

Original article

Can colchicine response be predicted in familial Mediterranean fever patients?

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Abstract

Objectives. The aims of this study were to explore whether the demographic and clinical features of paediatric familial Mediterranean fever (FMF) patients with different colchicine response vary or not and to determine whether colchicine response can be predicted in FMF patients.

Methods. Files of patients who have been on colchicine therapy for at least 6 months were retrospectively evaluated. Patients were divided into two groups: group I included patients with no attacks after colchicine and group II comprised patients with ongoing attacks. Thereafter group II was further divided into two groups according to the reduction rate of attack frequency: group IIA (>50%) and group IIB (≤50%).

Results. The study group comprised 221 FMF patients (116 females, 105 males). There were 131 patients in group I and 90 patients in group II (54 in group IIA and 36 in group IIB). Leg pain and M694V homozygosity were more frequent in group II ($P < 0.05$). Final colchicine doses, disease severity scores and number of patients with elevated acute phase reactant levels (attack-free period) were significantly higher and colchicine compliance was lower in group II when compared with group I ($P < 0.05$). Erysipelas-like erythema (ELE), leg pain and protracted arthritis/protracted febrile myalgia/vasculitis were more frequently detected in group IIB ($P < 0.05$).

Conclusion. Colchicine response is excellent in the majority of FMF patients, however, colchicine unresponsiveness cannot be predicted easily at onset. More rarely encountered clinical findings such as ELE, leg pain and protracted complaints and M694V homozygosity may be a clue for less colchicine response.

Key words: colchicine, familial Mediterranean fever, paediatric.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent irregular self-limited attacks of fever and polyserositis accompanied by an increase in acute phase reactants (APRs) [1]. In 1972, Goldfinger [2] and Özkan *et al.* [3] first described the effectiveness of colchicine in preventing FMF attacks. Colchicine, which has changed the disease course in many patients, prevents the development of systemic amyloidosis in the long term [1]. Previous studies have shown that under colchicine therapy 60–65% of the patients achieve complete remission, 30–35% achieve

partial remission and 5–10% are non-responders [4, 6]. In 1997, two independent groups defined the Mediterranean fever (MEFV) gene responsible for the disease and this was a major milestone in better understanding and treating this auto-inflammatory disease [7, 8]. After the discovery of the MEFV gene, some authors reported lower colchicine response rates in certain types of MEFV mutation [9, 10]. However, studies that describe and compare the clinical features of FMF patients with different colchicine responses are rare. Accordingly, the aim of this study was to explore whether the demographic and clinical features of paediatric FMF patients with different colchicine responses vary or not and to determine whether colchicine response can be predicted in FMF patients prior to colchicine therapy.

Patients and methods

Files of patients who had been seen in our department (during routine follow-up visits) between January 2009 and January 2013 and who have been on colchicine

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therapy for at least 6 months were retrospectively evaluated. Patients were interpreted with respect to demographic data, clinical and laboratory features of the disease and genetic analysis of *MEFV* mutations. The diagnosis of FMF was based on the presence of clinical criteria [11, 12]. Disease severity was determined by the use of scoring systems determined by Pras *et al.* [13] and Mor *et al.* [14] (with relevant changes made for children; i.e. the age factor and also the colchicine dosages) (see Table 1 and Mor *et al.* [14]). At least six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R and 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 [15, 16]. Patients were divided into two groups according to their attack frequency after colchicine therapy: group I included patients with no attacks after colchicine and group II comprised patients with attacks that were reduced in number but not disappeared completely or patients with a similar attack frequency after colchicine. Thereafter, group II was further divided into two groups according to the reduction rates of attack frequencies: group IIA (>50%) and group IIB (≤50%). The study was approved by the Ethics Committee of Ankara University.

Statistical analysis

Results are given as the median (minimum–maximum) or proportion. Categorical variables were evaluated by chi-square test or Fisher's exact test where applicable. Comparisons between two groups for the non-normally distributed continuous variables were assessed by the Mann–Whitney *U* test. Differences among three groups for the non-normally distributed continuous variables were evaluated by Kruskal–Wallis variance analysis. When the *P*-value from the Kruskal–Wallis test statistics was statistically significant, a multiple comparison test was used to determine which group differed from which others. SPSS for Windows 15.0 (IBM, Armonk, NY, USA) was used for statistical analysis. A *P*-value <0.05 was considered statistically significant.

