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ORIGINAL ARTICLE

The effect of colchicine and disease severity on physical growth in children with familial Mediterranean fever

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Abstract This study aimed to investigate the effects of colchicine on growth parameters in familial Mediterranean fever (FMF) patients. Fifty-one (29 girls, 22 boys) FMF patients were enrolled in the study. All of the patients were in the prepubertal stage and had not received colchicine treatment before the study. Anthropometric measurements, demographic features, clinical findings at diagnosis and during periods of attacks of FMF, disease activity, frequency of exacerbations, colchicine dosage, and weight and height measurements were recorded at an interval of 6 months. Height, weight, and body mass index standard deviation scores and Z-scores were calculated. The mean height standard deviation score (HSDS) was significantly increased from −0.64±1.20 to −0.26±1.07 ($p<0.001$), the mean weight standard deviation score (WSDS) was significantly increased from −0.60±1.03 to −0.45±0.98 ($p=0.008$), and the mean body mass index standard deviation score was decreased from −0.33±1.06 to −0.47±0.98 ($p=0.128$) at 1 year after colchicine treatment compared with before initiation of treatment. In patients who had no FMF attacks during colchicine treatment, height and weight were significantly increased at 1 year (HSDS: $p<0.001$ WSDS: $p=0.002$), but in patients who had recurrent attacks, height and weight did not change (HSDS: $p=0.051$, WSDS: $p=0.816$). Even when subclinical inflammation is present, preventing attacks of FMF with colchicine allows growth to continue. However, suppression of subclinical inflammation and control of attacks of FMF are required for weight gain.

Keywords Children · Colchicine · Familial Mediterranean fever · Growth · Inflammation

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever, abdominal pain, chest pain, arthritis/arthralgia, and erysipelas-like skin lesions. Impairment of growth is a common complication of chronic diseases [1, 2]. FMF differs from other chronic inflammatory diseases by its characteristic self-limited attacks that alternate with disease-free periods. However, despite these clinical remission periods, inflammatory activity may still continue [3, 4]. Limited numbers of studies have investigated the effect of colchicine on growth and development. Controlling attacks of FMF by early initiation of colchicine and suppressing subclinical inflammation has been shown to improve growth parameters [5, 7].

Therefore, this study aimed to evaluate growth parameters after starting colchicine in recently diagnosed prepubertal FMF patients, along with other identifying characteristics of the disease. Moreover, we aimed to investigate the status of inflammation and effects of disease severity on growth parameters.

Materials and methods

This study was prospectively performed between October 2012 and February 2013. The study was approved by the local hospital ethics committee and performed according to the

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Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from every participant. Fifty-one children (29 girls, 22 boys) who had diagnostic criteria for FMF [8, 9] were enrolled in the study. All of the patients were in the prepubertal stage and had not received colchicine treatment before the study. The disease history was obtained from patients and parents. The disease severity score was estimated according to Tel Hashomer criteria [10] accounting for age at disease onset, frequency of attacks at any site, presence of arthritis and erysipelas-like erythema, amyloidosis, and colchicine dosage. According to this system, 2–5 points indicate mild disease, 6–10 points indicate moderate disease, and >10 points indicate heavy disease (Table 1).

Anthropometric measurements were performed and pubertal stages were determined. Demographic features, clinical findings at diagnosis and during attack periods of FMF, disease activity, frequency of exacerbations, colchicine dosage, and weight and height measurements were recorded at an interval of 6 months. Height and weight standard deviation scores (SDS, Z-scores) were calculated. Patients were evaluated according to Tanner pubertal staging at each visit [11, 12]. Stage 2 thelarche for girls and a 4 mL testicular volume for boys were considered as the onset of puberty and these patients were excluded from the study.

Genetic data

Exons 2, 3, 5, and 10 were screened for MEFV mutations with DNA sequences.

