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ORIGINAL ARTICLE

# Is there an association between familial Mediterranean fever and celiac disease?

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**Abstract** Familial Mediterranean fever (FMF) and celiac disease (CD) shares some clinical features such as abdominal pain, diarrhea, arthralgia, and arthritis. Furthermore, both diseases are related to several inflammatory disorders. Based on these analogies, we have investigated whether there is any relationship between CD and FMF. The study had two groups. Group I: 50 children with FMF were questioned and examined for the evidence of CD, serum immunoglobulin A (IgA) levels, antigliadin antibodies (AGA) IgA, AGA IgG, and anti-endomysial antibodies (EMA) IgA were tested, and intestinal biopsy was performed when necessary. Group II: 17 children with CD were evaluated for the presence of clinical and laboratory features of FMF and mutation analysis for *MEFV* gene was performed to all of them. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the *MEFV* gene were studied. The results were as follows—group I: three patients had diarrhea, six had abdominal pain, one had positive AGA IgA, six had AGA IgG, and one had EMA IgA. Intestinal biopsy was performed in one patient who was normal, so none of the patients with FMF were diagnosed as CD and group II: none of the patients with CD had complaints consistent with FMF. Four of the 17 patients (23.5%) were found to carry *MEFV* mutations. Three of them had heterozygous p.E148Q mutation and one of them had heterozygous p.M680I mutation. None of the FMF patients had CD. *MEFV* mutation frequency in patients with CD was similar to the normal population in Turkey. Our study did not reveal any association between CD and FMF.

**Keywords** Celiac disease · Children · Familial Mediterranean fever

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## Introduction

Celiac disease (CD) is an immune-mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals [1]. Familial Mediterranean fever (FMF) is a genetic inflammatory disease, presenting with recurrent self-liming attacks of joint, chest, and abdominal pain associated with fever [2]. A large number of diseases have been reported to be associated with CD or FMF, many with a probable immunological pathogenesis [3–7]. FMF and CD share some clinical features including abdominal pain, diarrhea, arthralgia, and arthritis [8]. To the best of our knowledge, a relationship between CD and FMF in children has not been previously investigated. Since we are aware of a girl who had the diagnosis of FMF and CD, we undertook the present study to determine whether there is any relationship between CD and FMF.

## Materials and methods

Two study groups consisting of patients suffering from FMF and CD were prospectively studied between the June 2005 and March 2007. These were consecutive patients

attending the Pediatric Nephrology and Gastroenterology outpatient clinics who gave consent after reading the patient information sheet. The study was approved by the local research ethics committee.

In group I, consisting 50 patients with FMF, prevalence of CD was investigated. Diagnosis of FMF was established according to Tel Hashomer criteria [9]. The severity of the disease was estimated according to Tel Hashomer criteria, accounting for the age of onset, frequency of attacks at any site, presence of arthritis and erysipelas-like lesion, amyloidosis, and colchicine dosage [10]. None of the children was known to have CD. All patients were treated with colchicine. Their medical charts were reviewed and data obtained from each patient included the demographic characteristics, age at the diagnosis of FMF, and *MEFV* mutations. Patients with FMF were questioned and examined for evidence of CD. A specially designed questionnaire for the examination of CD was applied individually on each child (or his/her caregiver) by physician with subspecialty certification in pediatric gastroenterology. This questionnaire included sections assessing features of diarrhea (nature, onset, course, duration, frequency, severity, and its relation to other symptoms, impact on daily functioning), features of abdominal pain (intensity, frequency, duration, localization, type and impact on daily functioning), vomiting, nausea, fatigue, lack of appetite, weight loss, irritability, recurrent aphtous lesion, recurrent upper respiratory infection, constipation, convulsion, and menstrual dysregulation. The medical evaluation including medical history, family and social history, review of systems, and complete physical examination was performed in all participants. All patients were evaluated for serum immunoglobulin A level (IgA), serum IgA and IgG antigliadin antibodies (AGA), and IgA anti-endomysial antibodies (EMA). A small bowel biopsy for definite diagnosis of CD was offered for those in whom EMA IgA was positive and in patients with positive AGA IgG and low serum IgA levels.