Results

The study group comprised 221 FMF patients (116 female, 105 male) with a mean age of 12.7 years (s.d. 5.3). The mean duration of colchicine therapy was 58.9 months (s.d. 45.3). Mutation analysis was performed in 209 of the 221 patients. Sixty (28.7%) patients had homozygous, 69 (33%) had compound heterozygous and 56 (26.8%) had heterozygous mutations. Twenty-four patients (11.5%) had none of the screened mutations. The most frequent mutations were M694V/M694V (25.4%), M694V/– (18.7%), M694V/M680I (13.9%) and M694V/V726A (7.7%). Overall, 149 of the 209 patients (71.3%) had at least one M694V mutation.

There were 131 patients (59%) in group I and 90 patients (41%) in group II, in which attack frequency decreased in 85 (38.4%) patients and was unchanged in

TABLE 1 Severity score by Pras *et al.* modified for children

Parameter	Features	Score
Age of onset, years	11–20	2
	3–10	3
	<3	4
Number of attacks per month	<1	1
	1–2	2
	>2	3
Arthritis	Acute	2
	Protracted	3
Erysipelas-like erythema		2
Amyloidosis		3
Dose of colchicine, mg/m ²	<1	0
	1	1
	>1	2
	>2 mg/day ^a	3

^aNot responsive to 2 mg/day. The severity score is the sum of the scores for each parameter. A score of 3–5 is mild, 6–9 is moderate and >9 is severe disease. Adapted from Pras *et al.* [13].

5 (2.3%) patients. Mean age, sex, age at disease onset, age at colchicine onset, family history of FMF, attack frequency, attack duration, clinical features during attacks, duration of colchicine use and single M694V carriage were similar between the groups (*P* > 0.05). Leg pain and M694V homozygosity were more frequent in group II (*P* < 0.05). Final colchicine doses, disease severity scores and number of patients with elevated APR levels (during the attack-free period after colchicine therapy) were significantly higher in group II when compared with group I (*P* < 0.05). There was also a statistically significant difference in colchicine compliance between the two groups (*P* = 0.014) (Table 2).

The second analysis was done in order to compare groups I, IIA and IIB (Table 3). Mean age, sex, age at disease onset, age at colchicine onset, family history of FMF, attack duration, clinical features during attacks and single M694V carriage were similar between the groups (*P* > 0.05). In contrast to the previous comparison (group I vs group II), M694V homozygosity and colchicine compliance did not differ between the groups. Erysipelas-like erythema (ELE), leg pain and protracted arthritis (PA)/protracted febrile myalgia (PFM)/vasculitis were more frequently detected in group IIB (*P* < 0.05). Final colchicine doses and disease severity scores increased together with the increase in the attack frequency after colchicine therapy.

There were 16 (7.2%) patients with incomplete colchicine compliance in the entire group, the majority of them with partial (11 patients) compliance. In order to exclude the impact of colchicine compliance on our results, we eliminated these non-compliant patients and did all the statistical analyses again. The results of all the previous comparisons that were done between groups I and II were found to be exactly the same. Thus these non-compliant patients had no effect on our results. Then groups I, IIA

TABLE 2 Comparison of the patients with and without attacks after colchicine therapy

