INCREASED FREQUENCY OF MEFV GENES IN PATIENTS WITH EPIGASTRIC PAIN SYNDROME

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ABSTRACT

Atypical clinical forms of familial Mediterranean fever (FMF) can be misdiagnosed as therapy-resistant epigastric pain syndrome (EPS) for they share many of the same clinical features, such as abdominal pain. Thus, we aimed to determined the frequency of FMF in patients who were followed with a diagnosis of therapy-resistant EPS. Seventy-five patients with therapy-resistant EPS and 20 controls were involved in the study. To detect the FMF in patients with therapy-resistant EPS, Tel-Hashomer criteria, family history of FMF were researched and recorded. We performed MEFV gene analysis on all patients. Forty-three patients with EPS (57.3%) had MEFV gene mutations and the carrier rate was 30.0%. The most common MEFV gene alteration was R202Q (55.8%), followed by E148Q (16.2%), R761H (16.2%), V726A (9.3%), M680I (9.3%) and M694V (4.6%). Rarely seen mutations in the Turkish population were also identified: K695R (2.3%), L110P (2.3%) and G304R (2.3%). Eight patients with EPS were diagnosed with FMF and started on colchicine therapy. Three patients with compound heterozygosities for three mutations, two patients with compound het-erozygosities for two mutations (K695R/ V726A and R202Q/R761H), one patient with homozygous R202Q, one patient with heterozygous R202Q mutation and one patient with non-R202Q heterozygous mutation (G304R/–) had clinical FMF symptoms and were started on colchicine therapy. Patients who have therapy-resistant EPS should also be questioned about FMF, especially in high risk populations.

Keywords: Epigastric pain syndrome (EPS); Familial Mediterranean fever (FMF); Functional dyspepsia FD); MEFV gene mutations.

INTRODUCTION

Functional dyspepsia (FD) is a common functional gastrointestinal disorder in clinical practice [1,2]. The Rome III consensus proposed the subdivision of FD into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Diagnostic criteria for EPS include intermittent epigastric pain or burning of minimal to moderate severity at least once a week. This condition must have persisted for the last 3 months with the onset of symptoms occurring at least 6 months prior to diagnosis [3]. Functional dyspepsia is treated by two major categories of drug, acid inhibitors (H2-receptor antagonists and proton pump inhibitors) and prokinetic drugs, diet and life-style modification or helicobacter pylori (HP) eradication therapy [4,5]. However, all prescribed medications provide only limited or temporary improvement of dyspeptic symptoms. Thus, the healthy quality of life for patients with FD may deteriorate [1,6].

Familial Mediterranean fever (FMF) is an autosomal recessive inherited disorder, characterized by recurrent attacks of fever and polyserositis. The most frequent symptom is abdominal pain. Familial Mediterranean fever is especially common in Mediterranean populations such as Jews, Arabs, Turks, Greek and Armenians [7]. It is caused by mutations in the Mediterranean fever (MEFV) gene. The carrier rate is 37.0-39.0% in Armenians, and 20.0% in Turks, North African, Ashkenazi Jews, and Arabs [8].

The clinical profile of FMF is wide related to MEFV allelic heterogeneity (typical, atypic and silence type). An atypical clinical form (incomplete attack) was character-
ized according to several parameters: milder disease severity, the normal or <38 °C fever, attack duration longer or shorter than specific time (12 hours to 3 days), localized abdominal attacks without serositis signs. Non specific symptoms make it difficult to diagnose atypical FMF [9]. We thought that the atypical clinical forms of FMF could be confused with therapy-resistant EPS as these two conditions share the same clinical features (such as abdominal pain). This raises the possibility that FMF is currently being underdiagnosed in patients with therapy-resistant EPS in countries endemic for FMF. Thus, we aimed to determined the frequency of MEFV gene mutations and FMF clinical finding in patients who were followed with a diagnosis of therapy-resistant EPS.

**MATERIALS AND METHODS**

This study was performed at the Department of Gastroenterology, Kayseri Training and Research Hospital, Kayseri, Turkey, between January 2014 and December 2015. The study protocol was permitted by the local ethics committee of Cumhuriyet University, Sivas, Turkey. Written informed consent was obtained from all of the participants.

