Familial Mediterranean Fever – a common hereditary disease in Malta

by **Christian A Scerri** *MD PhD(Molecular Genetics)*
Clinical and Molecular Geneticist
Clinical and Molecular Genetics Clinic
Speciality Clinics, Mater Dei Hospital

Familial Mediterranean Fever (FMF), also known as recurrent polyserositis, is an autosomic recessive disease affecting the inflammatory pathway. Other related inherited conditions include hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) and the autosomal dominant Tumour Necrosis Factor Receptor-1-associated Periodic Syndrome (TRAPS). FMF is the most frequent of the group and as the name implies affects populations of the Mediterranean basin.

Though the disease is thought to be over 2000 years old, FMF was first identified as a distinct syndrome in 1945. Though it is considered to predominantly affect four populations (non-Ashkenazi Jews, Armenians, Turks and Arabs) it is also found in other populations of the Mediterranean.

FMF is a disorder of inappropriate inflammation, where an event that under normal conditions can cause a mild inflammation, causes a severe response. The major pathophysiological characteristic of FMF is an inflammatory reaction of serosal tissues (pleura, peritoneum and synovium) with increased chemotactic activity of leucocytes, massive invasion of granulocytes of the affected tissues and fever. Typical precipitating factors include physical and emotional stress, a high-fat diet and menstruation. Though the causative mutations have been identified within the MEFV (Mediterranean Fever) gene, located on the short arm of chromosome 16, the exact function of the product of this gene (pyrin or marenostrin) is still unclear. This protein is involved in the regulation of apoptosis and inflammation through its regulation of caspase-1 activation and consequently, IL-1β production. This protein is basically expressed in granulocytes, in the serosal cells of the peritoneal and pleural spaces and in synovial cells. The recurrent inflammatory episodes are thought to produce excessive amounts of amyloid A protein that tend to deposit in the kidneys.

In around 50% of cases, the symptoms of FMF start during the first decade of life though a number of cases can be asymptomatic. The typical attack consists of fever lasting 1 to 4 days usually accompanied by serositis, with symptoms becoming less severe as the patient gets older.

continues on page 18

Typical attacks	**Fever** • 38–40°C, might be preceded by chills, lasting between 12 h and 3 days • Rarely the only manifestation of FMF
	Peritonitis • Clinically typical acute peritonitis, accompanied by either constipation or diarrhea (mostly in children). • Abdominal pain may persists for 1–2 days after the temperature returns to normal • May remain localised and simulate appendicitis or cholecystitis, less frequently mimicking renal colic or acute pelvic inflammatory disease • Up to 40% of patients may have undergone exploratory surgery with either appendicectomy or cholecystectomy
	Pleuritis • Frequent manifestation of FMF • In some cases an effusion can be identified at the costophrenic angle • May last as long as 7 days and be the presenting manifestation
	Pericarditis • Appears in a minority of patients and tends to be present at a late stage of the disease • Failure to distinguish pericarditis from pleuritis, might be the reason for the relative lack of identification of pericarditis
	Arthritis (typically hip, knee, ankle) • Common and important feature of FMF • There are three forms of arthritis which can be encountered: *Asymmetrical, non-destructive arthritis (75%)* - Short duration, with large effusions in one or two joints. Usually resolves completely *Chronic destructive arthritis (2–5%)* - hips and knees most commonly affected. Permanent damage may result *Migratory polyarthritis* - Similar to rheumatic fever and due to similar age of incidence misdiagnoses is a possibility
	Myalgia • Can be severe • Usually appearing in the arms and legs • May be associated with arthritis • Very rarely presenting as sole manifestation of FMF. Attacks may last more than 3 weeks
	Erysipelas-like skin lesion • Appears on the extensor surfaces of the leg, ankle joint or dorsum of the foot • Most commonly unilateral • Resembles erysipelas or cellulitis • Fades away spontaneously within 2-3 days
	Amyloidosis • Most severe complications of FMF • If affects the kidneys it results in renal insufficiency progressing to end-stage renal disease • May affect the gastrointestinal tract, liver, spleen, and at a later stage the heart and testes • Frequency of amyloidosis differs among the various populations and is arrested by colchicine use • Patients may present with renal amyloidosis but no history of typical FMF attacks
Incomplete attacks (with variation in severity and duration) involving 1 or more sites	**Characterised by recurrent abdominal pain and/or recurrent arthralgia (multiple, lower back, upper extremities)** Defined as painful and recurrent attacks that differ from typical attacks in 1 or 2 features, as follows: 1) the temperature is normal or lower than 38°C 2) the attacks are longer or shorter than specified (but not shorter than 6 hours or longer than a week) 3) no signs of peritonitis are recorded during the abdominal attacks 4) the abdominal attacks are localized 5) the arthritis is in joints other than those specified

