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Case Report

FAMILIAL MEDITERRANEAN FEVER: UNUSUAL AGE OF PRESENTATION AND THE ROLE OF GENETIC DIAGNOSIS

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Familial Mediterranean fever (FMF) is a genetic disease characterized by periodic fever and/or painful inflammatory manifestations. Repeated attacks at irregular intervals and in an unpredictable sequence are typical of the disease. Most of the patients become symptomatic between ages 5 to 15 years. Rarely, the disease may manifest as early as during the first year.

Until recently, the diagnosis of FMF was mainly based on the presence of typical clinical picture and dramatic response to colchicine. Recent insight to the genetic basis of the disease has made DNA study available for diagnosis of FMF. We report a 20-month-old Iranian boy with recurrent attacks of abdominal pain and fever since the 4th month of birth. A molecular analysis was carried out, confirming mutation of the FMF-gene.

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Introduction

Familial Mediterranean fever (FMF) is an inherited, recurrent inflammatory disease prevalent among people of the near East, Arabs, Turks, Armenians, and Sephardic Jews. It is transmitted as an autosomal recessive trait. Symptoms usually appear between 5 and 15 years of age, but may begin earlier. The febrile, painful attacks are the hallmark of the disease and characterized by marked elevation of body temperature, acute inflammation of peritoneum, synovia or pleura, a duration of 12 to 48 hours, and complete health between attacks. Repeated attacks at irregular intervals and in an unpredictable sequence are typical of the disease.[1]

The most frequent manifestation is the painful, usually febrile abdominal attack, experienced by 90% of patients; in 68% of them it is the presenting sign.[2] Other less frequent manifestations include arthritis (75%),[3] pleuritis (45%), myalgia (20%), erysipelas—like erythema (11%), orchitis, headache, meningitis, convulsion,[4] adhesive small bowel obstruction (3%),[5] mild splenomegaly, hepatomegaly, Henoch-Shonlein purpura (5%), polyarteritis nodosa (1%),[6] and recurrent hyperbilirubinemia.[7]

The most ominous complication of FMF is amyloidosis, potentially leading to chronic renal failure.[8] Laboratory abnormalities are usually found during attacks and include leukocytosis (up to 30,000/mm^3), high ESR, and elevated acute phase reactants.[9] Attacks of FMF can be prevented by prophylactic colchicine therapy at a dose of 0.02 to 0.03 mg/kg/24 hr (maximum of 2 mg/24 hr) in one or two divided doses.[10]

Until recently the diagnosis of FMF was based on the typical clinical picture and the dramatic response to colchicine therapy. Several sets of criteria have been proposed for the diagnosis of FMF.[11-16] None of the existing criteria have become widely accepted and only one has been based on statistical evaluation with defined sensitivity and specificity. [16] The diagnosis of FMF has been revolutionized since 1997, when missense mutations in the Mediterranean fever gene (MEFV) on chromosome 16 were found to be responsible for the disease. [17 – 21]

We report an Iranian male infant with recurrent

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attacks of abdominal pain and fever, who finally was confirmed to have FMF by DNA study.

Case Report

A 20-month-old boy presented to the hospital because of recurrent abdominal pain. The patient had been well until the age of 4 months, when he began to have two or three bouts of abdominal pain weekly. The abdominal pain lasted about 30 minutes and was accompanied by irritability, restlessness, crying, and nonprojectile vomiting. These symptoms were followed by fever in the range of 39 to 40°C, which was continued for 16 to 24 hours. The episodes repeated roughly every three days. Antipyretics such as acetaminophen caused partial relief of the symptoms. During these episodes there were no associated symptoms or other complaints, and between attacks the patient was well. He had no history of chronic diarrhea, vomiting, or weight loss.

He was a full-term infant with a birth weight of 3.3 kg. His Apgar score was 9 at 5 minutes. He was breastfed until 20 month of age. His immunizations were up to date. There was a history of hypertension, atrial septal defect, and ovarian cyst among the patient's relatives. There was no family history of hereditary disorders, hemoglobinopathies, periodic fever, or abdominal pain syndromes. The boy was 85 cm tall (50% of percentile) and weighed 12.5 kg (60% of percentile).

Physical examination was normal and showed no abdominal tenderness or organomegaly. The results of laboratory studies are shown in Tables 1 – 3. Repeated peripheral blood smears were negative for *Borrelia* and malaria. Chest X-ray, abdominal ultrasonography, electroencephalography, brain CT-scan without contrast, and barium enema were normal.

Fulfilling the diagnostic criteria of Livneh et al[16] and based on the clinical presentations and laboratory data, the diagnosis of FMF was proposed and in June of 1998 he was started on colchicine at a daily dose of 0.25 mg, after which the pain episodes became less frequent with intervals of 10 to 30 days.

Table 1. Hematological values.

Variable	Value
Hb (g/dL)	12.2
Hematocrit (%)	34.7
ESR (mm/hr)	31
RBC (per mm^3)	4,900,000
WBC (per mm^3)	12,400
Platelet count (per mm^3)	469,000
WBC Differential count (%)	
Neutrophils	77
Lymphocytes	21
Monocytes	2
Eosinophils	2

Table 2. Blood chemical values.