**Patients.** A total of 75 patients aged between 18 and 65 years, who were diagnosed with therapy-resistant EPS, were included in this study. Patients were diagnosed according to the Rome III criteria (Table 1) [3]. Therapy-resistant EPS was defined as persistent epigastric pain despite a minimum 4 weeks of acid suppression, procinetics and HP eradication therapy [5]. All examinations of patients, including upper gastrointestinal endoscopy, abdominal ultrasonography, whole blood count and biochemical analyses (renal and liver function), were normal within 3 months of the study. Exclusion criteria were as follows: presence of ulcer or erosion in the upper gastrointestinal system endoscopy, patients who had gastroesophageal reflux symptoms or irritable bowel syndrome, inflammatory bowel disease, pancreaticobiliary tract disease, use of non steroidal anti-inflammatory drugs or alcohol, presence of malignancy (stomach/pancreatic cancer), previous abdominal surgery, other severe systemic disease (e.g., heart, liver, lung and kidney), presence of psychoactive disorders (e.g., anxiety and depression), pregnancy.

The control group consisted of 20 healthy age- and sex-matched subjects without any systemic illness such as diabetes mellitus, renal failure, pulmonary/heart disease and chronic inflammatory diseases. All patients and healthy controls were Turkish residents of Central Anatolia. Table 2 shows demographic and clinical findings in the EPS patients and control group.

**Methods.** To investigate the diagnosis of FMF in patients with therapy-resistant EPS, Tel-Hashomer criteria (recurrent fever attacks, abdominal pain, chest pain, arthralgia and erysipelas-like erythema), familial history of FMF and the presence of other autoimmune diseases, were recorded [10]. All patients and healthy controls were referred for genetic testing. Other laboratory findings (complete blood count, biochemical and urinary analyses), sedimentation and C-reactive protein were obtained from hospital records.

For FMF gene mutation analysis, genomic DNA was extracted from peripheral blood leukocytes using the QIAaamp blood kit (Qiagen GmbH, Hilden, Germany). A dideoxy sequencing method was used in this study. To perform mutational analysis, amplified polymerase chain reaction (PCR) products were purified by USB ExoSAP-IT (Affymetrix, Cleveland, OH, USA) and subjected to bidirectional sequencing (BigDye Terminator, version 3.1, Applied Biosystems Inc., Foster City, CA, USA) and further processed on Performa DTR Gel Filtration columns (Edge Biosystems, San Jose, CA, USA). The sequencing products were analyzed on an ABI PRISM™ 3500 genetic analyzer (Applied Biosystems Inc.). We performed sequencing in the forward and reverse directions.

**Statistical Analyses.** Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0) (SPSS Inc., Chicago, IL, USA). Descriptive statistics [e.g., mean and standard deviation (SD)] for normally distributed data were calculated for quantitative parameters. Qualitative data were summarized as frequency and percentage. The $\chi^2$ and unpaired $t$-student tests were used

| Table 1. Diagnostic criteria of epigastric pain syndrome (Rome III criteria). |
|---|
| 1 | Pain or burning localized to the epigastrium of at least moderate severity, at least once per week |
| 2 | The pain is intermittent |
| 3 | Not generalized or localized to other abdominal or chest regions |
| 4 | Not relieved by defecation or passage of flatus |
| 5 | Not fulfilling criteria for gallbladder or sphincter of Oddi disorders |

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
to compare EPS patients with and without MEFV gene mutations. A $p$ value of $<0.05$ was considered statistically significant in all analyses.

**RESULTS**

The EPS patients and controls had mean ages of $38.9 \pm 13.9$ and $34.6 \pm 7.6$, respectively. Seventy-two percent of EPS patients were female. Eighteen patients (24.0%) had a family history of FMF. The mean duration of abdominal pain was $10 \pm 2.5$ years (range from 5 to 22 years). Ten (13.3%) patients were the result of consanguineous parents. Episodic epigastric pain was the principal complaint reported by all patients. Other observed complaints consisted of several types: fever (28; 37.3%), arthralgia (27; 36.0%), chest pain (11; 14.6%), history of kidney stones (9; 12.0%) and oral ulcers (10; 13.3%). In the patients, the mean erythrocyte sedimentation rate was $21.4 \pm 11.4$ mm/h (normal value $<15$ mm/h), C-reactive protein was $8.0 \pm 3.3$ mg/dL (normal range: 0.0-6.0 mg/dL) and fibrinogen $311.8 \pm 85.0$ mg/dL (normal range: 180.0-400.0 mg/dL).

