Paediatr Croat. 2012;56:257-259

A PEDIATRIC PATIENT WITH FAMILIAL MEDITERRANEAN FEVER PRESENTED WITH VOMITING

NUR ARSLAN, PINAR GENCPINAR, BALAHAN MAKAY, ELCIN BORA, ERBIL UNSAL*

Familial Mediterranean fever is inherited as an autosomal recessive trait affecting mainly persons of Mediterranean descent, especially Arabs, Jews, Armenians and Turks. Fever, peritoneal and pleural inflammation, arthritis, erysipelas-like erythema, and arthralgia are well known features of familial Mediterranean fever. We herein report a three-year-old boy, who presented with vomiting and agitation attacks and was found to be a compound heterozygote for M694V/M680I mutation of the MEFV gene.

Descriptors: CHILD, PRESCHOOL; FAMILIAL MEDITERRANEAN FEVER; VOMITING

INTRODUCTION

Familial Mediterranean fever (FMF), also known as paroxysmal polyserositis, is an autosomal recessive inflammatory disease characterized by recurrent attacks of fever and inflammation of serosal membranes, resulting in acute abdominal, chest, and/or joint pain. The prevalence of FMF in Turkey is 1/1000 and the carrier rate is 1:5 (1-3). Consanguinity rate was found to be remarkably high (40.3%) in the families of children with FMF in Turkey (4). The marenostrin-encoding fever gene (*MEFV*) was recently cloned, and four missense mutations (M694V, M680I, M694I and V726A) have been identified in a large proportion of affected patients (5, 6). Pyrin/marenostrin, a product of the *MEFV* gene, is expressed in polymorphonuclear cells and monocytes, and is thought to regulate inflammatory responses at the level of leukocyte cytoskeleton organization. The most common clinical symptoms are fever, abdominal pain, arthritis, arthralgia, chest pain, myalgia, headache, and diarrhea.

* Dokuz Eylul University Medical Faculty, Department of Pediatrics Division, Turkey

Correspondence to:
Nur Arslan, MD, Dokuz Eylul University Medical Faculty, Department of Pediatrics İzmir, Turkey, e-mail: nur.arslan@deu.edu.tr

Frequent regurgitation alone affects over half of newborns, but generally resolves with age, affecting fewer than 5% of children after their first year (7, 8). Gastrointestinal signs, especially vomiting, are rare in FMF. In this article, we present a 3-year-old male patient who was admitted for recurrent vomiting and eventually diagnosed as FMF and confirmed by mutation analysis.

CASE REPORT

A 3-year-old male patient was admitted with the complaints of recurrent vomiting and respiratory tract infections. The vomiting had begun in the first days of life and it recurred 8-10 times daily. During this period, the patient had normal growth. A diagnostic work-up for the etiology of the vomiting was undertaken: electrolytes, upper gastrointestinal radiographic series and ultrasound were normal and specific immunoglobulin E to cow's milk was negative. Frequent feeding, small meals and solidification of foods were advised and his vomiting gradually decreased during the first year of life. His weight gain was normal during this period.

Thereafter, the child had no particular complaints, but in the last six months, vomiting episodes started recurring every 3-4 weeks (6-7 times/day for several days), sometimes with crying and pulling of the legs to the abdomen. High fever was detected during two of the attacks; the patient was hospitalized and treated with intravenous fluids and antibiotics with the diagnosis of respiratory tract infections. There were no complaints of diarrhea or constipation. It was first thought that vomiting may have been due to gastroesophageal reflux disease. Despite anti-reflux treatment, his vomiting episodes continued and he was admitted to our hospital at this stage. The parents stated that his appetite was normal between the vomiting episodes and he had normal weight gain. There was no consanguinity between the parents. Fever and abdominal pain attacks and dyspepsia were not detected in the family history.

On admission, the patient was in the non-vomiting phase. His weight (13.5 kg, 25-50 p) and height (94 cm, 25-50 p) were within the normal limits. On physical examination, there was no rash, hepatosplenomegaly or epigastric tenderness, and the lungs were normal on auscultation. Other physical findings were normal.

