SURGERY FOR ACUTE ABDOMEN AND MEFV MUTATIONS IN PATIENTS WITH FMF

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Abstract

Objectives: Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent fever, peritonitis, arthritis, pleuritis, and secondary amyloidosis. In the current study, we sought to determine the frequency of acute surgical abdominal intervention and MEFV gene mutations in FMF patients.

Patients and Methods: A total of 159 patients were referred to our department with a diagnosis of FMF. Twenty-six patients (16.4%) had a history of surgical intervention. Of these, 17 (10.7%) were operated on due to appendicitis, and 9 (5.7%) were operated on due to other acute abdomen reasons. Genomic DNA was isolated from the blood samples, and in the isolated DNA samples, 12 MEFV gene mutations were studied.

Results: Mutation frequency was detected to be 80.8% in the patients with acute abdomen surgery intervention and 56.4% in the patients without acute abdomen surgical intervention. Upon mutational evaluation of these patients, we noted that the M694V (40.5%) and E148Q (21.4%) mutations occurred most frequently.

Conclusions: The MEFV gene mutation frequency in FMF patients with acute abdomen surgical intervention was significantly higher than that in patients without such intervention. Increased mutation scanning in FMF patients will significantly decrease unnecessary surgical interventions in this patient group.

Keywords: FMF; Acute abdomen; Genetic mutations.

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Introduction

Familial Mediterranean Fever (FMF) is an autosomal, recessively inherited disease with an expression determined by mutations in MEFV gene, which is located on the short arm of chromosome 16.[1] The frequency of MEFV mutations in the Turkish population is 20%.[2] The MEFV gene consists of 10 exons, and 133 of the 177 known mutations are located primarily on the 2nd, 3rd, 5th and 10th exons.[3] The 12 most frequently occurring and most highly studied mutations *(i.e., E148Q, P369S, F479L, M680I(G/C), M680I(G/A), I692del, M694V, M694I, K695R, V726A, A744S,* and *R761H)* are located on the 2nd, 3rd, 5th and 10th exons.[3]

Acute abdomen is an abdominal pathology that begins suddenly, regardless of its relationship to trauma, and requires surgery.[4] Pathologies causing stomachache in acute abdomen are divided into two main groups: intraperitoneal or gastrointestinal, and extraperitoneal.

Acute appendicitis is the most common acute abdomen diagnosis requiring surgery. It is followed by cholecystitis with gallbladder-stones, perforated peptic ulcer, and mechanic ileus, and it is a more common cause of emergency intervention in women than men.[4-6] Roughly 80% of the distinguishable diagnoses of acute surgical abdomen are made by anemnesis and physical examination. In cases without diagnosis, procedures such as, imaging methods (ultrasonography, computed tomography, or magnetic resonance imaging), and biochemical tests are useful; however, predictive tests for appendicitis are not available.[7]

The frequency of appendicitis is between 5-10%, and it is particularly common in individuals younger than 20 years old. In Surgery Departments, the surgical intervention rate in patients with abdominal pain is nearly 25-30%; this rate increases to 30--40% in patients with cholecystitis, perforation, and mechanical colonic obstruction.[8-11]

FMF is characterized by recurrent fever, peritonitis, arthritis, pleuritis and secondary amyloidosis.[12,13] The clinical and laboratory findings of FMF patients during attacks perfectly mimic the symptoms of acute abdomen.[14,15] These two conditions are frequently confused, especially in patients without FMF diagnosis.[16-18] Before FMF diagnosis, patients typically undergo unnecessary surgery due to mis-diagnoses of cholecystitis, perforated gallbladder, perforated stomach, or acute appendicitis.[19,20] Frequent surgical interventions may lead to adhesions and ileus, which may result in these patients, to be operated even more.[21] Due to all of these reasons, elective appendectomy is suggested in some studies in order to prevent unnecessary surgical intervention.[18]

In the current study, we tried to examine whether FMF patients undergo acute abdominal surgery more frequently than patients in other sections of the population. Additionally, we evaluated the relationship between this practice and the MEFV gene mutations.