Of the 75 patients, 43 (57.3%) had *MEFV* gene mutations. Thirty out of 43 patients (69.7%) were heterozygous, three patients (6.9%) were homozygotes (R202Q/R202Q), six patients (13.9%) were compound heterozygotes for two mutation and four patients (9.3%) were compound heterozygotes for three mutations. The most common *MEFV* gene mutation was R202Q (55.8%), followed by E148Q (16.2%), R761H (16.2%), V726A (9.3%), M680I (9.3%) and M694V (4.6%). In addition, the rare mutations were identified as: K695R (2.3%, $n = 1$), L110P (2.3%, $n = 1$) and G304R (2.3%, $n = 1$). R202Q was detected in 24 patients, of which 15 (34.8%) were heterozygous, three (6.9%) were homozygous and one (6.9%) were a compound heterozygote for three mutations. The demographic, clinical and laboratory characteristics of the patients with EPS and the control group are shown in Table 2.

In the control group, eight subjects (40.0%) had *MEFV* gene mutations. The frequency of *MEFV* mutation in EPS patients was significantly higher than in the control group ($p <0.05$). All participants in the control group were heterozygous (R202Q in one patients, E148Q in two patients, V726A in two patients, M680I in two patients and M694I in one patient). The frequency of *MEFV* mutations in EPS patients and the control group are shown in Table 3.

No significant differences were observed in the frequencies of consanguinity, fever, arthralgia, chest pain and FMF family history in EPS patients with or without the *MEFV* mutation. In the EPS group, three patients with compound heterozygosities for three mutations, two patients with compound heterozygosities for two mutations (K695R/V726A and R202Q/R761H), one patient with homozygous R202Q, one patient with heterozygous R202Q, and one patient with a heterozygous G304R/– mutation had clinical FMF symptoms and were started on colchicine therapy. Proteinuria was not detected in patients who were diagnosed with FMF. The genotype, clinical and demographic findings in FMF patients are shown in Table 4. The remaining EPS patients with *MEFV* gene mutations have no FMF clinical symptoms or family history of FMF. The other clinically asymptomatic patients who have *MEFV* gene mutations (homozygotes or compound heterozygotes) were followed with urine analysis to development of amyloidosis, without colchicine.

| Parameters | Patient Group ($n = 75$) | Control Group ($n = 20$) |
|------------|-------------------------|-------------------------|
| Gender     | F: 54; M: 21            | F: 12; M: 8             |
| Age (years)| $38.9 \pm 13.9$         | $34.6 \pm 7.6$          |
| Family history of FMF | 18 (24.0%)            | 0 (0.0%)               |
| Consanguinity | 10 (13.3%)          | 0 (0.0%)               |
| Homozygotes | 3 (4.0%)               | 0 (0.0%)               |
| Heterozygotes | 30 (40.0%)          | 8 (40.0%)              |
| Compound heterozygotes | 10 (13.3%)       | 0 (0.0%)               |
| Fever      | 28 (37.3%)             | –                      |
| Arthralgia | 27 (36.0%)             | –                      |
| Chest pain | 11 (14.6%)             | –                      |
| Oral ulcers| 10 (13.3%)             | –                      |
| Kidney stones | 9 (12.0%)         | –                      |

FMF: familial Mediterranean fever.
Table 3. The frequency of MEFV gene mutations in patients with epigastric pain syndrome and the control group.