Variable	Value	Normal range
BUN (mg/dL)	5	5 – 18
Creatinine (mg/dL)	0.5	0.3 – 0.7
Calcium (mg/dL)	9.4	8.8 – 10.8
Phosphorus (mg/dL)	4.5	3.8 – 6.5
AST (U/L)	43	5 – 46
ALT (U/L)	25	5 – 46
LDH (U/L)	648	109 – 245
Alkaline phosphatase	390	15 – 113

He was referred to Children's Medical Practice, Johns Hopkins Bayview Medical Center on March 19, 1999 for genetic analysis. Genetic testing for FMF was performed at the National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland. The MEFV gene mutations were investigated in the patient. DNA was extracted from the peripheral blood lymphocytes according to the standard procedures. Mutation identification was performed with two previously-described PCR-based methods: the amplification refractory mutation system (ARMS) and restriction-enzyme analysis.[22 – 26] As a result, two FMF-associated mutations in patient's DNA sample were identified. He was tested for a panel of 13 known FMF mutations and found to be a carrier for the M694V and R761H mutations. This finding strongly supported the diagnosis of FMF. Subsequently, the colchicine dose increased to 1 mg daily and abdominal pain episodes were completely resolved.

Discussion

The constellation of typical symptoms and signs in this 20-month-old boy as well as his susceptible ethnic background suggested the diagnosis of FMF. The unusual age of presentation, however, and the incomplete response to initial management by colchicine (0.25 mg per day) were not so reassuring. Therefore, the patient was subjected to genetic study, which ultimately confirmed the diagnosis.

Although the peculiar ethnic restriction and the familial aggregation in FMF had suggested a genetic etiology, it was not until 1997 when mutation in the gene MEFV was distinctly found to be responsible for the disease.[25, 27] The gene is

Table 3. Additional laboratory findings.

Variable	Value	Normal range
Serum IgG (mg/dL)	740	345 – 1236
Serum IgA (mg/dL)	46	14 – 159
Serum IgM (mg/dL)	130	43 – 207
Serum IgE (U/mL)	136	0 – 230
CD 3 (%)	61.8	55 – 82
CD 4 (%)	41.6	27 – 57
CD 8 (%)	11	14 – 34
CD 19 (%)	20.8	9 – 22
HLA-DR (%)	27.3	
NBT (%)	98	80 – 100
ANA	Negative	
Anti-DNA (IU/mL)	4.7	0 – 7
ANCA	Negative	
HbsAg	Negative	
Anti-HCV	Negative	
C3 (mg/dL)	97	50 – 120
C4 (mg/dL)	32	20 – 50
CH 50 (% pool)	90	70 – 130
Direct Coombs test	Negative	
Urinalysis	Normal	

located on chromosome 16 and contains 10 exons and 781 codons.[28] So far, 29 mutations, mostly located in the last exon, have been identified to be associated with FMF. Five of them account for up to 91% of FMF chromosomes that are: V726A, M694V, M680I, M694I, and B148Q.[29, 30]

In our case, DNA study showed two mutations in MEFV alleles identified as R761H and M694V. The latter is one of the known prevalent mutations. It has been known that the frequencies and distribution of mutations, vary between different ethnic groups.[31 – 34] While there is no data to demonstrate that these differences may have a role in phenotypic characteristics of FMF patients (i.e. causes different kinds of symptoms in individual patients), there are some evidence to relate the diversity of mutations to severity of the disease. For instance, it has been suggested that the presence of homozygous M694V mutation is significantly associated with a more severe form of disease characterized by earlier age of presentation and more frequent and prolonged abdominal attacks. Homozygousity for M694V mutation predominates among North African Jews and is associated with a severe course and more guarded prognosis. This mutation is less common among Arabs and, when present, occurs almost only in heterozygous form.[35] The detection of M694V mutation in our case not only is consistent with diagnosis of FMF but also may explain the increased disease severity characterized by the early age of presentation and high frequency of painful abdominal attacks.

The gene MEFV encodes for a 781-amino acid protein called pyrin.[36] Homology searches indicate that pyrin is a new member of the RetRo gene family and suggests that pyrin itself may be a transcription factor presumably regulating the expression of target genes, at least some of which are probably involved in the suppression of inflammation. The gene is expressed in neutrophils, but not lymphocytes and monocytes. Therefore, it is not surprising that neutrophils are the main inflammatory cells involved in FMF attacks and colchicine, which specifically inhibits polymorphonuclear leukocyte function, is so effective in preventing the attacks.[37]

Sixty-five percent of patients enjoy complete remission of attacks after treatment with colchicine.[38] Partial remission, defined as either a significant decrease in the frequency and severity of all forms of attacks or the remission of one form (usually abdominal) but not of another (usually arthritic) is experienced by the rest 30%. The response to colchicine could be dose-dependent, although the gastrointestinal side effects may limit achieving the optimal dose.[39] The clinical response to colchicine should be considered as a strong evidence for diagnosis of FMF. Our case experienced a partial response on 0.25 mg daily colchicine doses. A complete clinical remission was observed by increasing the dose to 1 mg per day, further supporting the diagnosis.

In summary, the clinical suspicion of FMF in this 20-month-old Iranian boy was confirmed by DNA study and complete clinical response to colchicine. Molecular analysis of FMF should complement the investigation of at least a subset of patients with difficult diagnosis. This test enables a definite diagnosis of the disease and may promote the diagnosis and treatment of patients with an unusual or incomplete clinical picture of FMF.[40, 41]

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