherent and non-adherent groups in terms of age, disease severity according to the International severity score for FMF, attack rate, colchicine dosage, M694V homozygosity, and family type (p=0.005, p=0.04, p=0.025, p=0.045, p=0.04, and p=0.046, respectively).

Conclusion: Patients with FMF should be questioned about their medication adherence at every visit, and children with a high risk of colchicine non-adherence should be followed up more closely.

Keywords: Adherence, children, colchicine, familial mediterranean fever, non-compliance

Introduction

Familial Mediterranean Fever (FMF) is the most frequent monogenetic autoinflammatory disorder characterized by fever and polyserositis (1). It is caused by a point mutation in the *Mediterranean Fever (MEFV)* gene located on chromosome 16p13.3 encoding an immune regulatory protein, pyrin (1,2). In FMF, the mainstay of treatment is life-long colchicine use (2,3). However, up to 5% of patients are resistant to this medication (4). Adherence to colchicine is one of the main factors affecting colchicine response, and thus the long-term outcomes in patients with FMF (5,6). There are some scales developed to measure medication adherence. The Morisky medication adherence scale, developed as a self-report measure of antihypertensive medication adherence (7), has been used to evaluate adherence to drugs used for the treatment of many diseases, including FMF (8,9). In 2015, Yesilkaya et al. (10) developed the Medication compliance scale in FMF MASIF (Table I) to measure medication adherence specifically for pediatric patients with FMF. In the current study, we planned to investigate colchicine adherence in children with FMF using MASIF.

Materials and Methods

After the ethics committee approval was obtained from Manisa Celal Bayar University Faculty of Medicine, Health Sciences Ethics Committee (29.12.2021-20.478.486/1117),

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this cross-sectional observational study was conducted in February-April 2022 among the children who were diagnosed with FMF based on the pediatric criteria described by Yalçinkaya et al. (11) and treated with colchicine at our pediatric nephrology and rheumatology clinic. Informed consent was conducted from the parents/guardians of the patients. Patients using medication other than colchicine, those with cognitive dysfunction that would prevent them from completing the questionnaire, patients with proteinuria or amyloidosis, and those that were followed up for less than six months were excluded from the study. The demographical and socio-economic data, family history, number of attacks experienced within the previous year, and genetic mutation analysis of the patients were retrospectively assessed by screening the hospital database and patient files. The international severity score for FMF (ISSF) was used to evaluate disease severity (12). A total score of ≥6 was interpreted to indicate severe disease, 3-5 intermediate disease, and ≤2 mild disease. The Turkish version of MASIF (Table I) was completed by the parents/guardians of the patients under seven years old and by the patients themselves if they were over seven years. The participants responded to each of the 18 items on a Likert scale (1=strongly agree, 2=agree, 3=no idea, 4=disagree, 5=strongly disagree). A cut-off value of 60 points was accepted as good adherence for MASIF (10). The children were assigned into two groups according to medication adherence and compared demographically and genetically. The patients were given regular colchicine treatment (≤0.5 mg/day for patients under five years of age, 0.5-1 mg/day for five to 10 years, 1-1.5 mg/day for >10 years) (13).

Statistical Analysis

International business machines (IBM) statistical package for the social sciences statistics v. 26 was used for statistical analyses (IBM Corp., Armonk, NY, USA). Descriptive statistics were utilized as mean±standard deviation or median (minimum-maximum) values for measured data, and frequencies and percentages (%) for categorical data. The normality of the distribution of parameters was evaluated visually (histogram and probability graphics) and by analytical methods (the Kolmogorov-Smirnov and Shapiro-Wilk tests). Student's t-test or the Mann-Whitney U test was carried out to analyze the differences in continuous variables, while the chi-square test was used to compare categorical variables. The Kruskal Wallis-H test was performed to compare multiple variables. The association between the variables was assessed with

Table I. Medication compliance scale in FMF (MASIF)

No	Items
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 realize 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.

MASIF: Medication adherence scale in FMF, FMF: Familial Mediterranean Fever

the Spearman correlation coefficient. A p-value of <0.05 was used for statistical significance.

Results

A total of 82 children (38 male, 44 female) with FMF were enrolled in this study (Table II). The mean current age of the patients was 13.5±4.5 years. The mean age at FMF diagnosis was 6.9±4.5 years. Fifty-five (67%) of the patients had a family history of FMF. Genetic mutation analysis was conducted in each patient with FMF. There were 19 patients with M694V homozygous mutations, 41 with heterozygous mutations (M694V mutation positivity in 18), and 12 with compound heterozygous mutations (M694V mutation positivity in 8). Ten patients (12%) had no mutation in the *MEFV* gene.