| Genotype          | Patient Group (n = 75) | Control Group (n = 20) |
|-------------------|-----------------------|-----------------------|
| Mutation/-        | 32                    | 12                    |
| Heterozygotes for one mutation: |                     |                       |
| R202Q/-           | 15                    | 2                     |
| R761H/-           | 5                     | 0                     |
| E148Q/-           | 5                     | 2                     |
| V726A/-           | 1                     | 2                     |
| M680I/-           | 2                     | 1                     |
| G304R/-           | 1                     | 0                     |
| M694I/-           | 1                     | 1                     |
| Homozygotes for one mutation: |                     |                       |
| R202Q/R202Q       | 3                     | 0                     |
| Compound heterozygotes for two mutations: |               |
| R202Q/R761H       | 2                     | 0                     |
| K695R/V726A       | 1                     | 0                     |
| P396S/R408Q       | 1                     | 0                     |
| L110P/E148Q       | 1                     | 0                     |
| M680I/V726A       | 1                     | 0                     |
| Compound heterozygotes for three mutations: |               |
| R202Q/M694V/V726A | 2                     | 0                     |
| R202Q/R408Q/E148Q | 1                     | 0                     |
| R202Q/R202Q/P369S | 1                     | 0                     |
| Total             | 75                    | 20                    |

Table 4. The genotype, clinical and demographic findings in familial Mediterranean fever patients.

| Patient | MEFV Gene Mutations | Sex-Age | Family History | Abdominal Pain | Fever | Arthalgia | Chest Pain | Microscopic Hematuria |
|---------|---------------------|---------|---------------|----------------|-------|-----------|------------|-----------------------|
| #1      | G304R/-             | F-38    | [-]           | [-]            | [-]   | [-]       | [-]        | [-]                   |
| #2      | R202Q/-             | F-27    | [+]           | [+]            | [+]   | [+]       | [+]        | [+]                   |
| #3      | V726A/K695R         | F-28    | [+]           | [+]            | [+]   | [+]       | [+]        | [+]                   |
| #4      | R202Q/R761H         | F-19    | [+]           | [+]            | [+]   | [+]       | [+]        | [+]                   |
| #5      | R202Q/R202Q         | M-31    | [-]           | [+]            | [+]   | [+]       | [+]        | [+]                   |
| #6      | V726A/M694V/R202Q   | M-29    | [+]           | [+]            | [+]   | [+]       | [+]        | [+]                   |
| #7      | V726A/M694V/R202Q   | M-41    | [-]           | [+]            | [+]   | [+]       | [+]        | [+]                   |
| #8      | R202Q/E148Q/R408Q   | F-37    | [+/-]         | [+]            | [+]   | [+]       | [+]        | [+]                   |

Table 5. Comparison of clinical findings between epigastric pain syndrome patients with/without MEFV gene mutations.

| MEFV Gene Mutations | Negative (n = 32) | Positive (n = 12) | p Value |
|---------------------|-------------------|-------------------|---------|
| Family history      | 5 (5.8%)          | 12 (14.1%)        | 0.54    |
| Positive consanguinity | 3 (9.4%)      | 7 (16.3%)         | 0.38    |
| Fever               | 10 (31.3%)        | 18 (41.9%)        | 0.35    |
| Arthalgia           | 12 (37.5%)        | 19 (44.2%)        | 0.56    |
| Chest pain          | 3 (9.4%)          | 8 (18.6%)         | 0.26    |
| Oral ulcers         | 1 (3.1%)          | 9 (20.9%)         | 0.02    |
| Kidney stones       | 0 (0.0%)          | 9 (20.9%)         | 0.01    |
comparison of clinical findings between EPS patients with/without MEFV gene mutations, are shown in Table 5.

**DISCUSSION**

Our study aimed to determine the frequency of MEFV gene mutations and FMF clinical findings in patients who were followed with a diagnosis of EPS. Familial Mediterranean fever is an autoinflammatory disease characterized by recurrent and self-limited episodes of fever, abdominal pain and serositis with a duration of 1-3 days. The prevalence of FMF is 1/1000 and the carrier rate is 15.0-34.0% in Turkey [3,4]. It is caused by mutations in the MEFV gene. More than 300 mutations of the MEFV gene have been reported [11]. A diagnosis of FMF was established according to clinical criteria (Tel Hashomer criteria), rather than genetic analysis [12,13]. However, genetic analyses are helpful in detecting atypical FMF presentations, presymptomatic patient’s relatives and confirmation of the FMF diagnosis [14]. There are also many studies indicating that there are FMF patients who do not carry MEFV gene mutations (10.0-20.0%) [15,16]. In the present study, EPS patients were evaluated according to both the Tel Hashomer criteria and genetic analysis for the diagnosis of FMF. The FMF diagnosis has not been established in EPS patients who do not carry MEFV gene mutations.

