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Growth and IGF-1 levels of children with familial Mediterranean fever on colchicine treatment

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ABSTRACT

Objective

To evaluate growth process and insulin like growth factor-1 (IGF-1) levels in children with familial Mediterranean fever (FMF).

Methods

This prospective study group consisted of 51 children with FMF under colchicine therapy (20 boys, 31 girls) and 42 healthy children (22 boys, 20 girls). All children were prepubertal. Bone ages and IGF-1 levels were determined in all cases. Height velocity (HV), height standard deviation score (SDS), target height and target height SDS were calculated.

Results

There was no statistical difference in age, HSDS, target height SDS and bone ages between healthy and diseased subjects. HV of children with FMF did not differ significantly from the control group. There was no statistical difference in age, HSDS, target height SDS and bone ages between healthy and FMF subjects. HV of children with FMF did not differ significantly from the control group. There was no significant correlation between disease duration, number of attacks, erythrocyte sedimentation rate and HV, HSDS and IGF-1 levels of FMF patients. There was positive correlation between cumulative colchicine dose and HV (r = 0.29).

Conclusion

Growth and IGF-1 levels of children with FMF do not differ from their healthy peers. However, there was positive correlation between HV and cumulative colchicine dose. This study suggests that colchicine not only has no adverse influence on growth, but more by suppressing disease activity and inflammation it has an enhancing role.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder which is characterized with recurrent attacks of fever and polyserositis (1-5). The disease characteristically affects certain ethnic groups living in the Middle East and around the Mediterranean basin; mainly Sephardic Jews, Armenians, Turks and Arabs (1-6). Colchicine, which is used in the treatment of the disease not only decreases the frequency and severity of attacks, but also prevents amyloidosis (1-7).

FMF is a chronic disease with inflammatory attacks. The distinguishing feature from other chronic diseases is the fact that the attacks are self-limited and children are symptom free in between the attacks (3-6). Chronic diseases in children are frequently complicated by growth impairment (8). Multiple and complex mechanisms are likely to be involved in growth retardation. It is proposed that alterations in the growth hormone- insulin like growth factor-1 (GH-IGF-I) system play the major role in chronic diseases (8,9).

There is no prospective and detailed study on growth of children with FMF. In only two studies where long term effects of colchicine use were reviewed growth of children with FMF was reported to be normal (6,7). However these were retrospective studies where all data were obtained from medical reports (6, 7).

The aim of this study was to compare growth and IGF-I levels of children with FMF and of healthy controls and to analyze the relationship between growth and age of disease onset, disease severity score (DSS), number of attacks and cumulative colchicine dose in FMF.

Materials and methods

This study was conducted between June 1998 and February 1999 in a prospective manner.

Fifty-one prepubertal children with FMF (31 males, 20 females, mean age: 7.7 ± 2.18 years, range 3.08 - 11 years) were enrolled. The diagnosis was based on the Tel-Hashomer criteria in all children and they were all on colchicine treatment. Age of disease onset, clinical findings, cumulative colchicine dose and duration of colchicine treatment were recorded. DSS was calculated according to the Tel-Hashomer severity score (10). The number of attacks during the study period (6 months) was also recorded.

Forty-two healthy prepubertal children (22 males, 20 females, mean age: 7.73

± 1.75 years, range 4 - 10.9) who were admitted to the Outpatient Department of Pediatrics of the Cerrahpasa Faculty of Medicine were used as the healthy controls in this study.

All subjects and their parents had their standing height measured by the same investigator using the same Harpenden stadiometer. Six months later a second measurement was taken by the same investigator (ESG) using the same stadiometer, and the height velocity (HV) over the period of 6 months for the children was calculated. HV, height SDS (HSDS), target height and target HSDS were calculated according to the Neyzi percentile curves for healthy Turkish children (11). Weight measurements were carried out and the body mass index [BMI = weight (kg)/height^2 (m)] was calculated for all subjects.

Venous blood was collected and plasma was separated by centrifugation and stored at -70°C until assayed for IGF-I. IGF-I levels were measured by a radio immunoassay method after acid-ethanol precipitation (Immunotech, IRMA kit, Marseilles). ESR was measured in all subjects by the Westergren method.

The skeletal ages of the children were determined according to the Greulich-Pyle Atlas (12). The bone age of every child was compared with age- and sex-matched standard deviation tables and those below acceptable limits were noted.

