Egypt J Pediatr Allergy Immunol 2004; 2(2):111-113.

Continuous Medical Education

Familial Mediterranean fever

Zeinab A. El-Sayed, MD
Professor of Pediatrics, Ain Shams University.

INTRODUCTION

Familial Mediterranean Fever (FMF) is a recessive genetic disease characterized by recurrent brief self limited episodes of fever and polyserositis which if untreated may pass into end-stage renal disease due to the development of amyloidosis. FMF is one of the hereditary periodic fever syndromes (HPFSs) that include also hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and tumor necrosis factor receptor superfamily 1A-associated periodic syndrome (TRAPS).

The disease occurs within families and is much more common in individuals of Mediterranean descent mainly Sephardic Jews, Armenians, Arabs and Turks.

Arabs (from 1 study) are reported to have a prevalence of 1 case per 2600 population in children and a gene frequency of 1:50.

AETIOPATHOGENESIS

The disease is caused by missense and nonsense mutations in the MEFV gene that is located on the short arm of chromosome 16. This gene codes for a protein known as pyrin (because of the predominance of fever) that is expressed on neutrophils. Five different mutations were discovered and may explain the phenotypic differences observed among patients. Contrary to the methionine-694-valine mutation, which heralds a more severe disease and a higher incidence of amyloidosis, the valine-726-alanine mutation is associated with a milder disease.

The dysfunction of the protein pyrin results in deficiency of an inhibitor of a chemotactic factor (C5a). As a result, accumulation of C5a occurs in response to a minor inflammatory stimulus precipitating overt inflammation.

In a recent study, elevation of sIL-2R and IL-6 levels both before and during the attacks was noticed suggesting the existence of continuous cytokine activation in patients with FMF. The fact that there was no significant increase in the IL-10 levels during attacks supports the notion that compensation by the anti-inflammatory IL-10 does not seem to occur.

CLINICAL MANIFESTATIONS

The onset of the disease occurs before the age of 5 years in more than 60% of cases and before 20 in 90%. An onset as early as 6 mo has been reported. The preeminent feature of FMF is the paroxysmal attack that classically starts without warning, although some patients may be able to detect premonitory symptoms. The attacks usually last 48-96 hours. The typical attack manifests as fever +/- abdominal pain, arthralgia and chest pain.

- Fever: Temperature rises rapidly to 38-40°C and may precede other manifestations. In mild attacks, fever may be the only manifestation.
- Polyserositis:
  - Peritoneal manifestations: Almost all patients with FMF develop abdominal pain that may progress to peritonitis, resembling surgical abdomen. The abdomen is board like with abdominal tenderness and decreased bowel sounds. Patients frequently have appendectomies for the abdominal episodes if FMF has not been recognized. Often, patients will develop constipation during the attack and diarrhea after the attack resolves.
  - Pleuritis and pericarditis: The frequency of these attacks varies among ethnic groups, with 25-80% of patients reporting pleuritic chest pain. Effusions may occur occasionally. Pericarditis may develop, but tamponade and constrictive pericarditis are very rare.
- Musculoskeletal manifestations:
  - Arthralgia or even arthritis is common mostly affecting the knees, ankles, and wrists. Between the attacks, the joints are normal, and permanent damage does not occur.
  - Severe myalgia lasting 3-6 weeks has been described more recently.
- Dermatologic manifestations: An erysipelas-like rash (a well-demarcated, erythematous, warm rash with swelling) on the lower extremities, particularly below the knee, is reported in as many as 50% of patients.
- Female patients may have episodes of pelvic inflammatory disease. In males, inflammation of the tunica vaginalis testis may mimic episodes of testicular torsion.

- Vasculitis: An increased frequency of Henoch-Schönlein purpura and polyarteritis nodosa (PAN) is reported in FMF.
- Amyloidosis: In about one third to one half of untreated FMF, amyloid AA nephropathy develops presenting as proteinuria progressing to nephrotic syndrome. Renal failure inevitably occurs in some ethnic groups. Renal disease may be the presenting event in some patients with a family history of FMF. Renal vein thrombosis may develop in nephrotic patients.

Some patients may develop intestinal amyloidosis, leading to malabsorption.

DIFFERENTIAL DIAGNOSES

Acute Rheumatic Fever
Surgical abdomen
Pericarditis
SLE and other vasculitis syndromes
Other hereditary periodic fever syndromes (HPFSs)

LABORATORY DIAGNOSIS

- During the attacks, the erythrocyte sedimentation rate, the white blood cell count and acute phase reactants, such as C-reactive protein and serum amyloid A (SAA) protein, are elevated.
- Urine analysis may reveal proteinuria, indicative of amyloidosis, or less commonly hematuria.
- Renal biopsy or, alternatively, submucosal rectal biopsy, stained with Congo red, is indicated in FMF patients particularly those of North African descent who have proteinuria.
- A rapid test for the most common mutations have been developed from the successful cloning of the MEFV gene.

TREATMENT

The most important aspect of medical care is to make the correct diagnosis and to institute therapy as early as possible.

