Familial Mediterranean Fever (FMF) is a disease of unknown etiology prevalent in the Mediterranean Basin which has attained much attention recently resulting in revealing some of the ambiguities surrounding it. However, much remains to be unmasked about this disease that is being described in countries far away from the Mediterranean.

**Definition.** FMF is an autosomal recessive disorder of unknown etiology characterized by paroxysmal short lived fever and polyserositis commonly found in Sephardic Jews, Armenians, Turks, Arabs and Balkans.

**Historical background.** It seems that the disease is as old as history in the Mediterranean area. The first case described was by Janeway and Mosenthal in 1908; however it was until 1945 when it was recognized as a distinct disease by Siegal. In 1958, Heller gave the disease its current name: Familial Mediterranean fever.

**Epidemiology.** As the name of the disease implies, it was initially thought to be confined to the Mediterranean countries, however; it has been reported as far as Japan in the East and Sweden and U.S.A. in the west. Other sporadic cases have been reported in almost all countries. Most patients are Jews, Armenians, Turks, or Arabs. In Jews it is much more prevalent among Sephardic rather than Ashkenazi Jews. In Arabs most patients are from the eastern Mediterranean Countries while the disease is said to be more rare in the Arab Peninsula and Sudan. It is of interest to notice that the ethnic groups highly-affected by the disease have been living in proximity for long periods so that the disease is believed to spread both by geographic proximity and common ancestry. The mean gene frequency among Armenians was found to be 0.073 which yields a carrier rate of 1/17 and a disease rate of 1/187, while the carrier rate was 1/6 in North African Jews, 1/8 in Iraqi Jews, and 1/12 in Ashkenazi population. Among Arabs, no data about gene frequency is so far available. A genetic cause for FMF has been suspected on the basis of familial aggregates and marked increased frequency among those of Mediterranean origin; however, the definitive proof for the genetic basis of the disease...
came by Shohat et al in 1991 who showed that in 10 monzygotic twin pairs, the concordance for FMF was 100% while it was found only in 3 pairs out of 11 dizygotic twin sets. The familial nature of the disease is not disputed; however, the mode of inheritance was a subject of much debate till recently when it became evident after extensive studies of the family aggregation and population distribution that autosomal recessive inheritance is the mode of inheritance in all ethnic groups with incomplete penetrance in females.

Most series show a male predominance with a mean ratio of 1.7:1.2

**Pathogenesis.** FMF is characterized by inflammation of serosal surfaces with exudation of polymorphs and mononuclear cells. Small blood vessels show hyperemic changes. Thin adhesions occur and may lead to bowel obstruction. Despite extensive research, a solid basis to explain the mechanism of the disease does not exist. Recent theories include lipocortin deficiency. These proteins control the biosynthesis of inflammatory mediators such as prostaglandins and Leukotrienes by inhibiting arachidonic acid. Another hypothesis is linking FMF to novel structural changes in the serum Amyloid A (SAA) gene family but this was rejected later. Other immune mechanisms such as interleukines and complement component abnormality were unable to stand against the lack of evidence.

The proposal by Barakat et al that FMF may be due to over activity of catecholamines has also lost its clinical support in later studies. A major breakthrough was the work carried out by Pras et al who mapped the gene causing FMF to the short arm of chromosome number 16. This was the first real step toward defining the biochemical events in the disease.

**Clinical features.** FMF is a disease - predominantly of childhood and the mean age of onset is between 5-7 years. However, the disease is known to present later in adult life although 75% present before the age of twenty. It is expected that with increased awareness of the disease both by people and physicians, fewer cases will present in late adulthood. The hallmark of the disease is, as mentioned above, recurrent attacks of fever and polyserositis.

**Fever.** This occurs almost in all patients and few never mention it since they seek medical attention for their serositis. There is no specific pattern of the fever although it tends to be of low grade and usually accompanies other manifestations of the disease.

**Abdominal pain.** This is the cardinal feature of the disease and occurs in more than 90% of cases in most series. The peritoneal attack starts suddenly although some patients have prodromal-like illness. The picture mimics acute peritonitis with fever, guarding, and tenderness. Many patients are subjected to laparotomies because of failure to recognize the disease. The attack usually subsides completely within 24-72 hours and the patient is completely normal in between the attacks. Some advocate elective laparoscopic appendectomy for patients with FMF. Vomiting, constipation or diarrhea may occur.

**Chest pain.** This occurs in almost 30-50% of cases and is usually pleuritic, unilateral and may be overlooked by the patient unless asked for. Not many physical signs will be detected but small pleural effusions, atelectatic bands, and rarely, friction rub may be found. One interesting observation is the low incidence of bronchial asthma in FMF patients.

**Arthritis.** Joint involvement is a common manifestation of FMF especially so in Sephardic kids and may be the presenting feature in some cases. About 55% of patients experience arthropathy which is usually monoarticular, non deforming and affects joints of the lower limbs. In around 2% of cases destructive arthropathy occurs predominantly in the hip which may necessitate hip replacement. The attacks of arthropathy are usually short-lived and self-limiting. Typically lasting for 1-3 days or they may be protracted for 2 weeks to one year in a minority of cases. The frequency of arthritic attacks tends to decrease with time. The synovial fluid is typically turbid but uniformly sterile. Recently temporo mandibular arthritis has been described in FMF.