Patients and controls were divided into male and female subgroups. The data for patients and controls of the same sex were compared by the Student's t-test and the Mann-Whitney U test.

Results

The age distribution of the children with FMF was not different statistically from that of the healthy children. The results of the study are summarized below.

FMF group

The mean age at disease onset was 3.27 years. The mean number of attacks and DSS were 1.95 and 6.29, respectively. Comparisons of the height, HV, BMI, HSDS, target height, target height SDS and bone age between the FMF subjects and control subjects were carried out and the results are summarized in Table I.

The height standard deviation score in 2 of the FMF children was found to be below -2 SDS. The HSDS, HV and bone age SDS in the first subject were -2.5 SDS, 1.8 cm/6 months and < -2 SDS, respectively. His mother's and father's height SDS were -2.2 and -1.3, respectively and his target height SDS was -1.7. The SDS, HV and bone age SDS of the second subject were -2.9 SDS, 1.7 cm/6 months and -2.3 SDS, respectively. The height SDS of both of his parents were below -2 SDS and his target height was -2.3 SDS.

BMI was found to be below normal (< 5 percentile) in 5 of the children with FMF. ESR was above 20 mm/hour in 50.9% (26 children) of the cases. The bone age in 12 of the patients was found to be below the acceptable lower limits(< -2 SDS) when compared with the age- and sex-matched standard limits.

The mean cumulative dose of colchicine was 533.3 ± 472.8 mg (range 32 - 2036 mg).

There was no statistical correlation between disease duration, number of attacks, DSS, ESR and HV, HSDS and IGF-I levels in the FMF group. There was a positive correlation between the cumulative colchicine dose and HV ($p < 0.001$; $r = 0.33$). There was no correlation between age and IGF-I levels in the disease group ($p > 0.50$, $r = 0.21$).

Healthy control group

The height SDS in the children from the control group was within normal limits. BMI was found to be below normal (< 5 percentile) in 3 of the healthy subjects. Bone age retardation was noted in 4 of the children. Their HV and HSDS were within normal limits.

Comparison of the two groups

Both the disease and control subjects were divided into male and female subgroups (Table I). There was no statistical difference between age, BMI, HSDS, target height SDS or bone age in girls with FMF and control subjects ($p > 0.05$). There was also no statistical difference between age, BMI, HSDS, target height SDS or the bone age in boys with FMF and healthy subjects ($p > 0.05$).

HV of children with FMF did not differ from that of the control group ($p > 0.05$).

Discussion

It is a well known fact that chronic diseases in childhood are frequently complicated by growth retardation (8).

Table I. Comparison of data between FMF and healthy control groups.

	FMF (boys) n = 20	Healthy children (boys) n = 22	p	FMF (girls) n = 31	Healthy children (girls) n = 20	p
Age (years) (mean ± SD)	8.25 ± 1.87	8.12 ± 1.68	0.81	7.34 ± 2.33	7.29 ± 1.76	0.93
BMI (mean ± SD)	15.31 ± 1.705	15.81 ± 2.81	0.49	14.96 ±3.207	14.85 ± 1.52	1
Height velocity in cm/6 mos. (mean ± SD)	2.53 ± 0.72	2.58 ± 0.56	0.80	2.55 ± 0.629	2.55 ± 0.626	1
HSDS (mean ± SD)	-0.38 ± 1.02	0.11 ± 0.72	0.07	-0.47 ± 0.73	0.047 ± 0.82	0.70
Target height SDS (mean ± SD)	-0.82 ± 0.817	-0.25 ± 0.86	0.77	-0.509 ± 0.75	-0.3 ± 0.71	0.156
IGF-1 (ng/ml) (mean ± SD)	98.05 ± 80.2	128.36 ± 101.2	0.17	101.67 ± 82.8	154.5 ± 121.56	0.83
Bone age (years) (mean ± SD)	6.61 ± 2.47	7.14 ± 2.18	0.46	6.41 ± 2.27	7.03 ± 2.05	0.32

BMI: body mass index, HSDS: height standard deviation score, target height SDS: target height standard deviation score.