In group II, 17 patients, all fulfilled the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition criteria for the diagnosis of CD, were evaluated for the presence of FMF [11]. Compliance with gluten-free diet was checked in all patients by EMA and AGA testing. None of the children was known to have FMF. Their medical charts were reviewed and data obtained from each patient included the demographic characteristics, age at the diagnosis of CD, type of CD, and duration of gluten-free diet. Seventeen patients with CD were questioned and examined for evidence of FMF. A specially designed questionnaire for the examination of FMF was applied individually on each child (or his/her caregiver) by physician with subspecialty certification in pediatric nephrology. This questionnaire included sections assessing characteristics of abdominal pain (type, severity, onset, duration, localization, frequency, impact on daily functioning, and its relation to other symptoms), lack of appetite, attacks of fever, chest pain, arthralgia, arthritis, muscle pain, and erysipelas like erythema. The medical evaluation including medical and family histories were asked. Review of the systems and complete physical examination were performed to all participants. Blood samples were taken from the patients for *MEFV* gene mutation analysis, complete blood count, C-reactive protein (CRP), fibrinogen, erythrocyte sedimentation rate (ESR), and urine analysis. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the *MEFV* gene were studied. Data are expressed as percentages and mean±SD.

### Laboratory assessment

IgA and IgG AGA assays were carried out by enzyme-linked immunosorbent assay (Aida GmbH, Germany). Cut-off values were 12 IU/mL set by the manufacturer. Semiquantitative immunofluorescence for the presence of anti-endomysial IgA antibody using a commercially available kit, employing monkey esophagus as the substrate (Scimedx in NJ, USA). Sample of duodenal mucosa was graded according to the modified Marsh classification [12].

### *MEFV* mutation analysis

DNA was isolated from peripheral blood lymphocytes by standard procedures. Exon 10 of the *MEFV* gene was screened using direct sequencing of the polymerase chain reaction (PCR) amplified fragments. Beckman Coulter cycle sequencing kits (CA, USA) and a Beckman Coulter CEQ 2000 XL automated sequencer were used during these investigations. The p.E148Q mutation was analyzed with a previously reported PCR–restriction fragment length polymorphism protocol [13].

## Results

### Prevalence of CD in FMF patients

Thirty of 50 patients with FMF were female, the mean age was 12.9±3.8 years (range, 4 to 18 years), and the mean duration of disease was 5.1±3.4 years. Disease severity was mild in ten (20%), moderate in 39 (78%), and severe in one patient (2%). The most frequent symptom was lack of appetite (30%) followed by vomiting (22%), weight loss (18%), fatigue (16%), abdominal pain (12%), recurrent oral aphtous lesion (10%), abdominal distention (6%), diarrhea (6%), menstrual dysregulation (6%), and constipation (2%; Table 1).

**Table 1** Results of questionnaire for celiac disease in patients with familial Mediterranean fever

| | Children with FMF ($n$=50) (%) |
|---|---|
| Lack of appetite | 15 (30) |
| Fatigue | 8 (16) |
| Abdominal pain | 6(12) |
| Vomiting | 11(22) |
| Weight loss | 9 (18) |
| Abdominal distention | 3(6) |
| Diarrhea | 3 (6) |
| Recurrent oral aphtous lesion | 5 (10) |
| Menstrual dysregulation | 3 (6) |
| Constipation | 1 (2) |
| Convulsion | 0 |
| Recurrent upper respiratory infection | 0 |

Three patients (6%) had diarrhea and abdominal distention suggesting CD. Dose of colchicine was 2 mg/day in one patient and 1.5 mg/day in two patients. Duration of diarrhea varied from 2 months to 2 years. Stool was watery and without mucus. Steatorrhea or bloody stool was not reported. In these children, stool examination was normal which was carried out for three different times. Screening tests for CD were negative in these patients.