**Skin manifestations.** Various skin lesions have been described in FMF, the most typical lesion which is considered by some as very specific for the disease is the erysipelas - like lesion around the ankle joint and over the lower leg mostly in children. Henoch Schönlein Purpura (HSP) has been reported in association with FMF which tends to be more severe and necessitates steroids in most cases. Other lesions described in FMF include urticaria, diffuse facial erythema, bullous lesions, and most recently pyoderma.

**Renal involvement.** Apart from amyloidosis which will be discussed later, certain types of Glomerulonephritis have been reported in FMF including both IgA and IgM nephropathy and most recently rapidly progressive glomerulonephritis.

**Vasculitis in FMF.** In addition to (HSP), polyarteritis nodosa (PAN) was reported at a higher frequency compared with the general population and at a younger age group.

Another interesting syndrome named Protracted Febrile Myalgia (PFM) was recently described and is characterized by disabling myalgia, fever with marked elevation of the ESR, leukocytosis, and polycyonal hyperglobulinemia. Here colchicine was ineffective and prompt response followed corticosteroid therapy. Antiphospholipid syndrome has recently been reported in one patient.
with FMF. Other associations. The list of FMF manifestations and associations is growing, to mention just a few that include: Spleenomegaly which is more common in Jewish kids than Arabs,2,24 pseudo tumor cerebri29 optic neuritis,40 pulmonary hypertension complicating FMF amyloidosis,41 recurrent pericarditis,42,43 orchitis,44 Mollaret meningitis which appears to be provoked by metaraminol.45,46 It may be well evident in the future that new associations with FMF become apparent as we are becoming more aware of the disease and its protean manifestations.

Diagnosis. Unfortunately, no clinical, biochemical or immunological test is currently available to diagnose FMF and hence the diagnosis is based on clinical findings and family history which is positive in 28-52% of patients.23 However, exclusion of other diseases is mandatory. To simplify the issue, criteria have been laid down for diagnosis by Armenian and Khachadurian and were modified by Majeed, but these are not universally accepted.47 As mentioned earlier, the provocative test (Metaraminol) lost its initial glory since it is not reproducible and carries its own risks: elevation of blood pressure, palpitations, Mollaret’s meningitis.20,21 Typically the attack lasts for 1-3 days and the patient is completely well in between. The frequency of the attacks is highly variable, ranging from 1-40/year and the combination of symptoms is not necessarily family specific. During the acute attack, acute phase reactants are usually elevated (high ESR, Leukocytosis, hyper fibrinogenemia) but none is specific, so a high index of suspicion is essential to minimize the delay in diagnosis and hence commencing treatment.

Complications. The most ominous complication of FMF which has been recognized for a long time is the development of Amyloidosis.48-53 This has a high ethnic variation for unknown reasons; however, it is believed that the inheritance of FMF and amyloidosis might be independent of each other.23 Two phenotypes of FMF exist: Phenotype I presents with the typical painful episodes that may end with amyloidosis; and phenotype II in which amyloidosis precedes the painful attacks.23,53 The highest incidence of amyloidosis complicating FMF was reported in Turkish patients (60%),51,52 followed by Sephardic Jews9 (12-29%). In Arabs and Armenians it is much less.24 The commonest presentation of this grave complication is edema. However, the process starts with proteinuria which may be intermittent, then becomes constant and progresses to frank nephrotic syndrome and once amyloidosis develops, renal failure ensues within six months to five years with a mean duration of 2.7 years.23

It is of interest to notice that the development of amyloidosis in FMF has nothing to do with the frequency, severity, and duration of the FMF attacks.23,49 The amyloid is of the type A (A.A) which is characterized by peri vascular as well as parenchymal infiltration.

The diagnosis can be established by renal, rectal, submucosal fat or bone marrow biopsy. However, renal or rectal biopsy may well have the highest yield.53 It is now proven beyond any doubt that amyloidosis is largely prevented by Colchicine therapy.23,49

Another complication of FMF is the development, by virtue of repeated attacks of peritonitis, of peritoneal adhesions that may cause adhesive small bowel obstruction (ASBO) requiring surgical intervention.

(ASBO) is considered now, in the colchicine era, the commonest complication of FMF56 and occurs in the absence of previous surgical interventions.

Management. The goals of treatment should be the prevention of the painful attacks and more importantly the occurrence of the drastic complication, namely, Amyloidosis A. This can be achieved today only by colchicine therapy on a daily basis as soon as the diagnosis is made and irrespective of the natural history of the disease. Colchicine is effective in preventing or ameliorating the attacks in up to 90% of cases.4,57,58 The dose ranges between 0.5 - 2 mg daily depending on the weight and age of the patient. It’s cheap and usually well-tolerated as the side effects are much less seen in practice than in text books. The ability of colchicine to prevent amyloidosis is now well-established.23,49,63 The effect extends to prevent additional deterioration of the renal function in patients with amyloidosis who have proteinuria and may even reverse the nephrotic syndrome;64 however, the dose of colchicine should be more than 1.5 mg daily to achieve this last goal.65 The drug is found also to prevent the development of amyloidosis in patients who had renal - transplant for amyloidosis complicating FMF at higher doses than 1.5mg/day.66 The mechanism of action of colchicine in FMF is still speculative and theories include: Arrest of mitosis at metaphase by binding microtubular proteins, prevention of synthesis of serum Amyloid A protein (SAA) by hepatocytes, anti-inflammatory action, or through its inhibitory effects on cell mediated Immunity.67

References