FMF is a chronic inflammatory disease with recurrent inflammatory attacks. The distinguishing feature from other chronic diseases is the fact that the attacks are self-limited and children are symptom-free between the attacks (1-7). However, increased cytokine levels detected during attack-free periods in several studies point to the possibility of ongoing subclinical inflammation in FMF (13, 14). Although there are many publications on FMF, growth in children with FMF has not been studied before. There have been two publications where growth in children with FMF was evaluated (6,7). In the first study, where long term colchicine treatment in children was reviewed, the growth of children was observed to be normal (6). This study was based on past medical records obtained at the compulsory medical examination prior to military service at the age of 17. The mean height of the colchicine-treated cohort with FMF was found to be increased when compared with the mean height of untreated FMF patients. However, this was a retrospective study and the number of subjects, the height measurement technique and the HSDS of the children were not given (6). In the second study, growth in 7 children with FMF on colchicine treatment was reported to be normal. This study only reported the height and weight curves of 4 children; the HV and HSDS were not mentioned (7).

There was no statistical difference between HV and HSDS in the children with FMF and healthy children. Two of 51 children with FMF had an HSDS below -2 SD. The height SDS was -2.2 SD and the weight was below the third percentile in the first subject. His mother's and father's HSDS were -2.2 and 1.3 SD, respectively. Family history revealed delayed puberty in the father. Retarded bone age, family history and a normal target height SDS were all predisposing factors to constitutional growth retardation. The SDS, HV and bone age SDS of the second patient were -2.9 SDS, 1.7 cm/6 months, and –2.3 SDS, respectively. The HSDS of both of his parents was below -2 SDS and his target height was -2.3 SDS. The diagnosis of familial short stature seemed likely because of short parents, a below normal target height, and normal bone age in the second subject. Therefore, growth retardation in both children was not thought to be due to FMF, but due to a constitutional delay in the former and a familial trait in the latter.

The skeletal ages of 12 (23.5%) patients was found to be delayed. X-rays of the left hand in these children were evaluated by both a pediatric endocrinologist and a radiologist. Despite bone age retardation, all had normal growth parameters (normal HSDS, normal HV) with the exception of one child who had probable constitutional short stature. Evaluation of the hand films revealed significant retardation in the secondary ossification centers of the carpal bones. The explanation for bone age retardation despite normal growth and thyroid functions is not clear, but might be due to differences in the rate of skeletal maturation in different populations and/or inflammatory attacks of the disease. Recent studies have shown that there may be marked differences in bone maturation between different populations (15, 16). In our study, we used the Greulich-Pyle Atlas to determine bone ages (12). This atlas utilizes standards derived from American children. Therefore, the discrepancy between normal growth and delay in osseous maturation in our study group might be explained by genetic and environmental differences in skeletal maturation between different populations.

Another factor might be disease activity and recurrent inflammatory attacks. The development of the individual bones of the hand and wrist as well as those of other regions can be impaired by febrile and other illnesses (16). If an illness occurs at about the time when ossification is due to begin in a carpal or an epiphysis, that center of ossification may fail to appear on schedule. Recovery on such an occasion may require a period of months or even several years. Recent studies of FMF showed increased levels of cytokines during clinical remission, which suggest the presence of ongoing subclinical inflammation during attack-free periods as well (13,14). Given these findings we would suggest that inflammation may affect epiphysial ossification. We think that this delay in osseous maturation despite normal growth and normal IGF-I levels could be best explained by the prospective follow-up of these patients with regular monitoring of their hand films.

The aim of this study was to determine whether disease activity impairs growth in children with FMF or not. A recent hypothesis suggests that inflammation could interfere, by means of cytokines, with IGF-I production in response to GH stimulus in chronic inflammatory diseases such as JRA (8, 9). This led us to search for a correlation between DSS, the number of attacks and HV and HSDS, but none was found.

Cimaz *et al.* (9) in a multicenter study on IGF-I levels in children with chronic inflammatory diseases, reported that ESR was the parameter most significantly correlated with IGF-I (inverse correlation). In our study an analysis of the correlation between ESR and HSDS, HV, and IGF-I levels showed no correlation. There was also no correlation between the number of attacks, DSS, disease duration or IGF-I levels. The statistical results showed that inflammation in FMF did not impair growth under colchicine treatment.

In our study, there was no correlation between the cumulative colchicine dose and height SDS and IGF-I levels. However, there was a positive correlation between HV and the cumulative colchicine dose. This suggests that colchicine does not have a deleterious effect on growth. Furthermore, by suppressing disease activity and inflammation, it actually improves growth.

In conclusion, this study shows that growth and IGF-I levels are not different between colchicine treated children with FMF and their healthy peers. The absence of a disease control group without colchicine use in our study renders it impossible to make a comment on the effect of disease itself on growth.

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