The clinical characteristics of the patients are presented in Table III.

According to ISSF, 40 (49%) patients had mild, 25 (30%) had intermediate, and 17 (21%) had severe disease. Sixty-

Table II. Demographic data of patients

Variables		**Patients (n=82)**
Age (Mean±SD)		13.5±4.5
Age at diagnosis (Mean±SD)		6.9±4.5
Gender (M/F)		38/44
Family history of FMF, n (%)		55 (67)
Severity according to ISSF, n (%)	Mild disease	40 (49)
	Intermediate disease	25 (30.5)
	Severe disease	17 (20.5)
Attack rate per month in the previous year, n (%)	<1 attack	62 (75.5)
	1-2 attack	11 (13.5)
	>2 attacks	9 (11)
Colchicine doses (median, min.-max.) (mg/day)		0.5 (0.5-1.0)
Living place, n (%)	Rural	8 (10)
	Urban	74 (90)
Family type, n (%)	Nuclear family	65 (79)
	Extended family	17 (21)
Social security, n (%)	Available	74 (90)
	Unavailable	8 (10)
Socio-economic status, n (%)	Low income	32 (39)
	Middle income	43 (52)
	High income	7 (9)
Employment status, n (%)	Schoolers	50 (80.5)
	Employed	13 (16)
	Unemployed	6 (7)
Smoking in patients, n (%)	Yes	6 (7)
	No	76 (93)
Alcohol use in patients, n (%)	Yes	3 (4)
	No	79 (96)
Substant use of patients, n (%)	Yes	0
	No	82

n: Number, SD: Standard deviation, FMF: Familial Mediterranean Fever, ISSF: International severity score for Familial Mediterranean Fever, M: Male, F: Female, min.: Minimum, max.: Maximum, MASIF: Medication compliance scale in FMF

two (75.5%) of patients had under 1 attack per month. The median colchicine dosage was 0.5 mg/day.

According to MASIF, 31 (38%) patients had non-adherence to colchicine (Table IV). Colchicine adherence was found to be decreased when the child grew older. There was a significant difference among the colchicine-adherent and non-adherent groups in terms of age, disease severity according to ISSF, attack rate, colchicine dosage, M694V homozygosity, and family type (p=0.005, p=0.04, p=0.025, p=0.045, p=0.04, and p=0.046, respectively). However, the two groups did not statistically significantly different in age at diagnosis, gender, family history of FMF, place of residence, socio-economic status, smoking status of patients, and alcohol use of patients (p=0.6, p=0.8, p=0.56, p=0.9, p=0.3, p=0.5, and p=0.3, respectively).

Table III. Clinical data of patients

Variables		**Patients (n=82)**
Severity according to ISSF, n (%)	Mild disease	40 (49)
	Intermediate disease	25 (30.5)
	Severe disease	17 (20.5)
Attack rate per month in the previous year, n (%)	<1 attack	62 (75.5)
	1-2 attack	11 (13.5)
	>2 attacks	9 (11)
Colchicine doses (median, min-max) (mg/day)		0.5 (0.5-1)

n: Number, min: Minimum, max: Maximum, ISSF: International severity score for Familial Mediterranean Fever

Table IV. The relationship between demographic and clinical characteristics of patients and colchicine adherence according to MASIF

	Colchicine adherent patients (n=51)	**Colchicine non-adherent patients (n=31)**	**p-value**
Age	12.5±4	15±4	0.005
Age at diagnosis	6.7±4.4	7.2±4.7	0.6
Gender (M/F)	24/27	14/17	0.8
Family history of FMF	33/18	22/9	0.56
Severity according to ISSF, n (%)			0.04
Mild disease	27 (53)	12 (39)	
Intermediate disease	17 (33)	7 (22.5)	
Severe disease	7 (14)	12 (39)	
Attack rate, n (%)			0.025
<1 attack	43 (84)	19 (62)	
1-2 attack	5 (10)	6 (19)	
>2 attacks	3 (6)	6 (19)	
Colchicine dose (median, min.-max.) (mg/day)	0.5 (0.5-1)	1 (0.5-1.0)	0.045
M694V homozygousity, n (%)	8 (16)	11 (35)	0.04
Living place, n (V/T/C)	4/24/23	3/13/15	0.9
Family type (N/E)	44/7	21/10	0.046
Socio-economic status (H/M/L)	5/28/18	5/15/14	0.3
Smoking in patients, n (%)	3 (6)	3 (10)	0.5
Alcohol use by patients, n (%)	1 (2)	2 (6)	0.3

