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ORIGINAL ARTICLE

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Possible effect of subclinical inflammation on daily life in familial Mediterranean fever

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Abstract This study was performed to investigate the attack-free complaints of patients with familial Mediterranean fever (FMF) and the impact of colchicine on these symptoms and on subclinical inflammation. A questionnaire that includes information about the disease course and symptoms during the attack-free period was administered to the parents of 50 FMF patients. For evaluation of the attack-free period, questions were asked about four items concerning daily activities of the children—weakness, lack of appetite, sleep problems, and decreased activity. The respondents rated the items and the total score was taken as the sum of all of the specific items. The laboratory values were noted from the patients' files. During the attack-free period, patients with mild disease had higher total scores, higher weakness, and decreased activity scores than patients with moderate disease. When we compared the daily activity scores before and after colchicine therapy, a statistically significant increase was observed in the total scores and in all of the specific item scores. Also a significant decrease was seen in the erythrocyte sedimentation rate and white blood cell counts, and a significant increase was seen in the hemoglobin levels during the attack-free period after colchicine usage. Regression of inflammation together with improvement in daily activities were observed. FMF patients seem to have complaints during the attack-free period that may be related to subclinical inflammation. Moreover, colchicine besides preventing the FMF attacks and the dangerous complication of amyloidosis also seems to hinder the symptoms of the attack-free period in children with FMF.

Keywords Attack-free period · Children · Colchicine · Familial Mediterranean fever · Subclinical inflammation

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by recurrent, self-limited attacks of fever with serositis involving the peritoneum, pleura, and joints. The disease is caused by mutations in the FMF gene (MEFV) located on chromosome 16 and primarily affects Jewish, Armenian, Turkish, and Arab populations. Amyloidosis is the most severe complication of FMF [1–4]. Daily colchicine treatment was first suggested by Goldfinger [5] and Özkan et al. [6] in 1972. Later it was shown that it is an effective treatment for the prevention of FMF attacks and development of amyloidosis in all compliant patients [7–9]. Most of the previous reports revealed that acute phase reactants (APR) are generally elevated during the attacks of FMF and return to normal with clinical remission [10]. Recently, it was shown that in some patients, APR could remain high during the intervals between the attacks. This has led to the suggestion that subclinical inflammation continues during the attack-free periods [11, 12], but the influence of subclinical inflammation on daily life has not been investigated previously. The aim of this study was to investigate the attack-free complaints of patients with FMF and the impact of colchicine on these symptoms and on subclinical inflammation.

Methods

This was a cross-sectional study that comprised 50 children of the 500 FMF patients who have been

followed and regularly seen every 6–12 months. All patients fulfilled the clinical criteria for the diagnosis of FMF [13]. To evaluate the colchicine response, patients were required to be on colchicine therapy for at least 6 months. Patients were recruited during their routine follow-up visits to the clinic between the dates of February 2004 and June 2004 and all patients who came to control visits during that time were included. The parents of each patient signed an informed consent and all patients underwent a clinical interview and examination. A questionnaire that included patient age, age at disease onset, age of therapy, symptoms before and after colchicine therapy, duration and dosage of therapy, compliance with the medication, and side effects was prepared and administered to the parents of each patient by the same clinician. The overall severity of their disease was estimated according to Tel Hashomer criteria, accounting for the age of onset, frequency of attacks at any site, presence of arthritis and erysipelas-like lesion, amyloidosis, and colchicine dosage [14]. For evaluation of the attack-free period, questions were asked about four items concerning daily activities of the children—weakness, lack of appetite, sleep problems (decrease in the duration or quality of sleep), and decreased activity (unwillingness to do daily activities). The respondents were asked to rate the items as "1" if their answers were "yes, exactly," "2" if "yes, sometimes," and "3" if their answers were simply "no." The total score was taken as the sum of all of the specific items. Patients who had no complaints about these four items would get a total score of 12, but if they had severe complaints they would only have taken a total score of four. Their hemoglobin (Hb), white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) and fibrinogen levels during the attacks and attack-free periods—before and after the use of colchicine—were noted from the patients' files. Laboratory values during attacks were routinely obtained when the patients were symptomatic and the attack-free values were obtained at least 10 days after the attack.