	Group I (no attacks) (n = 131)	Group II (with attacks) (n = 90)	P-value
Age, median (min-max), years	12 (2-27)	13 (3.5-27)	0.34
Sex, n (%)			
Male	67 (51.1)	38 (42.2)	0.19
Female	64 (48.9)	52 (57.8)	
Consanguinity, n (%)	28 (21.4)	19 (21.1)	0.96
Family history of FMF, n (%)	75 (57.3)	42 (46.7)	0.12
Age at disease onset, median (min-max), years	3 (0-17)	3 (0-15)	0.83
Age at colchicine onset, median (min-max), years	7 (1-20)	7 (1.5-24)	0.96
Patients with delay in diagnosis, n (%)	115 (87.8)	78 (86.7)	0.80
Attack frequency per year before colchicine, median (min-max)	12 (0-48)	24 (0.5-96)	0.14
Attack duration before colchicine, median (min-max), h	48 (0-168)	48 (4-168)	0.13
Clinical findings at onset, n (%)			
Fever	120 (91.6)	85 (94.4)	0.42
Abdominal pain	113 (86.3)	79 (87.8)	0.74
Chest pain	41 (31.3)	38 (42.2)	0.096
Arthritis	23 (17.6)	18 (20.0)	0.72
Arthralgia	50 (38.2)	33 (36.7)	0.82
ELE	5 (3.8)	8 (8.9)	0.11
Leg pain	29 (22.1)	33 (36.7)	0.014
Heel pain	17 (13)	15 (16.7)	0.28
PA/PFM/vasculitis	12 (9.2)	14 (15.6)	0.10
Presence of two mutations, ^a n (%)	76 (61.3)	53 (62.4)	0.49
M694V positivity, ^a n (%)	87 (70.2)	62 (72.9)	0.66
M694V homozygosity, ^a n (%)	24 (19.4)	29 (34.1)	0.013
Colchicine compliance, n (%)			
Complete	127 (96.9)	78 (86.7)	0.014
Partial	3 (2.3)	8 (8.9)	
None	1 (0.8)	4 (4.4)	
Duration of colchicine therapy, median (min-max), months	42 (6-204)	48 (6-210)	0.18
Final colchicine dosage, median (min-max), mg/day	1 (0.25-2)	1.12 (0.5-3)	0.001
Final colchicine dosage, median (min-max), mg/kg/day	0.026 (0.01-0.09)	0.031 (0.01-0.52)	0.001
Final colchicine dosage, median (min-max), mg/m ² /day	0.85 (0.7-1.59)	1.01 (0.52-1.89)	<0.001
Patients with elevated attack-free APRs, n (%)	17 (13.0%)	31 (34.4%)	<0.001
Pras score, median (min-max)	6 (2-12)	7 (4-11)	<0.001
Pras, n (%)			
Mild	47 (35.9)	19 (21.1)	0.019
Moderate	80 (61.1)	63 (70.0)	
Severe	4 (3.0)	8 (8.9)	
Mor score, median (min-max)	1 (0-5)	2 (0-6)	<0.001
Mor, n (%)			
Mild	73 (55.7)	25 (27.8)	
Moderate	30 (22.9)	36 (40.0)	<0.001
Severe	28 (21.4)	29 (32.2)	
Pras score ^b , median (min-max)	6 (2-10)	6 (4-10)	0.029
Mor score ^c , median (min-max)	1 (0-5)	1 (0-5)	0.034

FMF: familial Mediterranean fever; min: minimum; max: maximum; ELE: erysipelas-like erythema; PA: protracted arthritis; PFM: protracted febrile myalgia; APR: acute phase reactant. ^aMutation analysis was performed in 209 patients (124 patients in Group I and 85 patients in Group II). ^bPras score: total Pras score without dose of colchicine score. ^cMor score: total Mor score without dose of colchicine score. Statistically significant *P*-values are in bold.

and IIB were compared again. Two of the previous analysis results (sex and M694V homozygosity) that were found to be statistically insignificant ($P > 0.05$) became statistically significant ($P < 0.05$). These results were added to Table 3. The remaining results did not differ from the previous ones.

Discussion

Overall, our findings were compatible with the literature, with 59.3% with complete response, 38.4% with a partial response and 2.3% with no response to colchicine therapy. The presence of M694V homozygosity, ELE, leg pain

