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Sonographic evaluation of intra-abdominal organs in children with familial Mediterranean fever

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ABSTRACT

Objective: The reticuloendothelial system is rarely assessed in patients with familial Mediterranean fever (FMF). We aimed to evaluate the size of the liver and spleen by ultrasonography in children and adolescents with FMF and compare it to their healthy peers.

Material and Method: Patient data were evaluated by height, weight, and age and compared with those of healthy controls.

Results: A total of 86 children with FMF diagnosed using the Turkish Pediatric Criteria and 54 healthy children were included. The extent of splenomegaly was 27.9% in the FMF group. The mean spleen length was 99.84±17.4 mm in patients and 93.44+15.49 mm in controls (p=0.03). The mean liver length was 122.61±17.4 mm in patients and 117.71±16.04 mm in controls (p=0.104). FMF appears to affect spleen length independently of anthropometric data (t=2.182; p=0.031). Splenomegaly was accompanied by the M694V (32.55%, n=17) and E148Q (3.4%, n=3) mutations.

Conclusion: FMF affects spleen length independently of anthropometric data. Splenomegaly may reflect subclinical inflammatory activity in FMF patients in remission. Spleen size can serve as a marker of subclinical inflammation during remission.

Keywords: Familial Mediterranean fever, ultrasonography, splenomegaly, children, inflammatory markers.

INTRODUCTION

Familial Mediterranean fever (FMF) is an acute, repetitive, and self-limiting autoinflammatory disease inherited in an autosomal-recessive manner and characterized by fever and abdominal, joint, and chest pain (1). FMF is caused by mutations in the MEFV gene located on the short arm of chromosome 16. The MEFV gene encodes pyrin, a genetic defect that increases the inflammatory response (2). Many MEFV mutations have been reported. Colchicine halts or limits FMF attacks in most patients and prevents the development of amyloidosis, which is the most serious complication (3). Few studies have explored the effects of FMF on the reticuloendothelial system (4). Splenomegaly, hepatomegaly, and lymphadenopathy have been reported in FMF patients (5,6). Here, we measured the spleen and liver sizes of children with FMF who were in remission, as well as of healthy controls.

MATERIAL AND METHOD

The study was approved by the Gaziosmanpaşa University Clinical Researchs Ethics Committee (Date: 03.01.2016, Decision No: 16-KAEK-060). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 86 FMF patients diagnosed using the Turkish pediatric criteria and 54 healthy children were included (7). Patients who had congenital anomaly, connective tissue diseases, metabolic, renal, endocrine and infectious diseases were excluded from the present study. Disease severity was determined using the modified Pras scoring system (8). Sonographic measurements of the liver and spleen were obtained during symptom-free periods by a radiologist with 10 years of experience using the Toshiba Aplio 500 platform (Toshiba Medical Systems, Tokyo, Japan) and 3.5-MHz pvt-375BT Convex Probe. Spleen

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measurements were made with subjects supine in a slightly right lateral decubitus position. The spleen was measured between the superomedial and inferolateral boundaries. Liver measurements were made in the supine position. The longitudinal axis was measured on the midclavicular plane. The upper edge (under the diaphragm dome) served as the upper margin and the bottom edge as the lower margin. The data were evaluated with reference to height, weight and age standards and compared with those of healthy controls. Informed consent was obtained from all participants or their parents before inclusion.

Statistical Analysis

The data were evaluated using SPSS version 19 software.

RESULTS

Patient ages ranged from 3 to 17 years. A total of 49 (57%) were girls and 37 (43%) boys. The mean age of FMF patients was 11.1±3.77 years and that of controls 10.21±4.13 years (p=0.19). The mean body mass index of FMF patients was 18.01±4.1 kg/m² and that of controls 18.37±3.5 kg/m² (p=0.59). The average age at diagnosis was 7.49±3.94 years. The most common clinical findings were abdominal pain (87.2%, n=75), fever (74.4%, n=64), arthritis (62%, n=54), chest pain (30.2%, n=26), and an erysipelas-like rash (5.8%, n=5). The mean spleen length was 99.84±17.4 mm in FMF patients and 93.44±15.49 mm in controls (p=0.03). The mean liver length was 122.61±17.4 mm in patients and 117.71±16.04 mm in controls (p=0.104) (**Table 1**). The most common mutation was M694V (32.5%, n=28). Splenomegaly was often accompanied by M694V (32.55%, n=17) and E148Q mutations (3.4%, n=3).

Spleen size (as revealed by sonography) was affected by FMF, being 5.355 mm greater (with statistical significance) in FMF patients than in controls when spleen length was considered a dependent variable (t=2.182; p=0.031) (**Tables 2, 3**).

Statistical Analysis

Continuous variables are shown as means with standard deviations and categorical variables as numbers with percentages. The average values of quantitative variables were compared. Cross-tables and the chi-squared test were used to compare qualitative variables. Pearson correlation coefficients between quantitative variables were calculated. A p-value < 0.05 was considered to reflect statistical significance. Multivariate linear regression was used to explore the effects of selected variables on spleen and liver lengths. All calculations were made using IBM SPSS Statistics ver. 19 (SPSS Inc. and IBM Co., Somers, NY, USA).

Table 1. Demographic characteristics of FMF patients

Variables	Statistics
Age, years	10.76±3.9
Sex (M/F)	64 (45.7)/76 (54.3)
Weight, kg	38.06±17.7
Height, cm	140.59±22.0
BMI, kg/m²	18.15±3.87
FMF familial history	14 (16.3)
Appendectomy history	11 (12.8)
Age at onset (years)	6.05±3.8
Age at diagnosis (years)	7.49±3.9
Severity score	7.24±1.4
Liver length, mm	120.7±17.3
Spleen length, mm	97.4±18.1

Data are shown as means±standard deviation or as numbers (%).