The results were analyzed using the Social Package for Statistical Sciences 11.0 and expressed as median (minimum–maximum) for data not showing normal distribution and as mean ± standard deviation (SD) for data showing normal distribution. The paired samples *t*-test and Wilcoxon's test were used for comparison of the dependent groups. The independent samples *t*-test and Mann–Whitney U tests were used for comparison of independent groups. Values of $p < 0.05$ were considered statistically significant.

Results

Demographic features

Demographic features and colchicine dosages of the study group are summarized in Table 1. Past history revealed that colchicine was increased from 1 to 1.5 mg/day or from 1.5 to 2 mg/day in 25 patients: for frequent attacks in 17 (68%), for the elevated APR during the attack-free period in 6 (24%), and for intermittent proteinuria in 2 (8%) patients.

Colchicine and the attacks

The frequency and the characteristics of the clinical symptoms before and after colchicine therapy are shown in Tables 2 and 3. Antipyretic response was obtained in 73% of the 34 patients before therapy and in 100% of the 24 patients after therapy. Pretreatment and post-treatment mean attack WBC counts and CRP, ESR, and fibrinogen levels did not differ.

Colchicine and the attack-free period

When we compared the scores of daily activities before colchicine therapy, patients with mild disease had higher

Table 1 Demographic features and colchicine dosages of the study group

		Study group, $n = 50$ mean ± SD	Range
Sex	Boys	24 (48%)	
	Girls	26 (52%)	
Age at time of study (years)		11.91 ± 3.85	4–22.5
Age at disease onset (years)		4.18 ± 3.10	6 months–12
Age at onset of therapy (years)		7.36 ± 3.21	2–14
Mean duration of therapy (years)		4.54 ± 3.24	6 months–15.5
Disease severity	Mild	10 (20%)	
	Moderate	39 (78%)	
	Severe	1 (2%)	
Compliance to therapy	Yes	46 (92%)	
	No	4 (8%)	
Colchicine dosage	1 mg/day	28 (56%)	
	1.5 mg/day	15 (30%)	
	2 mg/day	7 (14%)	
Mean colchicine dosage per kilogram (mg/kg)		0.035 ± 0.015	0.01–0.08
Mean colchicine dosage per body surface area (mg/m^2)		1.11 ± 0.34	0.62–2.0

Table 2 Frequency of the clinical symptoms

	Before colchicine, $n=50$ (%)	After colchicine, $n=50$ (%)
Abdominal pain	46 (92)	27 (54)
Chest pain	18 (36)	13 (26)
Arthritis	11 (22)	5 (10)
Arthralgia	14 (28)	5 (10)
Erysipelas-like erythema	2 (4)	1 (2)
Fever	47 (94)	28 (56)
Myalgia	9 (18)	5 (10)

total scores (median: 11, min.: 9, max.: 12) than patients with moderate disease (median: 9, min.: 6, max.: 12) ($p<0.01$). Weakness and decreased activity scores of patients with mild disease (median: 3, min.: 2, max.: 3) were also higher than patients with moderate disease (median: 2, min.: 1, max.: 3) ($p<0.01$ and 0.05). Scores of appetite loss and sleep problems did not differ statistically between the two groups ($p>0.05$). Scores of daily activities during the attack-free period before and after colchicine therapy are given in Table 4. In attack-free periods, median ESR and mean WBC count decreased and mean Hb increased after colchicine therapy ($p<0.05$). Although mean CRP levels tended to decrease after colchicine therapy, no statistically significant difference was found in CRP and fibrinogen values (Table 5).

Hepatosplenomegaly was detected in four (8%) patients before colchicine. Hepatomegaly disappeared and splenomegaly was detected in only one (2%) patient after colchicine therapy. Two patients had intermittent proteinuria and none of the patients had developed amyloidosis. Diarrhea as a side effect of colchicine therapy was seen in 14 (28%) patients and 78% of the diarrhea episodes occurred at the beginning of therapy or together with increased dosage and disappeared shortly thereafter. Alopecia, leukopenia, myalgia, and myopathy did not occur in any patient.

Discussion

Although FMF is a periodic disease and the patients seem to be symptom free in between the episodes, we have observed that they have some subtle complaints, in other words they are not completely normal. We thus investigated the attack-free period by asking simple and short questions that could easily be answered by the parents. In our study, we found that as the severity of the disease increased the patients had more complaints between the attacks affecting their daily activities. When we compared the daily symptom scores, a statistically significant increase was observed in the total scores and in all of the specific item scores of all of the patients after colchicine therapy compared to the ones before therapy. Patients' weakness, lack of appetite, decreased activity, and sleep problems improved after colchicine therapy.