Abdominal pain was noted in six patients (12%) which was localized in periumbilical area, spontaneously relieved within 5 or 10 min and did not interfere with activity. Abdominal pain was not associated with systemic findings such as fever, vomiting, and nausea.

Height and weight of all patients were within normal limits for age. Hepatomegaly and splenomegaly were detected in three (6%) and two (4%) patients, respectively. Physical examination was normal in other patients.

One (2%) patient (patient no. 1) had positive AGA IgA. This patient had normal serum IgA level and negative EMA IgA and AGA IgG. Six patients (12%; patient numbers 2–7) had AGA IgG, and these patients had normal serum IgA levels and negative EMA IgA and AGA IgA. Only one patient (patient no. 8) was positive for EMA IgA and negative for AGA IgA and IgG. Histopathological examination was normal in this patient (Table 2). As a result, none of the 50 FMF patients had CD.

## Prevalence of FMF in CD

Nine of 17 patients with CD were female; the mean age was 13.5±3.3 years (range, 5–18 years). Of 17 patients with CD, 13 (76%) were classical-type CD, three (23.5%) were atypical-type CD, and one (5.8%) was silent-type CD. Mean duration of gluten-free diet was 4.9±3.1 years. Results of both AGA and EMA tests were negative, confirming adherence to the diet in 11 children. Family history for FMF was positive in three patients (17.6%). Results of questionnaire for FMF in children with CD are shown in Table 3. Abdominal pain was noted in five patients (29.4%). Except for one patient, all were on strict gluten-free diet. Pain was commonly reported to be in the periumbilical area and occurred in the daytime, and it did not interfere with the activity. Stool changes were not reported. Abdominal pain relieved with defacation or passage of flatus. There were no alarm symptoms such as unexplained weight loss, gastrointestinal blood loss, recurrent vomiting, and fever. Lack of appetite and fatigue were detected in three patients (17.6%). None of the patients had arthralgia, arthritis, and chest pain. Physical examination was normal in all patients. As a result, none of the patients with CD had complaints consistent with FMF. Complete blood count, urine analysis, and acute phase reactants including CRP, ESR, and fibrinogen were normal in all patients. Four of the 17 patients (23.5%) were found to carry *MEFV* mutations. Three of them had heterozygous p. E148Q mutation and one of them had heterozygous p. M680I mutation. There was no family history for FMF in these patients, and all of them had classical CD. There was no difference for presentation and course of CD between children with and without *MEFV* mutation.

**Table 2** Result of celiac screening in patients with FMF

| Patient Number | Age | Sex | Serum IgA level | AGA IgA | AGA IgG | EMA IgA |
|---|---|---|---|---|---|---|
| 1 | 14 | Male | Normal | + | − | − |
| 2 | 10 | Female | Normal | − | + | − |
| 3 | 4 | Female | Normal | − | + | − |
| 4 | 13.5 | Female | Normal | − | + | − |
| 5 | 14 | Male | Normal | − | + | − |
| 6 | 18 | Male | Normal | − | + | − |
| 7 | 12 | Male | Normal | − | + | − |
| 8 | 18 | Female | Normal | − | − | + |

**Table 3** Results of questionnaire for familial Mediterranean fever in patients with celiac disease in patients

| | Children with CD ($n$=17) (%) |
|---|---|
| Lack of appetite | 3 (17.6%) |
| Fatigue | 3 (17.6%) |
| Abdominal pain | 5 (29.4%) |
| Fever attack | 0 |
| Arthritis and/or arthralgia | 0 |
| Chest pain | 0 |
| Muscle pain | 0 |
| Erysipelas like erythema | 0 |