TABLE 3 Comparison of groups I, IIA and IIB

	Group I (n = 131) Median (min-max)	Group IIA (n = 54) Median (min-max)	Group IIB (n = 36) Median (min-max)	P-value
Sex, n (%)				
Male	67 (51.1)	27 (50)	11 (30.6)	0.083
Female	64 (48.9)	27 (50)	25 (69.4)	
Attack frequency per year before colchicine, median (min-max)	12 (0-48)	24 (0.5-96)	12 (2-60)	1 vs 2: 0.018 1 vs 3: 0.640 2 vs 3: 0.030
ELE, n (%)	5 (3.8)	2 (3.7)	6 (16.7)	0.011
Leg pain, n (%)	29 (22.1)	16 (29.6)	17 (47.2)	0.012
PA/PFM/vasculitis, n (%)	12 (9.2)	5 (9.3)	9 (25.0)	0.027
M694V homozygosity, n (%)	24 (19.4)	17 (34.7)	12 (33.3)	0.054
Colchicine compliance, n (%)				
Complete	127 (96.9)	47 (87)	31 (86.1)	0.065
Partial	3 (2.3)	5 (9.3)	3 (8.3)	
None	1 (0.8)	2 (3.7)	2 (5.6)	
Final colchicine dosage, median (min-max), mg/day	1 (0.25-2)	1 (0.5-2)	1.5 (0.5-3)	1 vs 2: 0.585 1 vs 3: <0.001 2 vs 3: <0.001
Final colchicine dosage, median (min-max), mg/kg/day	0.026 (0.01-0.09)	0.03 (0.01-0.23)	0.04 (0.02-0.52)	1 vs 2: 0.096 1 vs 3: <0.001 2 vs 3: 0.031
Final colchicine dosage, median (min-max), mg/m ² /day	0.85 (0.7-1.59)	0.94 (0.52-1.38)	1.19 (0.59-1.89)	1 vs 2: 0.071 1 vs 3: <0.001 2 vs 3: <0.001
Patients with elevated attack-free APRs, n (%)	17 (13.0)	19 (35.2)	12 (33.3)	0.001
Pras score, median (min-max)	6 (2-12)	7 (4-11)	8 (5-11)	1 vs 2: 0.129 1 vs 3: <0.001 2 vs 3: 0.004
Pras, n (%)				
Mild	47 (35.9)	17 (31.5)	2 (5.6)	0.002
Moderate	80 (61.1)	34 (63.0)	29 (80.6)	
Severe	4 (3.1)	3 (5.6)	5 (13.9)	
Mor score, median (min-max)	1 (0-5)	2 (0-5)	2 (1-6)	1 vs 2: 0.092 1 vs 3: <0.001 2 vs 3: 0.010
Mor, n (%)				
Mild	73 (55.7)	22 (40.7)	3 (8.3)	<0.001
Moderate	30 (22.9)	16 (29.6)	20 (55.6)	
Severe	28 (21.4)	16 (29.6)	13 (36.1)	
Pras score ^a , median (min-max)	6 (2-10)	6 (4-9)	6 (4-10)	0.034
Mor score ^b , median (min-max)	1 (0-5)	1 (0-4)	2 (0-5)	0.06
Sex ^c , n (%)				
Male	65 (51.2)	24 (51.1)	7 (22.6)	0.013
Female	62 (48.8)	23 (48.9)	24 (77.4)	
M694V homozygosity ^d , n (%)	23 (19.2)	16 (37.2)	11 (35.5)	0.027

min: minimum; max: maximum; FMF: familial Mediterranean fever; ELE: erysipelas-like erythema; PA: protracted arthritis; PFM: protracted febrile myalgia; APR: acute phase reactant. ^aPras score: total Pras score without dose of colchicine score. ^bMor score: total Mor score without dose of colchicine score. ^cSex: analysis after elimination of colchicine-non-compliant patients. ^dM694V homozygosity: analysis after elimination of colchicine-non-compliant patients. 1 vs 2: comparison of groups I and IIA; 1 vs 3: comparison of groups I and IIB; 2 vs 3: comparison of groups IIA and IIB. Statistically significant P-values are in bold.

and PA/PFM/vasculitis seems to be related to a lower colchicine response. Patients with less response to colchicine had higher disease severity scores, supporting the efficacy of these scores in determining disease severity in paediatric FMF patients.

In this current study, the majority of demographic and clinical features prior to colchicine therapy, such as age at disease onset, family history of FMF, attack frequency, attack duration and clinical features during attacks, were found to be similar between the groups. Hence it seems that we could not