Statistical analysis

Data analysis was performed with Statistical Package for the Social Sciences (SPSS) 15. At the beginning and at the end of the first year of colchicine treatment, growth parameters were compared using the dependent samples *t* test. For evaluation of differences in growth between groups with and without episodes, analysis of covariance was used. Linear regression analysis was used to assess the effect of growth on the severity of disease. Related to the severity of the disease, the chi-square test was used for comparisons. A value of $p<0.05$ was considered as statistically significant. Because of the wide range in values of laboratory tests, results are shown as median and range.

Results

All measurements and assessments were performed for the 51 prepubertal patients. Demographic, clinical, and laboratory features of the patients are shown in Table 2. None of the patients used any other drugs, such as steroids or non-steroid anti-inflammatory drugs, except for colchicine during the attack period. During colchicine treatment, 11 (21.5 %) patients had recurrent attacks and 40 (78.5 %) had no attacks.

The median white blood cell count, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR) were significantly higher in attack periods compared to attack-free periods ($p<0.05$). Laboratory values during the attack and attack-free periods are shown in Table 3. There was a significant improvement in acute phase reactants (CRP and ESR) after initiation of colchicine treatment ($p<0.05$). At the beginning of colchicine treatment, the median hemoglobin level was 11.9 g/dl, which increased to 12.7 g/dl at the end of the first year of colchicine treatment. Diagnosis of FMF was confirmed genetically in 88 % of patients. Forty-five patients had homozygous or compound heterozygous mutations, four patients had a single mutation, and two patients had no mutations. The most common mutation was M694V (64.5 %) and the most common genotype was homozygous for M694V (41.2 %). The frequency of FMF attacks was not affected by the type of mutation ($p=0.388$). However, the severity of FMF attacks was significantly higher in patients with the homozygous M694V mutation ($p=0.029$). The frequency and severity of FMF attacks were not correlated with the doses of colchicine. The mean colchicine dose was 0.03±0.02 mg/kg/d.

After 1 year of colchicine treatment, the mean height SDS (HSDS) significantly increased from −0.64±1.20 to −0.26±1.07 ($p<0.001$) and the mean weight SDS (WSDS) increased from −0.60±1.03 to −0.45±0.98 ($p=0.008$). The mean body mass index (BMI) SDS at the beginning of colchicine therapy was −0.33±1.06, which decreased to −0.47±0.98 at the end of 1 year of colchicine treatment ($p=0.128$, Fig. 1).

Table 1 Disease severity score

Disease severity	Age at disease onset	Attack frequency (month)	Arthritis	Erysipelas-like erythema	Amyloidosis	Colchicine dosage (mg/day)
0	>31					
1	21–31	<1				1
2	11–20	1–2	Acute	+		1.5–2
3	6–10	>2	Protracted		+	2
4	<6					

Table 2 Demographic, clinical, and laboratory features of the patients

Characteristics	*n* (%) or mean±SD
Male/female	22/29 (43.1/56.9)
Age at disease onset (years)	5±2.61 (range 1–10.0)
Age at diagnosis and onset of treatment (years)	6.4±2.39 (range 1.3–11.0)
Disease severity score	7 (range 4–10)
Fever	44 (86.3)
Abdominal pain	44 (86.3)
Arthritis and arthralgia	31 (60.8)
Chest pain	10 (19.6)
Erysipelas-like erythema	1 (2)
Limb pain with exercise	24 (47.1)
Myalgia	21 (41.2)
Heel pain	7 (13.7)
Vomiting	7 (13.7)
Constipation	7 (13.7)
Diarrhea	6 (11.8)
Lymphadenopathy	5 (9.8)
Oral apthous lesion	5 (9.8)
Splenomegaly	3 (5.9)
Vasculitis	2 (3.9)
Exudative tonsillitis	2 (3.9)
Conjunctivitis	1 (2)

In patients who had no attacks (n=40) during colchicine treatment, the mean HSDS significantly increased from −0.539±1.143 to −0.202±1.065 (p<0.001), and the mean WSDS significantly increased from −0.559±1.088 to −0.361±1.041 (p=0.002).