Table 2. Effects of age, height, weight, BMI, and FMF on spleen and liver measurements

DV	IV	β	SD	t	p
Spleen	Age	0.914	0.954	0.958	0.340
	Weight	0.096	0.396	0.243	0.808
	Height	0.127	0.284	0.445	0.657
	BMI	0.703	1.028	0.684	0.495
	FMF	5.355	2.454	2.182	0.031*
Liver	Age	-0.31	0.873	-0.355	0.723
	Weight	-0.274	0.364	-0.754	0.452
	Height	0.682	0.261	2.612	0.010*
	BMI	1.117	0.944	1.183	0.239
	FMF	3.657	2.252	1.624	0.107

DV: dependent variable, IV: independent variable.
The effects of independent variables on dependent variables as revealed by a multivariate linear regression model. *The difference was statistically significant. Reference: control group.

Table 3. Bivariate correlations between qualitative variables

Variable			Weight (kg)	Height (cm)	BMI (kg/m²)
FMF	Liver	r	0.595	0.708	0.361
		p	<0.001	<0.001	0.001
	Spleen	r	0.587	0.586	0.432
		p	<0.001	<0.001	<0.001
Control	Liver	r	0.708	.659	0.535
		p	<0.001	<0.001	<0.001
		n	54	54	54
	Spleen	r	0.536	0.486	0.489
		p	<0.001	<0.001	<0.001

Pearson's correlation coefficients were calculated. BMI: body mass index. Statistically significant at p < 0.01.

DISCUSSION

FMF is a repetitive autoinflammatory disease. The most common symptoms are fever, abdominal pain, arthritis/arthralgia, and chest pain; more rarely, long-term febrile myalgia, erysipelas-like erythema, and orchitis are observed. FMF is associated with splenomegaly. However, the reticuloendothelial features of FMF have received little attention (4, 9). We evaluated spleen and liver sizes by age, height, and body weight in FMF patients during remission, and healthy controls.

The levels of acute-phase proteins such as CRP, ESR, and SAA increase in FMF patients during attacks and usually return to normal during remission (10). However, subclinical inflammation continues during remission (11,12), increasing the risks of anemia, splenomegaly, decreased bone mineral density, heart disease, and (especially) secondary amyloidosis (13, 14). Inflammation develops when certain cytokines are secreted by macrophages and monocytes (15).

The spleen is a platelet reservoir. Splenomegaly may be associated with increased hemolysis or may reflect a vascular, infectious, infiltrative, or inflammatory disorder. A significant correlation was evident between thrombocyte activation and splenomegaly in FMF children in remission. The mean platelet volume, which reflects platelet function and activation, was higher in FMF patients (16).

Splenomegaly extending past the Costa edge (i.e., > 5 cm) has been reported in approximately 30% of FMF patients. Splenomegaly was usually not associated with amyloidosis but was linked to chronic inflammation (17). Korkmaz et al. (18) detected splenomegaly in approximately 25% of FMF patients (without amyloidosis) during attack-free periods. Ultrasonography revealed splenomegaly in 27% of patients with acute attacks and 13% of asymptomatic patients, but hepatomegaly in only 13% of asymptomatic patients (19). Dursun et al. (20) reported splenomegaly in 27.9% of FMF children in remission. Our figures were similar.

The phenotype–genotype relationship of FMF has been investigated extensively (20-23). Moradian et al. (24) found that all mutations were associated with hepatomegaly and splenomegaly. Exon 10 mutations associated with severe disease phenotypes (polyserositis, erysipelas-like erythema, splenomegaly, and vasculitis) reflected high-level M694V penetration. A homozygous M694V mutation has been linked to splenomegaly (25). We found that splenomegaly was usually accompanied by M694V and E148Q mutations.

Previous studies demonstrated correlations of longitudinal measurements of the liver, spleen, and kidneys with other bodily parameters and defined normal organ sizes (26, 27). Our longitudinal measurements were in line with such findings. As age, height, and weight increased, the spleen and liver sizes also increased (28). Safak et al. (26) evaluated schoolchildren and found no significant difference in organ size according to sex. Organ size was most correlated with body weight. Similarly, we found that organ size increased with age, height, and weight and did not differ according to. Age, height, and weight affected both liver and spleen sizes in FMF patients. In the present study, FMF was the most important parameter affecting spleen length, thus more significant than age, height, or weight.

A diagnosis of FMF is based on clinical criteria. Elevations in the levels of acute phase reactants, indicative of inflammation, support diagnosis of an acute attack. Subclinical inflammation was apparent in 25% of patients in remission (20). Ultrasonography is useful for evaluating the features of both an acute attack and remission. Splenomegaly during remission is considered to herald the development of an acute attack (20).

CONCLUSION

The spleen and liver dimensions were correlated with age, height, and weight. FMF affected spleen size (compared with that of healthy controls). To the best of our knowledge, this is the first study to compare the abdominal organ sizes of FMF patients in remission to anthropometric measurements. Splenomegaly may reflect low-level inflammatory activity during remission. In FMF patients, spleen size can serve as a marker of subclinical inflammation during remission.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Gaziosmanpaşa University Clinical Researchs Ethics Committee (Date: 03.01.2016, Decision No: 16-KAEK-060).

Informed Consent: Verbal and written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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