FMF: Familial mediterranean fever, MASIF: Medication compliance scale in FMF, n: Number, M: Male, F: Female, ISSF: International severity score for FMF, min.: Minimum, max.: Maximum, V: Village, T: Town, C: City, N: Nuclear, E: Extended, H: High, M: Middle, L: Low

Discussion

In this study, we demonstrated the factors affecting colchicine adherence in children with FMF according to MASIF. We found that 38% of our patients were non-adherent to colchicine. Age, disease severity, the number of attacks experienced in the previous year, colchicine dosage, M694V homozygosity, and family type were determined to be statistically correlated with colchicine adherence in pediatric patients with FMF.

Colchicine is defined as the best treatment option for reducing attacks and preventing complications of FMF, such as amyloidosis (2,3). Colchicine treatment also avoids the use of alternative drugs; e.g., biological therapeutics and their side effects (12,13). Colchicine resistance is an important challenge in the management of FMF. It is known that adherence to colchicine is one of the main reasons for colchicine resistance (14). MASIF is a scale developed to measure medication adherence in pediatric patients with FMF. Using MASIF, Yesilkaya et al. (10) and Sönmez et al. (15) reported that 70% and 40% of their patients with FMF were colchicine non-adherent in their respective studies. Similarly, the results of the current research on MASIF indicated that 38% of the patients were non-adherent to colchicine among pediatric FMF cases. Tekgöz et al. (16) determined that 83.8% of adult patients with FMF were non-adherent according to the compliance questionnaire on rheumatology. Sönmez et al. (15) reported a higher adherence rate in younger children (5). The higher rate of non-adherence to medication in adolescent patients with FMF confirms that when patients get older, drug non-adherence increases, as also observed in the current study. Adolescent patients are more non-compliant with colchicine, this may be due to the refusal of medication by the adolescent to avoid side effects.

Children with severe disease and frequent attacks are required to take higher doses of colchicine to manage the disease. It is reported that patients with severe disease and frequent relapses have higher rates of colchicine non-adherence (15). Similarly, in the current study, it was determined that as the colchicine dose increased, the rate of colchicine adherence of the patients with FMF decreased. Öztürk et al. (17) and Barut et al. (18) showed that colchicine resistance was more frequent in patients with FMF who had M694V homozygous mutations. In the current study, we observed that the colchicine non-adherent patients had a higher rate of M694V homozygosity. Due to the frequent attack rate and higher colchicine dosage required to control the attacks of M694V homozygous patients, their colchicine adherence might be lower. Family and social support are considered to be crucial in drug adherence in chronic diseases (19-21). Living in a nuclear family is related to the effective management of many chronic diseases, including hypertension and human immunodeficiency virus, as well as health-related quality of life (20,21). In the current study, the children with FMF living in a nuclear family were determined to be more adherent to colchicine.

The use of tobacco and alcohol is known to be a factor for non-adherence to treatment in various chronic diseases (22,23). However, a relationship between smoking or alcohol use and colchicine adherence was not detected in the current population with FMF.

Study Limitations

A limitation of this study is the small sample size.

Conclusion

It is crucial to predict the factors affecting colchicine adherence in the management of patients with FMF. Adolescent patients, children with severe disease and frequent relapses, those treated with higher doses of colchicine, those with M694V homozygosity, and those with homozygous M694V mutations were observed to have a higher risk of colchicine non-adherence. Patients with FMF should be questioned about their medication adherence at every visit. In particular, patients with a high risk of colchicine non-adherence should be followed up more closely.

Ethics

Ethics Committee Approval: The ethics committee approval was obtained from Manisa Celal Bayar University Faculty of Medicine, Health Sciences Ethics Committee (29.12.2021-20.478.486/1117).

Informed Consent: Informed consent was taken from the participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.N.A.O., E.E., Ö.B., P.E., Design: E.N.A.O., Ö.B., P.E., Data Collection and/or Processing: E.N.A.O., E.E., Analysis and/or Interpretation: Ö.B., P.E., Writing: E.N.A.O., E.E.

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