Recently, it was shown that enhanced APR is present in some of the FMF patients between the attacks. This finding was interpreted as subclinical inflammation in patients who had no complaints [11, 12]. Likewise, in our six patients the reason for the increment in colchicine dosage was elevated APR between the attacks. Accordingly, some points are extremely important and worth mentioning: one is the fact that some FMF patients could have complaints during the attack-free period, not so severe but seemingly affecting their daily activities. Second, in keeping with the aforementioned studies from Turkey [11, 12], these complaints seem to be related to chronic inflammation. We had also detected a significant decrease in ESR and WBC count and a significant increase in the Hb levels after colchicine therapy. Although not statistically significant, CRP levels decreased and thus regression of inflammation together with the improvement in daily activities were observed in the attack-free period. The rise in the Hb levels was suggested to be due to the regression of the inflammation, but also increased appetite after colchicine could have had a role.

The results of our study obviously show that prophylactic colchicine therapy is a safe and effective method of eliminating the attacks without any important side effects. We had no patient refractory to medical treatment. Complete remission was achieved in several of our patients, and the frequency and severity of the attacks decreased significantly in the remaining ones. Dosing regimens for colchicine therapy in childhood remain largely empirical and vary according to local practice. Recently, we had proposed a new dosing

Table 3 Characteristics of the clinical symptoms before and after colchicine therapy

		Before colchicine median (min.–max.), mean ± SD	After colchicine median (min.–max.), mean ± SD	p
Abdominal pain	Frequency (years^{-1})	24 (1–120)	2 (0.5–48)	<0.001
	Duration (h)	72 (10–168)	24 (1–96)	<0.001
Chest pain	Frequency (years^{-1})	24 (0.5–96)	2 (0.5–96)	<0.01
	Duration (h)	57.60 ± 20.23	37.20 ± 31.05	<0.05
Joint manifestations	Frequency (years^{-1})	17.87 ± 15.67	3.87 ± 3.94	<0.05
	Duration (h)	72 (24–168)	36 (24–120)	<0.05
Fever	Frequency (years^{-1})	24 (0.5–120)	2 (0.5–48)	<0.001
	Duration (h)	60 (12–240)	24 (1–72)	<0.001
	Degree of fever (°C)	39 (38–40)	38.5 (37–39)	<0.01

Table 4 Scores of daily activities during the attack-free period before and after colchicine

	Before colchicine ($n=50$)		After colchicine ($n=50$)		p
	Median	Min./max.	Median	Min./max.	
Weakness	2	1/3	3	2/3	<0.001
Lack of appetite	2	1/3	3	2/3	<0.001
Sleep problems	3	1/3	3	3/3	<0.05
Decreased activity	3	1/3	3	3/3	<0.001
Total score	10	6/12	12	10/12	<0.001

Table 5 Laboratory values during the attack-free period before and after colchicine therapy

	Before colchicine median (min./max.), mean ± SD	After colchicine median (min./max.), mean ± SD	p
WBC count (mm^{-3})	8000 ± 2619	6907 ± 1893	<0.05
ESR (mm/h)	21 (5/109)	14 (3/54)	<0.01
CRP (mg/dl)	0.90 ± 1.39	0.32 ± 0.35	>0.05
Fibrinogen (mg/dl)	308.27 ± 119.44	309 ± 52.90	>0.05
Hb (g/dl)	11.73 ± 1.15	12.86 ± 1.09	<0.001

regimen and showed that prescribing colchicine therapy according to body weight and body surface area would be more appropriate in childhood [15]. The cross-sectional design might be a limitation of our study. Therefore, we suggest that a prospective study including a higher number of patients might be done to support our preliminary results.

As a conclusion, this study seems to establish the value of daily colchicine administration in decreasing the complaints during the attack-free period in FMF. Recurrent attacks together with the complaints during the attack-free period may well affect the education and social activities of the children. Thus, we highlight the importance of colchicine treatment, which besides preventing the attacks and dangerous complication of amyloidosis also improves the daily symptoms in the interim between the attacks.

Take home message

FMF patients seem to have complaints during the attack-free period that may be related to subclinical inflammation, and colchicine improves these daily symptoms in the interim between the attacks.

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