EVALUATION OF PHYSICAL GROWTH IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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ABSTRACT

Objective: *Familial Mediterranean Fever (FMF) is a periodic inflammatory disease transmitted by autosomal recessive inheritance, which manifests itself as recurrent attacks of fever and polyserositis. During the period of complete clinical recovery, it has been demonstrated that subclinical inflammation endured. In this study, the aim is to evaluate the effects of subclinical inflammation on growth of children with FMF.*

Material and Method: *Prepubertal 35 patients diagnosed with FMF were followed up during the non-attack period and received a regular colchicine treatment. 30 healthy children with similar age and gender were enrolled into the study as control group. All cases in the study group underwent a physical and laboratory evaluation at the beginning and at the end of the study (12th month).*

Results: *All cases were within the normal percentile range of height and weight at the beginning of the study. No significant differences were recorded between the study and control groups in terms of height, weight, body mass index and body mass index standart deviation score, target height, bone age, growth rate, standard deviation score, serum insulin-like growth factor-1 and serum insulin-like growth factor-binding protein-3 (IGFBP-3) ($p>0.05$) at the beginning and during follow-up period. A negative correlation was detected between erythrocyte sedimentation rate and serum IGFBP-3 level.*

Conclusions: *It was determined that growth rate and serum insulin-like growth factor-1 did not differ from their peers; but children with FMF receiving regular colchicine treatment showed lower levels of serum IGFBP-3.*

Key Words: *Familial mediterranean fever, growth, colchicines* ***Nobel Med 2013; 9(2): 21-25***

AİLEVİ AKDENİZ ATEŞİ OLAN HASTALARDA FİZİKSEL BÜYÜMENİN DEĞERLENDİRİLMESİ

ÖZET

Amaç: Ailevi Akdeniz ateşi (AAA), tekrarlayan ateş ve poliserozit atakları ile kendini gösteren otozomal resesif geçişli, periyodik enflamatuvar bir hastalıktır. Ataklar dışındaki dönemde AAA'lı hastalar klinik olarak tamamen normale dönseler bile, ataksız dönemlerde de subklinik enflamasyonun devam ettiği gösterilmiştir. Bu çalışmada, subklinik enflamasyonun AAA'lı çocuklardaki büyümeye olan etkilerinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metod: Çalışmaya AAA tanısı ile takip edilen ve düzenli kolşisin tedavisi alan ataksız dönemdeki 35 puberte öncesi hasta ile yaş ve cinsiyeti benzer 30 sağlıklı çocuk kontrol grubu olarak alındı. Çalışmaya alınan tüm çocukların başlangıçta ve 12 ay sonra fizik muayeneleri ile laboratuar incelemeleri yapıldı.

Bulgular: Çalışmanın başlangıcında tüm olguların kilo ve boy persantilleri normal aralıkta idi. Çalışma ve kontrol grubu arasında boy, kilo, vücut kitle indeksi ve standart deviasyon skoru, hedef boy, kemik yaşı, büyüme hızı ve standart deviasyon skoru, serum insülin benzeri growth faktör-1 açısından anlamlı bir farklılık yoktu ($p>0,05$). Serum insülin benzeri growth faktör bağlayıcı protein-3 (IGFBP-3) düzeyi çalışma grubunda düşük bulundu ($p<0,05$). Tüm vakalar normal boy ve ağırlık persantilindeydi. Eritrosit sedimentasyon hızı ile serum IGFBP-3 düzeyi arasında negatif korelasyon saptandı.

Sonuç: Düzenli kolşisin tedavisi altındaki AAA'li çocuklarda büyüme hızının, serum insülin benzeri growth faktör 1 düzeyinin yaşıtlarından farklı olmadığı fakat serum IGFBP-3 düzeyinin düşük olduğu saptandı.