The most commonly seen mutations in FMF patients are M694V, M680I (G/C), E148Q, V726A, and frequency of the mutations change according to ethnicity [17,18]. Erden et al. [19] reported that 68.6% of FMF patients had at least one of the several mentioned mutations: M694V; 46.2%, E148Q; 16.4%, V726A; 13.4% and M680I; 5.9%. In our study population, 43 EPS patients (57.3%) had MEFV gene mutations and the carrier rate was 30.0%. The most common mutation was R202Q (55.0%), followed by E148Q (16.2%), R761H (16.2%), V726A (9.3%), M680I (9.3%) and M694V (4.6%). While the frequency of M694V, which is the most commonly observed MEFV gene in Turks, was quite low, the frequencies of other genes were approximately consistent with previous studies [20,21]. The different frequency distribution of mutations may be related to the small sample size, the geographical region, genetic heterogeneities, patients’ inclusion criteria, and the use of different genetic analytical techniques.

The R202Q was another common mutation in the Turkish population. Some studies have also recently reported that frequency of R202Q was higher than the frequency of the M694V mutation in FMF patients [22,23]. In a study by Yigit et al. [24] conducted on 191 FMF patients and 150 control patients; the frequency of the R202Q mutation was higher than that found for the M694V mutation. The frequency of heterozygous R202Q was similar between FMF patients and controls (59.7 vs. 44.7%; p >0.05), while the frequency of homozygous R202Q mutations was higher than that in the controls (14.7 vs. 0.0%; p <0.05) [24]. Giaglis et al. [25] reported that homozygous R202Q was detected in 14/152 (9.2%) FMF patients and in 1/140 (0.7%) in a Greek study population. They also reported that the heterozygous state of R202Q produced no symptoms and only the homozygous and compound heterozygous states were associated with the development of symptoms [25]. In present study, the most common MEFV gene mutation in EPS patients was R202Q. In our geographic region, MEFV genetic analysis showed that R202Q gene mutations in FMF patients and healthy controls were not found.

However, contrary to the above data, Comak et al. [26] found that some patients with a heterozygous R202Q mutation had typical episodes of FMF. In addition, Cankaya et al. [27] compared the clinical symptoms between R202Q/– and non-R202Q/– in FMF patients. It was shown that there were no differences in the frequencies of symptoms and definitive diagnosis of FMF in either group. In our study of 24 EPS patients with the R202Q gene mutation, 15 were heterozygotes, three were homozygotes, two were compound heterozygotes, and four carried the compound heterozygotes for three mutations [27]. We did not find a homozygous R202Q in the control group, which was in agreement with results from previous studies. In our study, one patient with the heterozygous R202Q mutation had arthralgia, fever, and a familial history of FMF. While only one of the patients with the homozygous R202Q mutation had FMF clinical findings, the remainder were silent carriers. We also observed that there were no clinical symptoms in either R202Q/– or non-R202Q/– in EPS patients.

E148Q and V726A are other commonly observed mutations in Turkish FMF patients. The carrier frequencies of E148Q and V726A have been reported as 12.0 and 3.0-14.0%, respectively. The frequency of E148Q in Turks is similar with other ethnicities [25,28,29], while V726A is especially common in Arabs [30]. Ben-Chetrit et al. [31] found a similar frequency of E148Q mutations between patients and controls and suggested that E148Q is a benign polymorphism. However, some authors accepted that E148Q was a pathogenic mutation because of substitution of the glutamine for glutamic acid at codon 148 in exon 2 [32]. Familial Mediterranean fever patients with homozygous and compound heterozygous mutations.
have moderate/severe disease. In addition, several studies reported that E14Q was also associated with vasculitis (Henoch-Schonlein purpura, polyarteritis nodosa) and rheumatic diseases [33]. In the present study, E14Q was the second most common mutation with a frequency of 16.2%. While one patient who was a compound heterozygote for three mutations (R202Q/E148Q/R408Q) had FMF symptoms, five patients heterozygous for E148Q/–, and one patient with a compound heterozygosity for two mutations (L110P/E148Q) had no FMF symptoms.