## Discussion

One of genes for FMF, *MEFV*, encodes a protein called pyrin which participates in the regulation of apoptosis, inflammation, and cytokine processing. Mutations in the *MEFV* gene prevent the normal pyrin-mediated negative feedback mechanism and trigger inflammation [2]. Increased transcription of the proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-8 has been reported in sera and cultured monocytes of FMF patients [14]. Several studies suggested that having a *MEFV* mutation might act as an additional susceptibility factor in inflammatory conditions [5, 15]. The prevalence of *MEFV* gene mutations were investigated in some of these inflammatory diseases. Gershoni-Baruch et al. [16] evaluated the frequency of *MEFV* mutations in patients with Henoch–Schönlein purpura and found homozygous or heterozygous mutations in 27% of the patients. Patients with Behçet disease were found to have higher frequency of *MEFV* gene mutations than the control group [15]. Similarly, Tutar et al. [17] showed that *MEFV* mutations were more frequent among patients with rheumatic heart disease than in the normal population in Turkey.

Celiac disease is precipitated, in genetically predisposed persons, by the ingestion of gluten. Today, there is evidence that CD is a T cell-mediated chronic inflammatory bowel disorder. It is known that cytokines play an important role in the pathogenesis of CD. In susceptible individuals, activation of T cells results in release of proinflammatory mediators by a Th1 pattern dominated by interferon-γ causing damage to enterocytes resulting in villous atrophy. Activated T cells not only induce a Th1 cytokine response but also stimulate B lymphocytes and epithelial cell apoptosis [18, 19].

FMF and CD share some clinical features such as abdominal pain, diarrhea, arthralgia, and arthritis and tend to be commonly associated with other inflammatory and autoimmune diseases. To our knowledge, a relationship between CD and FMF has not been previously investigated in children. In adults, the association between CD and FMF was investigated by Mor et al. [20]. These authors suggested that intestinal damage in CD might lead to colchicine malabsorption, thus CD might be the underlying mechanism of colchicine treatment failure in FMF. They examined 50 FMF patients—with and without diarrhea—for CD, but none of them had positive EMA IgA. So, they could not support their hypothesis.

We have recently encountered a patient with FMF and CD. We hypothesized that inflammation induced by FMF may trigger potentially pathogenic intraepithelial lymphocytes and in genetically susceptible individuals for CD, this may turn into a persistent pathogenic signaling. Therefore, we planned this study. Although symptoms suggesting CD such as diarrhea, abdominal pain, and distention were observed in some patients, using both AGA and EMA as screening tests, followed by gold standard upper gastrointestinal endoscopy and biopsy, we found no evidence of CD in children with FMF.

In our study, abdominal pain was recorded in some patients with CD. However, features of pain were different from abdominal pain that can be seen in FMF. None of the patients had joint manifestations or fever attacks. By screening a small population of patients with CD, we have found no case of FMF. The frequency of *MEFV* mutations in celiac patients was 23.5% which was similar to the normal population in Turkey [21]. The *MEFV* genotype has been reported as an independent modifier of disease severity in other inflammatory diseases, such as multiple sclerosis and Crohn's disease [5, 22]. In our study, presentation and course of CD appeared to be similar in carriers and noncarriers. It seems that being a *MEFV* carrier does not affect the clinical manifestations of CD. The relatively small sample size may be a limitation for our study. Studies with larger populations would bring more accurate results.

Our study shows that lack of appetite and fatigue were the most common symptoms in both FMF and CD, but these symptoms were nonspecific. FMF and CD shared some clinical features such as abdominal pain, diarrhea, and abdominal distention; however, features of these symptoms were different. We emphasize that detailed information about these symptoms such as nature, onset, duration, frequency, severity, and its relation to other symptoms is helpful for differential diagnosis.

In conclusion, we have found no support for a relationship between CD and FMF and do not recommend screening for CD in every patient with FMF or screening for FMF in every patient with CD, unless there are symptoms such as chronic diarrhea, growth failure, delayed puberty, anemia, or arthropathy.

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