Anahtar Kelimeler: Vitamin B12, holotranskobalamin, homosistein, folat **Nobel Med 2013; 9(2): 21-25**

INTRODUCTION

Familial Mediterranean Fever (FMF) is a chronic and periodic inflammatory disease with recurrent attacks of fever and polyserositis. The most characteristic feature of FMF which distinguishes FMF from other chronic inflammatory diseases is the complete clinical recovery of the patient during the period without inflammatory attacks.[1-3] However, several studies conducted in recent years showed an increased level of cytokines and inflammatory markers, also during non-attack periods. Further more subclinical inflammation also endured.[4-7] In FMF, loss of appetite, decrease in physical activity during attacks, and the presence of persistent subclinical inflammation may affect the growth. Although it was reported again in some studies that growth hormone and insulin-like growth factor axis might be affected by the inflammation enduring during the period with no attacks, pathogenesis of the possible growth retardation in these patients could not be explained sufficiently.[8-11] In this study, the aim is to evaluate the effects of subclinical inflammation on growth in children with FMF.

MATERIAL and METHOD

A total of 35 (21 male, 14 female) cases with a mean age of 8.19±1.97 years diagnosed with FMF in prepubertal period were included in this study. Diagnosis of cases with FMF was established according to Tel-Hashomer criteria and colchicine treatment was initiated for all children. The diagnoses for all cases were also confirmed by examining their mutations. Clinical and laboratory parameters measured for all cases at the beginning of the treatment are indicated in Table 1. A total of 30 healthy prepubertal children, (15 male and 15 female) with ages and genders compatible with the patient group, were taken as control group. None of the cases in study were examined during attack. Cases with any chronic systemic diseases other than FMF were excluded.

All patients were questioned regarding age at disease onset, age at diagnosis, accompanying findings, number of attacks, administration period of colchicine, presence of co-morbid diseases, and puberty. Moreover, cumulative dose of colchicine received by the patients was calculated by multiplying the treatment period with dose of colchicine received by patient. Parents of the cases included in the study were informed about the study, and their verbal and written consent was obtained.

Body weight (kg) and height (cm) of cases and parents were measured at the beginning of the study (0 month), at the 6 and the 12 month. Using a Harpenden Stadiometer, height was measured appropriately by the same person between 08:00-10:00. Body weight and height percentiles, standard deviation scores (SDS), body mass index (BMI), target height, growth rate SDS, and BMI SDS were calculated for all cases. Left wrist X-ray was performed in order to determine bone age of cases. Bone age of cases was determined using Greulich-Pyle Radiologic Atlas. Analysis of data acquired from this study was carried out by using Statistical Package for →

Social Sciences 15.0 software. Shapiro-Wilk test was applied to analyze whether the data in both groups was normally distributed. Intergroup comparison of data fitted to normal distribution was analyzed with Independent Group Student's t Test. Variables that did not fit normal distribution were evaluated by Mann-Whitney U test. Relationship of variables with normal distribution was analyzed by Pearson's Correlation, whereas Spearman Correlation test was performed for determining the relationship of those not fitting to the normal distribution. p value smaller than 0.05 was accepted as statistically significant.

RESULTS

Sixty-six percent of cases (14/21) in the study and 50% of cases in the control group (15/30) were male, and forty four percent of cases (7/21) in the study and 50% of cases in the control group (15/30) were female subjects. Mean age of cases was 8.55±2.25 years for male and 7.62±1.34 years for female subjects. Mean ages of children in control group were 8.34±1.88 for male and 8.24±1.98 years for female subjects. No differences were found between case and control groups with regard to age and gender (p=0.42).

Mean age at diagnosis of cases with FMF was 4.88±2.56 years, disease period was 2.76±2.01 years, and administration period of colchicine was 2.64±1.55 years in average. Total colchicine dose (cumulative dose of colchicine/mg) that patients had received starting from the date of diagnosis was 868.1±473.7 mg. Mean weight score at disease was 6.74±1.26.

At the beginning of the study, body weight and height of all children in case and control groups were within normal limits. A comparison of clinical and laboratory parameters for patient and control groups are demonstrated in Table 1.

Accordingly, no statistically significant differences were detected between case and control groups especially in terms of height, height SDS, and serum insulin-like growth factor-1 (IGF-1) and IGFBP3 levels, despite of the fact that the cases had received colchicine for 2.64±1.55 years.

When cases with Familial Mediterranean Fever were evaluated by gender, no statistically significant differences were found in terms of age, height and height SDS, body weight and body weight SDS, BMI and BMI SDS, growth rate and growth rate SDS, target height, and bone age compared to the control group (p>0.05).