The patient was evaluated for the etiology of vomiting. The patient was in the non-vomiting phase while the initial laboratory work-up was performed. Complete blood count, routine urine analysis, blood glucose, electrolytes, liver and kidney

function tests, serum immunoglobulin levels, serum ammonia and blood gases were tested and found to be normal. Erythrocyte sedimentation rate was 6 mm/h (normal range: 0-15 mm/hour) and C-reactive protein 0.96 mg/L (normal range: 0.1-8.2 mg/L). Anti-gliadin and anti-endomysium antibodies and stool examination for fat were negative. Skin prick test for foods and other allergens was negative. Abdominal ultrasonography was normal. Because of the periodic vomiting episodes accompanied by high fever on two occasions, a genetic study for FMF was performed in Dokuz Eylul University Medical Faculty Department of Genetics, and M680I/M694V mutations were detected. Colchicine 0.5 mg/day was started.

On his 3-year follow-up, his weight and height were at 50th percentile. His vomiting episodes regressed. In this period, he had two episodes accompanied by abdominal pain and fever lasting for 3 days. At the time of these episodes, his white blood cell count was 12 000/mm^3 and 20 000/mm^3, and his C-reactive protein 20 mg/L and 12 mg/L, respectively. After the second episode, his colchicine dose was increased to 0.75 mg/day. He did not have any complaints in the last year. His blood glucose, liver and kidney function tests and urinalysis were normal on his last visit. His acute phase reactants were also within the normal limits.

DISCUSSION

In this article, a 3-year-old patient is described whose primary complaint was periodic vomiting despite gastroesophageal reflux treatment and who was diagnosed as FMF on the basis of mutation analysis. To our knowledge, FMF presenting with recurrent vomiting episodes is rare. At a very young age, as in our patient, abdominal pain may not be recognized and vomiting can be the predominant finding during the attacks. On the other hand, the absence of other objective findings such as pleurisy, peritonitis, arthritis, erysipelas-like rash and splenomegaly may be related to the patient's younger age. In a study including pediatric FMF patients, it was found that serositis was detected in later years (mean age of patients who had only fever: 1.7±1.6 yrs *vs*. patients with serositis 5.0±4.1 yrs, p<0.0001) (9). In addition, 80% of the FMF patients had only fever during their attacks; abdominal pain, erysipelas-like rash and chest pain were added to the fever a few years later (9). Because of our patient's young age, vomiting could have been the major finding during his attacks, rather than the more specific signs and symptoms of polyserositis.

The most predictable finding was vomiting during FMF attacks in our patient. The M680I/M694V mutation was detected by genotype analysis. Gastrointestinal involvement is not rare in FMF patients. Intestinal amyloidosis, intestinal obstruction, ascites, diarrhea, hepatosplenomegaly, elevated liver enzymes, and inflammatory bowel disease are among the findings that can be seen (10). In a study including 124 pediatric FMF patients, diarrhea (10%), hepatomegaly (6.5%) and vomiting (5.6%; only 7 patients) were detected (4). No particular genotype was associated with vomiting in that study. Additional symptoms and age distribution of patients with vomiting were not investigated. In another study including adults, vomiting was found in 54% during attacks in patients carrying heterozygous M680I mutation, but it was not significantly different from other genotypes (11). Our patient's heterozygous genotype including M680I mutation can be associated with vomiting.

In our patient, not every vomiting episode was accompanied by fever. The clinical spectrum of FMF has expanded in recent years and many patients with atypical presentations were identified (12, 13). Özçakar et al. (12) report on a patient with recurrent vomiting episodes lasting for one month and accompanied by abdominal pain, who was finally diagnosed as FMF. Like our patient, this patient also did not have fever during the attacks.

In children whose FMF symptoms begin early in life, the time lag to diagnosis is longer than in patients whose symptoms begin later (9, 14). In their study including 814 patients, Padeh et al. (14) showed that delay in diagnosis was 3.2±3.2 years in patients whose symptoms began before 2 years of age, whereas it was 1.9±7.2 years in patients whose symptoms began later (p<0.001). In our patient, periodic emesis episodes began after the age of 2 years. The diagnosis of FMF was made after six-month follow-up with careful history and keeping the FMF diagnosis in mind.