Patients and Methods

Ethics committee approval was obtained for the current study and an "Informed Consent Form" was signed by all the patients included in the study. Using the Tel Hashomer Diagnosis criteria, clinical assessments of 159 patients with a diagnosis of FMF or possible FMF were performed. After taking a detailed history of the cases, 2 ml of blood was drawn into tubes containing EDTA for molecular investigations. Genomic DNA was isolated from the blood samples using a Puregene DNA Isolation Kit (Gentra Systems Inc, Minneapolis, MN, USA).

In the isolated DNA samples, 12 mutations (E148Q, P369S, F479L, M680I(G/C), M680I(G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H) located on the 2nd, 3rd, 5th, and 10th exons were studied. We investigated the presence of the mutations via reverse hybridization. First, the 2nd, 3rd, 5th, and 10th exons were amplified by multiplex PCR using biotinylated primers. Later, the amplicons were denatured with denaturation solution and selectively hybridized with oligonucleotide probes on the FMF strip (wild-type specific probes were fixed on the top half of the strip, and mutant-specific probes were fixed on the bottom half of the strip). Biotinylated sequences of the hybridized oligonucleotide probe were visualized with streptavidin alkaline phosphatase and colored substrates. Data obtained as a result of the genetic investigation were evaluated by a Student's t-test, and p-values of <0.05 were considered to be statistically significant.

Results

In this study, a total of 159 cases pre-diagnosed with FMF were investigated. Of these cases, 85 (53.5%) were women, and 74 (46.5%) were men (Table I). Seventeen (10.7%) appendectomy cases, 9 (5,7%) different acute abdomen cases, and 26 (16.4%) of the 159 cases pre-diagnosed with FMF were scheduled to undergo abdominal surgery (Table I). Of those undergoing abdominal operation, 12 (46.2%) were women, and 14 (53.8%) were men (Table I).

In 21 (80.8%) of the 26 cases undergoing acute abdominal surgery, the existence of a mutation was detected. Of these cases, 8 (38.1%) were hete-

Table I. Investigated FMF patients and the frequency of mutations

Study Group		n (%)	Women (n%)	Men (n%)	Mutation Rates (n%)
Cases with surgical abdomen Intervention	Cases with appendectomy	17 (10.7%)	9 (52.9%)	8 (47,1%)	15 (88.2%)
	Other	9 (5.7%)	3 (33.3%)	6 (66.7%)	6 (66.7%)
Cases without surgical abdomen Intervention		133 (83.6%)	73 (54.9%)	60 (45.1%)	76 (57.1%)

(Number of investigated cases = 159)

rozygous for one allele, 7 (33.4%) were compound heterozygous, and 6 (28.6%) were homozygous. In 5 of the studied cases, mutations could not be detected. The mutation distribution of the 42 alleles from the 21 cases with mutations is given in Table II.

In 75 (56.4%) of the 133 cases that did not undergo acute abdomen surgery, the existence of a mutation was also detected. Of these cases, 40 (53.4%) were heterozygous for one allele, 22 (56.5%) were compound heterozygous, and 13 (9.8%) were homozygous. The mutation distribution of the 150 alleles from the 75 cases with mutations is given in Table III. In 58 of the cases, the mutations under examination could not be detected.

The frequency of homozygous mutations was higher in patients who underwent surgical intervention than in the remaining patients (28.6% in operated vs. 9.8% in non-operated patients, Table II).

The frequency of homozygosity for the M694V mutation was high in both groups. The frequency of heterozygosity and compound heterozygosity for one allele was lower in operated than non-operated patients. All of the patients who underwent abdominal surgery were diagnosed with FMF during attack periods after the surgery.

Table II. The frequency of MEFV gene mutations detected in the cases

	Cases with the mutations	
	Cases with surgical abdomen intervention (n=21)	Cases without surgical abdomen intervention (n=75)
Mutation	42 alleles	150 alleles
M694V	17 (40.5%)	50 (33.3%)
E148Q	9 (21.4%)	24 (16%)
M680I	3 (7.1%)	15 (10%)
V726A	3 (7.1%)	12 (8%)
M694I	–	2 (1.3%)
R761H	1 (2.4%)	3 (2%)
F479L	–	1 (0.7%)
A744S	–	1 (0.7%)
P369S	–	1 (0.7%)