In females with Familial Mediterranean Fever; serum IGF-1 level was 134±78 ng/mL and serum IGFBP-3 level was 3.5±1.1 ng/mL, whereas in males with Familial Mediterranean Fever; serum IGF-1 level was 131±88 ng/mL and serum IGFBP-3 level was 3.26±1.01 ng/mL. In female control group, IGF-1 and IGFBP3 levels were 169±66 and 4.3±0.88 ng/mL respectively, whereas in male control group, IGF-1 and IGFBP3 levels were 134±63 and 3.85±1.02 ng/mL respectively. No statistically significant differences for both genders were found between serum IGF-1 and IGFBP3 levels of case and control groups (p>0.05).

Relationship between disease period, age at disease onset, treatment period, weight score of disease, total colchicine dose, erythrocyte sedimentation rate, C-reactive protein, fibrinogen, white cell count and growth rate, height SDS, IGF-1, and IGFBP-3 were evaluated in cases with FMF (Table 2). Accordingly, a negative correlation was detected only between the level of erythrocyte sedimentation rate and IGFBP-3 (p:0.001 r:-0.523). →

Table 1: Comparison of Clinical and Laboratory Parameters of Patients with FMF and Control Group

	Patient n: 35 Mean±SD	Control n: 30 Mean±SD	p
Age (year)	8.19±1.97	8.34±1.88	0.750
Weight (kg)	24.92±5.75	26.82±7.02	0.236
Height (cm)	125±11	128±12	0.318
Height SDS	-0.45±0.87	-0.09±0.89	0.104
Weight SDS	-0.42±0.66	-0.13±0.80	0.115
AGR (cm/year)	5.65±0.93	5.99±0.57	0.080
AGR SDS	0.13±1.11	0.41±0.82	0.248
BMI (kg/m²)	15.80±1.71	16.16±2.09	0.585
BMI SDS	-0.41±1.10	-0.12±1.19	0.322
Target height (cm)	166.04±8.70	167.00±7.94	0.527
Bone age (year)	7.38±2.09	7.81±1.97	0.396
IGF-1 (ng/ml)	132±83	152±66	0.104
IGFBP-3 (ng/ml)	3.39±1.08	4.10±0.97	0.05
ESR (mm/hour)	22.46±18	13.90±7	0.067

SDS (standart deviation score), AGR (Annual Growth Rate), BMI (Body Mass Index), IGF-1 (insulin-like growth factor-1), IGFBP-3 (insulin-like growth factor-binding protein-3), ESR: Erythrocyte Sedimentation Rate

Table 2: Relationship between some parameters in cases with FMF and some clinical and laboratory parameters

Weight score during disease	p:0.14 r:0.25	p:0.46 r:0.12	p:0.37 r:0.15	p:0.96 r:0.007	p:0.58 r:0.07
Total colchicine dose	p:0.8 r:0.43	p:0.2 r:0.22	p:0.07 r:0.31	p:0.96 r:0.01	p:0.79 r:-0.05
Treatment period	p:0.25 r:0.19	p:0.22 r:0.21	p:0.054 r:0.33	p:0.65 r:-0.08	p:0.28 r:0.19
Delay time in diagnosis	p:0.57 r:0.09	p:0.31 r:-0.18	p:0.43 r:-0.14	p:0.92 r:-0.02	p:0.25 r:0.2
ESR	p:0.97 r:0.001	p:0.58 r:0.09	p:0.55 r:0.10	p:0.06 r:-0.31	p:0.001 r:-0.52
C-reactive protein	p:0.57 r:-0.9	p:0.058 r:0.33	P:0.059 r:0.33	p:0.38 r:-0.15	p:0.08 r:-0.29

ESR: Erythrocyte Sedimentation Rate

DISCUSSION

It is well established today, that chronic systemic diseases in childhood cause weight loss in the acute period, and shortness or growth retardation in long-term. Recently, it has been reported that one of the most important factors leading to growth retardation in case of chronic systemic diseases is chronic inflammation. Growth retardation observed in chronic inflammation is held responsible for the reduced response of IGF-1 to the growth hormone caused by some cytokines released during chronic inflammation.[11,12]

FMF is a chronic inflammatory disease characterized by recurrent inflammatory attacks. The most important features distinguishing this disease from other chronic inflammatory diseases are its course accompanied with attacks, spontaneously resolving attacks, and the normal condition of patients during the period between attacks. However, studies have reported that the inflammatory course of the disease endured in these patients also during non-attack periods.[6,13] In this study, effects of subclinical inflammation on growth regarding clinical and laboratory parameters were evaluated in children with FMF.