predict colchicine response according to these parameters alone. In previous studies it has been shown that patients with disease onset at younger age had a more severe disease course, although they had similar attack frequencies and clinical features [17]. Disease severity scores developed by Pras *et al.* [13] and Mor *et al.* [14] also included age at disease onset as one of the parameters that influence the score rates. Therefore age at disease onset is an important but not sufficient parameter for predicting colchicine response. After discovery of the *MEFV* gene, genotyping has shown that the disease is associated with a wide variety of symptoms [18]. However, the genotype–phenotype relationship is not well established and the spectrum of clinical findings may differ considerably from one patient to the other. In this study we found that patients with no attacks after colchicine had similar carrier rates of homozygous and compound heterozygous mutations and similar single M694V carriage when compared with patients with attacks. Although M694V homozygosity was more frequently detected in group II patients, patients with >50% and ≤50% response rates had comparable M694V homozygosity. Some of the previous studies showed that M694V homozygosity was related to more severe disease. Lidar *et al.* [9] compared M694V homozygotes with two groups of patients, M694V/V726A compound heterozygotes and V726A homozygotes. They found that M694V homozygotes had earlier age at diagnosis, more frequent attacks prior to treatment and more frequent arthritis attacks. Further, those patients were treated with higher doses of colchicine and were much less responsive to colchicine. Alternatively, a paediatric study from Turkey showed that M694V homozygotes had similar clinical features to other patients but a lower response to colchicine treatment [10]. It has again been shown that FMF patients with early disease onset have more M694V carriage and more severe disease [17]. Overall, it seems that M694V homozygosity is related to more severe disease and lower response to colchicine therapy. In our study a total of 53 patients had M694V homozygosity, and 24 (45%) of those had complete colchicine response. On the other hand, 20% of our patients in the complete response group had M694V homozygosity. In daily practice, physicians dealing with FMF incidentally encounter subjects carrying homozygous M694V mutations without any clinical findings. In this regard, Lidar *et al.* [19] mentioned that colchicine treatment failure in FMF is associated with inadequate colchicine mononuclear cell concentrations and not with an *MEFV* gene defect, suggesting that it is not just a reflection of genetically determined more severe FMF. Therefore, although M694V homozygosity was more frequently detected in patients with a lower colchicine response, it seems that we could not actually predict colchicine response according to genetic results.

Overall, colchicine compliance was excellent in our series; non-compliant patients constituted only 7% of the population. Compliance with colchicine therapy was low in patients with ongoing attacks (complete compliance 87%) when compared with patients without attacks (complete compliance 97%). Some of those patients with ongoing attacks might have a complete response if they adhered fully to their therapy. On the other hand, the significance in

colchicine compliance disappeared when we compared group IIA and IIB patients, with similar compliance rates for patients that had >50% and ≤50% response rates. In order to rule out the effect of colchicine compliance on our results we repeated all the statistical analyses after elimination of non-compliant patients. The majority of the results did not differ. Two of the previous analysis results (sex and M694V homozygosity) that were found to be statistically insignificant became statistically significant. Interestingly, girls constituted ~80% of the patients in group IIB, in contrast to groups I and IIA in which there were equal numbers of male and female patients. We think that further studies are needed to determine whether hormonal, psychiatric or environmental factors affect colchicine response, especially in female patients.

An expected finding was that patients with ongoing attacks after colchicine therapy had increased disease severity scores, especially in group IIB. These patients with continuing attacks under colchicine therapy were on higher colchicine dosages as well. The dose of colchicine is one of the parameters of severity scores developed by both Pras *et al.* [13] and Mor *et al.* [14]. According to our results, the dose of colchicine seems to be the most important determinant of severity score, which can be more easily appreciated when comparisons of the Mor and Pras scores, with or without the colchicine scores that are presented in Tables 2 and 3, are carefully interpreted. Patients with attacks despite colchicine therapy had elevated attack-free APR levels and we think this is a predictable finding. In our daily practice we referred to patients with no response to colchicine therapy as severe FMF patients, but we could not predict severe FMF patients at the onset of therapy. In the light of our results, we could not foresee colchicine response according to the majority of clinical findings, including age at disease onset and attack frequency. The presence of more rarely encountered clinical findings such as ELE, leg pain and protracted complaints and M694V homozygosity may be a clue for a lower colchicine response. In addition, as is well known, we could not presume which patients would develop amyloidosis; there is no correlation between the frequency and severity of febrile attacks and amyloidosis [20].

In conclusion, colchicine response is excellent in the majority of FMF patients, however, clues about colchicine unresponsiveness are unclear, thus it is hard to predict prior to therapy. It seems that clinicians do not have another reasonable strategy other than wait and see.

Rheumatology key messages

- Colchicine response is excellent in the majority of familial Mediterranean fever patients.
- Leg pain, erysipelas-like erythema, protracted complaints and M694V homozygosity could suggest less colchicine response in familial Mediterranean fever.

Disclosure statement: The authors have declared no conflicts of interest.

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