Table 1 – *Typical features of Familial Mediterranean Fever*

Familial Mediterranean Fever – a common hereditary disease in Malta

continued from page 16

The frequency of attacks can vary between one every couple of weeks to one every 3-4 months, with the patient appearing completely normal in between attacks. The typical features of the disorder are listed in Table 1. Utilising these features one can arrive to the clinical suspicion of FMF by utlising a set of criteria, the most commonly used being the Tel Hashomer criteria (Table 2).[1]

The prevalence shows wide ethnic variation with a high prevalence amongst Armenian, non-Ashkenazi Jews, Levantine Arabic and Turkish groups with carrier frequencies of 1:7, 1:5, 1:5 and 1:5 respectively. Up to this date, over 80 disease-causing mutations have been identified in the MEFV gene. Most of the FMF cases are caused by four mutations within Exon 10 (M694V, V726A, M680I and M694I). The disease-causing role of another common mutation, E148Q, is still under discussion though there is a growing body of evidence that it is not a neutral polymorphism and as such it is recommended to consider it as a pathological mutation.

A preliminary analysis of the population frequency of the mutations that have been identified amongst Maltese patients (M694V, V726A and E148Q), has shown a carrier frequency of 1.6%, 2.2% and 6.4% respectively. From these data, the estimated carrier frequency amongst the Maltese population is of 1:17 (1:10 if one includes the E148Q mutation).

Major Criteria	Recurrent Fever Recurrent Peritonitis Recurrent Pleuritis Recurrent Pericarditis Recurrent Mono-arthritis Recurrent Erysipeloid erythema Mediterranean ancestry Positive family History
Minor Criteria	Incomplete abdominal attacks Incomplete chest attacks Incomplete joint attacks Exertional Leg pain Response to colchicine Recurrent Arthralgia Childhood onset Remissions during pregnancy Leukocytosis
Supportive Criteria	Family history of FMF Appropriate ethnic origin Age <20 years at disease onset Severe attacks, requiring bed rest Spontaneous remission Symptom-free interval Transient inflammatory response, with 1 or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen Episodic proteinuria/hematuria Unproductive laparotomy or removal of white appendix Consanguinity of parents
FMF Diagnosis: Requirements	Recurrent Fever with one of the following: ⩾1 major criteria ⩾2 minor criteria 1 minor criteria plus ⩾5 supportive criteria 1 minor criteria plus ⩾4 of the first 5 supportive criteria

Table 2 – *Criteria set for diagnosis of Familial Mediterranean Fever*[1]

All of the studies on the phenotype/genotype relationships done so far, have shown that the M694V allele is associated with a more severe form of disease, with an earlier age of onset, higher frequency of attacks and presence of arthritis, with (as expected) homozygotes showing a worse clinical picture when compared to compound heterozygotes with either the V726A, M680I and E148Q mutations and in those who carry these three mutations in any combination.

Considering that from the preliminary local results, FMF seems to be the most common single gene disorder on the Island and as this disorder has a high degree of morbidity and mortality and an effective (and relatively cheap) treatment is available, a population screening programme should be considered.

Reference

1. Livneh A, Langevitz P, Zemer D et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40:1879-85.