V726A is associated with a mild form of the disease. However, V726A homozygotes and compound heterozygotes for the V726A/E148Q variants are associated with severe disease, and patients can develop renal amyloidosis. Hence, the authors proposed that patients carrying this complex allele should have been given colchicine prophylaxis [9,34]. In the present study, V726A is the third most common mutation with a frequency of 9.3%. While two patients who had compound heterozygosity for two or three mutations (V726A/K695R and V726A/M694V/R202Q), presented with FMF symptoms, one patient with heterozygous V726A/– and one patient with a compound heterozygosity for V726A/M680I, did not.

In this study, the rare MEFV gene mutations were also identified as K695R (2.3%), L110P (2.3%) and G304R (2.3%). Dogan et al. [35] reported that the frequency of rare mutations were identified as L110P (0.2%) and K695R (0.1%) in 731 participants. In another study, Gunesacar et al. [36] found that the frequency of rare mutations were as follows: K695R (0.20%), L110P (0.10%) and G304R (0.05%). Moreover, they also detected the G304R mutation for the first time in Turkey. To date, it has been detected in a total of 33 patients carrying K695R in Turkey. It has been reported in the literature that some patients carrying K695R (compound heterozygotes) have severe FMF symptoms [37]. L110P is a more common MEFV gene mutation in Japan and is associated with a milder form of the disease [38]. In the present study, two patients carrying rare MEFV gene mutations were diagnosed with FMF (K695R/V726A and G304R/–), and another patient (L110P) was asymptomatic. We also detected a second case carrying the G304R mutation in Turkey.

Familial Mediterranean fever can be divided into three clinical phenotypes: type 1 or typical FMF phenotype (attacks of abdominal pain, arthritis, fever); type 2 characterized by the presence of amyloidosis in asymptomatic subjects and (incidence of 7.0-25.0%); type 3 ‘silent type’ homozygous or compound heterozygous state and is estimated to occur in 1:300 Ashkenazi and 1:25 Iraqi Jews. In recent years, it has been observed that heterozygous mutation carriers can suffer also from a mild or incomplete form of FMF, named ‘FMF-like’ disease (a new phenotype) [9]. In recent years, a new phenotype termed ‘FMF-like disease,’ which is characterized as a mild or incomplete form of FMF in patients with heterozygous mutations has been defined. The reason why some carriers experience FMF clinical symptoms, while others present with only mild or no symptoms, is largely unknown, but it is assumed that the MEFV gene mutations combined with other potential modifier genes and environmental factors determine the FMF phenotype [9,14].

Thus, we also speculated that the heterozygous state of the MEFV gene may be associated with the atypical inflammatory forms of FMF. Epigastic pain might be an incomplete FMF attack, and physicians should keep this in mind in high-risk populations.

Treatment for asymptomatic individuals with heterozygous mutations is unknown. Guidelines recommend that they should be followed with urine analyses [39]. Familial Mediterranean fever-like disease may initiate periodic follow-up, and administering colchicine should be considered. The patients with the ‘silent’ carrier status of two mutations (homozygous or compound heterozygous) could predispose to developing renal amyloidosis, and particularly patients with a family history of FMF should be administered colchicine prophylaxis [40]. In our study, we started colchicine therapy for FMF patients and patients who have an asymptomatic homozygous R202Q mutation and family history of FMF for increased risk of developing amyloidosis.

Conclusions. Our results demonstrated a high carrier rate of MEFV gene mutations in the EPS patients. The EPS patients showed only homozygous or compound heterozygous MEFV gene mutations. Eight patients with EPS were diagnosed with FMF and colchicine therapy was started. Thus, therapy-resistant EPS patients should also be examined for FMF, especially in high risk populations such as the Turks. However, additional and larger studies are needed to identify the association between EPS and FMF.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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