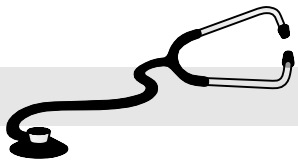

Infantile Familial Mediterranean Fever

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Familial Mediterranean fever is an autosomal recessive disorder characterized by recurrent attacks of fever and polyserositis. Most patients begin to suffer during childhood – 60% before the age of 10 and 90% before age 20. The disease is characterized mainly by fever with abdominal pain and/or arthritis. Some patients suffer from episodes of pleuritis, erysipelas-like disease, orchitis, and pericarditis [1]. An accurate diagnosis of FMF based upon clinical features alone may be difficult to establish in very young children due to the array of non-specific clinical manifestations in this age group. The recent cloning of the *MEFV* gene and its various mutations has improved our ability to more rapidly diagnose this intriguing disease [2]. In addition, molecular testing helps to establish the diagnosis of patients with FMF in the absence of the full clinical syndrome, thus allowing the institution of colchicine therapy to prevent amyloidosis and to significantly reduce morbidity and disability. We describe three infants under 2 years of age with non-specific clinical symptoms in whom the diagnosis of FMF was established by genetic testing.

Patient Descriptions

Patient 1

A 4 month old Druze girl was referred to our FMF clinic because of recurrent episodes of high fever and irritability lasting for 2–3 days and occurring at least once a week. During these episodes she was extremely uncomfortable and moved her legs repeatedly. The physician diagnosed "colic pains," and her mother believed that she had "leg pains" that did not respond well to analgesics. She was hospitalized three times at a local hospital with the diagnosis of "occult bacteremia, not bacteriologically proven." On physical examination the child was irritable and restless and had a slightly enlarged spleen. The rest of the examination was within normal limits.

Her father and three brothers had been diagnosed as having FMF at an early age, based on severe attacks of abdominal pains and synovitis; the diagnosis was subsequently confirmed by genetic studies. Considering the family history and the patient's clinical features, diagnostic tests were done at 6 months of age, and the child was found to be compound heterozygote for both V726A-E148Q and the M694I alleles. With the consent of her parents, the infant began receiving colchicine treatment (0.25 mg/day) and has not experienced further bouts of fever or episodes of abdominal or limb pain.

Patient 2

A 13 month old North African Jewish boy was referred to the Rheumatology Clinic because of recurrent episodes of "transient synovitis of hip." Since the age of 6 months his parents had noted that the infant experienced episodes of high fever during which he refused to move his legs and adopted a "frog-like" position. On two occasions ultrasound of the hip joints demonstrated a substantial accumulation of fluid in both hip joints.

The family was well known to the clinic because his two brothers suffer from "classical" FMF. Genetic investigation revealed that this patient, like his brothers, is homozygote for the M694V mutation. He was put on colchicine treatment and the episodes did not reoccur.

Patient 3

This 2 year old North African Jewish boy was diagnosed with FMF after a long history of recurrent episodes of fever. He had been repeatedly hospitalized since the age of 4 months because of "fever of unknown origin." In all the hospitalizations the physicians described "a restless child" with high fever and increased sedimentation rate, but a thorough laboratory and imaging work-up never disclosed the origin of the fever .

Although there was no history of FMF in the family, genetic studies were done and revealed homozygosity to the M694V mutation. Colchicine therapy was instituted, which led to a very satisfactory response.

Comment

We present three young children with recurrent episodes of fever that conform to the criteria for "hereditary periodic fevers" [3]. Hereditary periodic fevers are a group of disorders characterized by seemingly unprovoked episodes of fever and localized inflammation, most typically involving the serosa, synovium, or skin. They include the recessively inherited FMF and hyperimmunoglobulinemia D with

FMF = familial Mediterranean fever

periodic fever syndrome, and the dominantly inherited tumor necrosis factor receptor-associated periodic syndrome, Muckle-Wells syndrome and familial cold urticaria. Among these, the first two syndromes were applicable to our patients. Patients with the hyper-IgD syndrome have recurrent attacks of fever that usually start before the end of the first year of life and are typically provoked by the first vaccination. Cervical lymphadenopathy and abdominal pain with vomiting, diarrhea, or both, almost always accompany the attack. Most patients are Caucasian and are from west European countries; some 60% are either Dutch or French [3]. Our patients did not have increased levels of IgD and did not exhibit the classical clinical picture of this syndrome. In addition, to our knowledge, there is no description of HIDS among the Israeli population. FMF, on the other hand, is very common in our population, with estimated carrier rates of 1:6 among North African Jews and 1:10 among Arabs . From previous phenotype-genotype studies we already know that patients who are homozygote for the M694V mutation in the *MEFV* gene have a more severe form of disease, manifested by an earlier age of onset, higher frequency of attacks, and more frequent episodes of arthritis [4]. Indeed, two of the three children were homozygote to this particular mutation. Although there are descriptions in the literature of patients who remember having had attacks during early childhood, none of these patients was diagnosed or treated before age 2 years [5].

In conclusion, FMF can manifest very early in life in children of Mediterranean origin and should therefore be included in the differential diagnosis of unexplained recurrent episodes of fever accompanied by irritability or discomfort. When confronted with such a non-specific picture in this population of children, genetic investigation for mutations in the FMF gene can help the clinician to achieve a correct diagnosis.

IgD = immunoglobulin D
HIDS = hyperimmunoglobulinemia D syndrome

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