In patients who had recurrent attacks (n=11) during colchicine treatment, the mean HSDS increased from −0.984±1.394 to −0.494±1.122 (p=0.051), and the mean WSDS decreased from −0.761±0.850 to −0.789±0.707 (p=0.816).

In 18 patients who had no attacks, at least one of the acute phase reactants was elevated during the follow-up. In these patients, the mean HSDS significantly increased from −0.50±0.84 to −0.22±0.80 (p=0.026), the mean WSDS increased from −0.70±0.77 to −0.57±0.81 (p=0.182), and the mean BMI SDS decreased from −0.53±0.83 to −0.64±0.71 (p=0.522).

Table 3 Attack and non-attack values of acute phase reactants

	(*N*)	Median (minimum–maximum)
CRP (mg/dl)	Attack (47)	5.765 (0.4–34)
	Non-attack (49)	0.35 (0.1–6.8)
ESR (mm/h)	Attack (47)	48 (8–100)
	Non-attack (47)	19 (4–61)
Leukocyte (mm^3)	Attack (49)	12.150 (4600–35.100)
	Non-attack (50)	6950 (3500–12.400)

The mean colchicine dose (0.03±0.02 mg/kg/d, 0.98±0.045 mg/m^2/d) was not significantly different between patients who had no attacks and those with recurrent attacks (p>0.05). Patients were divided in two groups according to low (<1 mg/m^2/d) and high doses (>1 mg/m^2/d) of colchicine to determine the effect of drug doses on CRP levels and the value of CRP in predicting episodes. The area under the curve of CRP with low-dose colchicine was 0.386 (p=0.474) and that for high-dose colchicine was 0.576 (p=0.568). Although there was no statistical significance, the area under the curve was variable depending on drug doses.

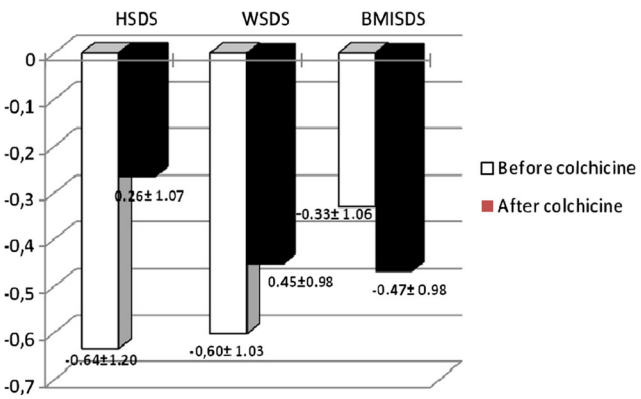
In patients with and without episodes during the follow-up, colchicine dose and disease severity did not affect WSDS and HSDS. There were no significant relationships between disease severity and height and weight gain.

The median hemoglobin level before treatment with colchicine was significantly lower than that at the first year of colchicine treatment (11.9 vs 12.7 g/dl, p<0.05).

Discussion

In this study, the positive effects of colchicine on growth in prepubertal patients with newly diagnosed FMF were investigated. Our prospective study examined the defining features of FMF, disease activity, subclinical inflammation, and the relationships between disease severity and growth. Patients were evaluated regularly according to Tanner pubertal staging and pubertal patients were excluded from the study. Therefore, the effect of puberty on growth was excluded.

Problems of growth and development in children have been known to occur in many chronic diseases. Most of the mechanisms have not been clarified. Therefore, further information is needed on this issue. Growth retardation in



HSDS: height deviation score (mean±SD)

WSDS: weight deviation score (mean±SD)

BMISDS: body mass index deviation score (mean±SD)

Fig. 1 HSDS, WSDS, and BMI SDS at the beginning and 1 year after colchicine

inflammatory diseases is thought to be due to inflammatory cytokines and steroid therapy. Studies with transgenic mice models have shown that some cytokines that are increased in FMF attacks might prevent linear growth independent of other nutritional factors [1, 2]. Moreover, attack periods, loss of appetite, fatigue, and weakness block weight gain. FMF is a chronic disease with self-limited attacks and recovery periods. The frequency of attacks of FMF varies from patient to patient. Although symptoms are not apparent, subclinical inflammation may continue in the long term in FMF.