Mean disease period, mean administration period of colchicine, and mean weight score of disease were found respectively 2.76±2.01 years, 2.64±1.55 years and 6.74±1.26 kg. No differences were determined between case and control groups in terms of height, weight, and growth rate parameters at the beginning and during the follow-up of the disease. In a study conducted by Gurol ES, it was reported that early administration of colchicine treatment in cases with FMF affected growth positively.[14] It was indicated that this effect of colchicine treatment revealed itself by suppressing disease activity and inflammation.[14-16] In another retrospective study performed on cases with FMF, it was reported that cases receiving colchicine treatment gained more height compared to those receiving no treatments.[17] Zung et al. retrospectively compared pre-treatment and post-treatment growth parameters in 30 prepubertal patients with FMF.[16] It was determined that height SDS and weight SDS were significantly improved, that an improvement of 0.5 SDS in average heights and of 0.3 SDS in body weights was found in patients with FMF, and that height SDS showed a negative correlation with onset age of colchicine administration. Yet again in this study, similar to our study, no relationship between the number of attacks and growth rate could be established during the treatment (p>0.05). Similar results were reported by Cimaz et al. and Gurol ES as well.[11,14]

In our study, cases were followed-up both prospectively and at the beginning with regard to growth parameters. No statistically significant differences were detected between case and control groups in terms of body weight, height, growth rate, height SDS, etc, and clinical parameters for growth. Zemer et al. evaluated the results of long-term treatment of colchicine in patients with FMF and reported that patients receiving colchicine had normal growth and development.[15] Cases with FMF receiving colchicine or not were compared with healthy control subjects. It was demonstrated that the group receiving colchicine had greater mean heights. There was no data regarding number of cases in control group and percentile and SDS values of cases.

In our study, cases are also evaluated in terms of serum IGF-1 and IGFBP-3, which were used to follow-up of shortness and growth retardation, and indicative of the effect of growth hormone. No statistically significant differences were found between case and control groups in terms of serum IGF-1 and IGFBP3 levels at the beginning and during the follow-up period (1st year). In a prospective study conducted by Savgan et al. growth of 51 prepubertal cases with FMF were followed-up and no differences were recorded when compared to their healthy peers.[14] In this study where IGF-1 levels were also evaluated and determined to be normal, similarly to our study, a positive correlation was detected between the cumulative colchicine dose and growth rate. Moreover, in this study, weight score during disease was also found to have no effect on growth statistically.

On the other hand, relationship between disease period and erythrocyte sedimentation rate during non-attack period, and between C-reactive protein and IGF-1, IGFBP-3, growth rate, and height SDS were investigated in our study. Among these parameters, a negative correlation was detected between the level of erythrocyte sedimentation rate during the non-attack period and IGFBP-3 (p:0.001, r:-0.523). This condition may be interpreted as the negative effect of inflammation on growth. However, no significant correlation was determined between serum IGF-1 and IGFBP-3 levels, and other indirect indications of inflammation such as C-reactive protein, fibrinogen, and white cell count. In their study investigating IGF-1 levels in children with chronic inflammatory disease, Cimaz et al. emphasized that the most important parameter showing a negative correlation with IGF-1 was erythrocyte sedimentation rate.[11] This finding supports the view that growth retardation in children with chronic inflammatory results from negatively affected IGF-1 and IGFBP-3 axis rather than from growth hormone.[11,18] Again in our study, no correlation was determined between disease period →

and body weight, height, height SDS, IGF-1, IGFBP-3. These findings support the view that inflammation did not affect growth negatively in children with FMF receiving colchicine treatment.

In conclusion, growth, growth rate, serum IGF-1 and IGFBP-3 levels did not differ among children with FMF receiving regular colchicine treatment in comparison to their peers.

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