Colchicine is so effective in preventing the attacks of FMF and the development of amyloidosis. Colchicine may also lead to partial regression of existing amyloid nephropathy.

Ashkenazi Jewish people and Armenians in America seem to be at extremely low risk of amyloidosis and may need to be treated only to prevent attacks. If the attacks are rare and the patient can determine when an attack is beginning, treatment with intermittent colchicine at the onset of an attack may be sufficient therapy.

Treatment with weekly IV colchicine injections in addition to oral colchicine therapy is effective and safe in patients with FMF refractory to oral colchicine.

Colchicine dose:

0.02-0.03 mg/kg/24 hr in 1 or 2 divided doses. In patients who do not respond to twice a day dosing, administer colchicine 3, or even 4, times a day (maximum 2 mg/24 hr).

Children less than 5 years of age might need colchicine doses as high as 0.07 mg/kg/day or 1.9 mg/m^2/day.

Contraindications:

Documented hypersensitivity, severe renal, hepatic, or cardiac disorders, and blood dyscrasias.

Side effects and toxicity:

- Colchicine can induce bone marrow suppression. A young patient with FMF has been reported to develop leukopenia each time she took colchicine. In such circumstances, colchicine should be continued in conjunction with injections of granulocyte colony-stimulating factor (G-CSF).
- Some patients develop lactose intolerance and may respond to a lactose-free diet. In patients who have difficulty tolerating colchicine, start therapy at 4 times a day dosing and gradually increase.
- Clinicians should be aware that colchicine can induce myopathy in patients with FMF who have normal renal and hepatic function.
- Coadministration of colchicine and macrolides may impair colchicine elimination, resulting in excess drug exposure and toxicity. This manifests as fever, abdominal pain, diarrhea, dehydration, pancytopenia, metabolic acidosis, and alopecia.

Other lines of therapy:

- Non steroidal anti-inflammatory drugs and oral prednisone may be indicated for severe musculoskeletal symptoms.
- In patients who do not respond to colchicine, the use of interferon-alpha or the tumor necrosis factor (TNF)–blocking drug etanercept may be effective.
- Hemodialysis is indicated in patients who develop renal failure. Peritoneal dialysis tends to increase the number of abdominal attacks.
- Renal transplantation: The long-term outcome of transplantation in patients with amyloidosis secondary to FMF is similar to that in the general transplant population and maintenance colchicine, even at low dose, appears to

effectively prevent recurrence of amyloidosis in the allograft.

PROGNOSIS

- Patients who are compliant with daily colchicine probably can expect to have a normal lifespan if colchicine is started before proteinuria develops.
- Death results from infections, thromboembolism or uremia.

BIBLIOGRAPHY

Bagci S, Toy B, Tuzun A, Ates Y, Aslan M, Inal A, et al. Continuity of cytokine activation in patients with familial Mediterranean fever. Clin Rheumatol 2004;23(4):333-7.

Ben-Chetrit E, Navon P. Colchicine-induced leukopenia in a patient with familial Mediterranean fever: the cause and a possible approach. Clin Exp Rheumatol 2003;21(4 Suppl 30):S38-40.

Calguneri M, Apras S, Ozbalkan Z, Ozturk MA. The efficacy of interferon-alpha in a patient with resistant familial Mediterranean fever complicated by polyarteritis nodosa. Intern Med 2004;43(7):612-4.

Calguneri M, Apras S, Ozbalkan Z, Ozturk MA, Ertenli I, Kiraz S. The efficacy of continuous interferon alpha administration as an adjunctive agent to colchicine-resistant familial Mediterranean fever patients. Clin Exp Rheumatol 2004;22(4 Suppl 34):S41-4.

Gedalia A. Familial Mediterranean fever. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics, 16th ed. Philadelphia: WB Saunders 2000:724.

Keven K, Sengul S, Kutlay S, Ekmekci Y, Anadol E, Nergizoglu G, et al. Long-term outcome of renal transplantation in patients with familial Mediterranean fever amyloidosis: A single-center experience. Transplant Proc 2004;36(9):2632-4.

Lange-Sperandio B, Mohring K, Gutzler F, Mehls O. Variable expression of vasculitis in siblings with familial Mediterranean fever. Pediatr Nephrol 2004;19(5):539-43.

Lidar M, Kedem R, Langevitz P, Pras M, Livneh A. Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. J Rheumatol 2003;30(12):2620-3.

Meyerhoff J. Mediterranean fever, familial. Cited on: http://www.emedicine.com/med/topic1410.htm. Sep 7th, 2004.

Ozkaya N, Yalcinkaya F. Colchicine treatment in children with familial Mediterranean fever. Clin Rheumatol 2003;22(4-5):314-7.

Rollot F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kelaidi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. Ann Pharmacother 2004;38(12):2074-7.

Touitou I, Lesage S, McDermott M, Cuisset L, Hoffman H, Dode C, et al. Infevers: an evolving mutation database for auto-inflammatory syndromes. Hum Mutat 2004;24(3):194-8.