In conclusion, vomiting is a rare manifestation of FMF. Especially in young children, objective findings of FMF such as rash, arthritis and splenomegaly cannot be detected by the physicians, and vomiting may be the only symptom. FMF should be taken in consideration on differential diagnosis in young children in whom vomiting is not a consequence of gastroesophageal reflux or other gastrointestinal obstructive or inflammatory diseases, especially if accompanied by fever.

Autori izjavljuju da nisu bili u sukobu interesa.
Authors declare no conflict of interest.

REFERENCES

1. Ozen S, Karaaslan Y, Ozdemir O, et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a Weld study. J Rheumatol. 1998;25:2445-9.
2. Dinc A, Pay S, Turan M, et al. Prevalence of familial Mediterranean fever in young Turkish men. Clin Exp Rheumatol. 2000;18:292.
3. Yilmaz E, Ozen S, Balci B, et al. Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet. 2001;9:553-5.
4. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet. 1997;17:25-31.
5. International FMF Consortium. Ancient missense mutations in a new member of the Roret gene family are likely to cause familial Mediterranean fever. Cell. 1997;90:797-807.
6. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during childhood – A pediatric practice-based survey. Arch Pediatr Adolesc Med. 2000;154:150-4.
7. Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498-547.
8. Padeh S, Livneh A, Pras E, et al. Familial Mediterranean fever in children presenting with attacks of fever alone. J Rheumatol. 2010;37:865-9.
9. Mor A, Gal R, Livneh A. Abdominal and digestive system associations of familial Mediterranean Fever. Am J Gastroenterol. 2003;98:2594-604.
10. Inal A, Yılmaz M, Kendirli SG, Altıntaş DU, Karakoç GB. The clinical and genetical features of 124 children with familial Mediterranean fever: experience of a single tertiary center. Rheumatol Int. 2009;29:1279-85.
11. Çağlayan AO, Demiryılmaz F, Özyazgan I, Gümüş H. MEFV gene compound heterozygous mutations in familial Mediterranean fever phenotype: a retrospective clinical and molecular study. Nephrol Dial Transplant. 2010;25:2520-3.
12. Ozçakar ZB, Yalçinkaya F, Yüksel S, Ekim M. The expanded clinical spectrum of familial Mediterranean fever. Clin Rheumatol. 2007;26:1557-60.
13. Majeed HA, Rawashdeh M, el-Shanti H, Qubain H, Khuri-Bulos N, Shahin HM. Familial Mediterranean fever in children: the expanded clinical profile. QJM. 1999;92:309-18.
14. Padeh S, Livneh A, Pras E, et al. Familial Mediterranean fever in the first two years of life: a uniqe phenotype of disease in evolution. J Pediatr. 2010;156:985-9.

S a ž e t a k

OBITELJSKA MEDITERANSKA GROZNICA S POVRAĆANJEM U TROGODIŠNJEG DJETETA

N. Arslan, P. Gencpınar, B. Makay, E. Bora, E. Ünsal

Obiteljska mediteranska groznica nasljeđuje se autosomno recesivnim putem i zahvaća uglavnom osobe mediteranskih korijena, poglavito Arape, Židove, Armence i Turke. Dobro poznata obilježja obiteljske mediteranske groznice su vrućica, upala peritoneuma i pleure, artritis, eritem nalik erizipelu i artralgija. Opisuje se slučaj trogodišnjeg dječaka koji je dovezen zbog povraćanja i izraženog nemira; utvrđeno je da je dječak složeni heterozigot za mutaciju M694V/M680I gena MEFV.

Deskriptori: DJETE, PREDŠKOLSKO; OBITELJSKA MEDITERANSKA GROZNICA; POVRAĆANJE

Primljeno/Received: 7. 12. 2011.
Prihvaćeno/Accepted: 9. 5. 2012.