Limited numbers of studies have investigated the positive effect of colchicine on growth and development in pediatric patients. Normal growth in children with FMF under treatment was reported by Zemer et al. for the first time [13, 14]. In 2001, Savgan et al. compared FMF patients who were treated with colchicine and healthy controls and found no significant difference between the rate of height growth and insulin growth factor-1 levels [15]. Zung and colleagues studied the severity of FMF and the effect of colchicine on the development of 30 prepubertal children and showed a positive effect on both height and weight [6]. They emphasized that early initiation of colchicine had a more positive effect on height growth. Özçakar and colleagues reported that colchicine, besides preventing FMF attacks, also significantly improved the development of height [5]. In our study, we evaluated 51 prepubertal FMF patients at diagnosis and after 1 year at follow-up with colchicine therapy. FMF patients showed a significant increase in height and weight values at first year of treatment compared with before treatment. The participants' BMI SDS did not change with treatment. The reason for this lack of finding in BMI SDS could be because WSDS and HSDS scores increased.

The youngest patient was 1 year old and the colchicine dose was 1 mg/m^2 or 0.02 mg/kg, without any complications. Colchicine is a safe drug in the treatment of children with FMF, even in infancy. The only significant adverse effect reported was diarrhea (in a small number of patients), which can be controlled by a decrease in colchicine dose and transitory elevation of transaminases [16]. Our patients did not develop any severe side effects due to colchicine use.

Colchicine prevents attacks and subclinical inflammation in FMF [17–20]. In our study, during the 1 year follow-up, of the 51 patients treated with colchicine, only 11 (21.5 %) had attacks of FMF. In patients with recurrent FMF attacks, increases in HSDS and WSDS were not significant. In the evaluation of patients without episodes with subclinical inflammation, prevention of clinical episodes with colchicine was sufficient for height growth. However, prevention of clinical episodes and subclinical inflammation was necessary for weight gain.

A previous study showed that treatment of FMF patients with colchicine significantly increased hemoglobin levels and they were positively correlated with height growth [5]. In our study, median hemoglobin levels increased after treatment and were directly proportional to growth.

It was reported that a total of 65 % of FMF patients respond completely to colchicine treatment, 30 % show a partial response, and 5 % did not respond to colchicine therapy (9). In our study, 78.5 % of the patients showed a complete response to colchicine treatment and none of the patients was colchicine resistant. We reported in a previous study that anti-interleukin-1 drug treatment with anakinra or canakinumab was beneficial in eight patients who were unresponsive to colchicine [21], as in other case series [22].

Various studies have examined the effect of age of disease onset and disease severity on growth. In a study by Zung et al., the mean age at initiation of colchicine treatment was 4.32± 1.82 years and the mean severity score of the disease was 8.33 ±1.65. In Özçakar et al.'s study, the age at initiation of colchicine treatment was 6.5 years and the severity score of the disease was six (range, 4–11) [5, 6]. In our study, the age of disease onset was 5 years (1–10 years), age of diagnosis and onset of therapy was 6.4 years (1.3–11 years), and the disease severity score was seven (range, 4–10). In these previous studies, similar to our study, the severity of disease did not affect growth [5–7, 15].

Conclusion

Our study shows that early disease onset and homozygosity of the 694 mutation in FMF cause more severe attacks. Colchicine prevents attacks of FMF and inflammation. The frequency and severity of attacks of FMF are not correlated with the dose of colchicine. Even when subclinical inflammation is present, colchicine allows growth to continue by preventing attacks. However, suppression of subclinical inflammation and control of FMF attacks are required for weight gain.

Disclosure None.

Compliance with ethical standards

Ethics approval The study was approved by the local hospital ethics committee and performed according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Consent to participate Written informed consent was obtained from every participant.

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