Discussion

FMF is a clinically diagnosed disorder determined by an autosomal, recessively inherited genetic mutation. In FMF, febrile attacks are usually associated with serositis. A typical FMF attack is associated with fever and abdominal pain lasting one to three days, and patient discomfort exists only during the attacks. During the attacks, 90% of FMF patients experience abdominal pain and fever; roughly 75% of patients experience joint pain, and 40% experience chest pain.[17,20] During the attacks, the clinical condition of FMF closely resembles and is usually indistinguishable from acute abdomen. Because of this similarity, the frequency of acute abdomen surgical intervention is rather high among FMF patients. In some studies, this rate was reported to be as high as 30-40%.[17,18] In the current study, the rate was detected to be 16.4%. Although this rate is higher than that of the general population, it is lower than rates reported in previous studies. The recent development of diagnostic methods and increase of interest in diagnosing FMF in populations with a high incidence of the disease may have decreased unnecessary interventions. Even though the frequency of acute surgical abdomen in the general population is two-fold higher in women than men, a statistically significant difference between genders was not detected in the current study. However, the frequencies of appendectomy in the general population and among surgical interventions are 6% and 25-30%, respectively. We found these values to be significantly higher in our patient group with FMF (10.7% and 65.4%, respectively). It is noteworthy that all 26 patients in the current study received a diagnosis of FMF during attack periods after surgical intervention.

In the current study, the frequency of mutations in FMF patients who have had acute abdomen surgical intervention (80.8%) was found to be significantly higher than that in patients who did not undergo such an intervention (p=0.02). M. Lidar et al. reported in 2008 that the frequency of MEFV gene mutations in FMF patients undergoing appendectomy was 60%.[17] The number of mutations that we investigated was higher in patients who underwent abdominal surgery.

Genotypes of the cases included in our study were evaluated and mutation for one allele was detected most frequently in the patients who underwent acute surgical abdomen intervention whereas compound heterozygosity was detected

Table III. MEFV gene mutations in the investigated FMF cases

Study Group	Cases with the investigated mutations (n%)	Homozygous mutation (n%)	Heterozygous mutation n% Compound mutation (n%)	Heterozygous mutation n% Single mutation (n%)	Unknown (n%)
Cases with surgical abdomen intervention	21 (80.8%)	6 (28.6%)	7 (33.3%)	8 (38.1%)	5 (19.2%)
Cases without surgical abdomen intervention	75 (56.4%)	13 (17.3%)	22 (29.3%)	40 (53.3%)	58 (43. 6%)

most frequently in the patients who did not undergo surgery (Table II). Homozygous mutation was detected to be three-fold higher in FMF patients who underwent surgery than those who did not have surgery.

Although the M694V mutation (50%) was the most frequently observed mutation in these patients, the M680I (25%) and E148Q (25%) homozygous mutations were also detected. Different study groups have reported frequencies between 19.1-24.6% for the homozygous M694V mutation in the Turkis population.[22,23] Our data are compatible with these findings. As reported in many studies, the clinical findings of the patients carrying a homozygous mutation were more severe: the frequency of attacks was higher, symptoms began at an earlier age, and amyloidosis was observed in a higher percentage in patients with homozygous mutations than patients with other genotypes.[24] The severe clinical symptoms associated with the homozygous mutations increase the risk of patients undergoing acute surgical abdomen intervention. Although the frequencies of the M694V, E148Q, M680I, and V726A mutations were similar in our genetic investigation, the M694I, F479L, A744S, and P369S mutations were not detected in patients who did not undergo acute surgical abdomen intervention (Table II).

The diagnosis of FMF is based on clinical findings, and there are no specific biochemical parameters of the disease; this combination of issues makes diagnosis difficult. Diagnosing these patients is important because symptoms mimicking acute surgical abdomen arise during attack periods. It is also important to prevent patients from being exposed to unnecessary surgical interventions.

In populations with a high incidence of FMF, with patients presenting symptoms of acute surgical abdomen and other similar complaints in their families, evaluation of potential FMF patients will prevent unnecessary surgical interventions. Early diagnosis will be particularly useful in preventing unnecessary surgical interventions in populations with a high incidence of FMF, and thereby avoid situations of multiple surgeries and mis-diagnoses.

Conclusions

The MEFV gene mutation frequency in FMF patients with acute surgical abdomen intervention (80.8%) was significantly higher than that in patients without such intervention (56.4%). Increased mutation scanning in FMF patients may significantly decrease unnecessary surgical interventions in this patient group.

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