no further recurrence of his attacks of fever and joint pain. He continued to have neurologic and renal deterioration due to amyloidosis and expired two years after diagnosis.

Haemotological and other laboratory investigations were within norm for all cases.

DISCUSSION

Familial Mediterranean fever is an inherited disease of unknown aetiology; characterised by recurrent, self-limited episodes of fever and serosal inflammation. The first case report was by Siegal in 1945[1]. It was not until 1958 that Heller, Sohar and Sherf[3] described and defined the clinical manifestations of FMF. Barakat[4] described in 1986 the largest series of Arab patients affected but stated that no patient from the Arabian Peninsula was described with this disease. In this paper the first Bahraini patient with FMF is described.

The disease affects Arab, Sephardic Jews, Armenians and Turks. It has been described in Italians, French, Persians and Anglo-Saxons. Family history can be obtained in 50% of the cases. Sohar[5] collected 470 cases and analysed 229 families; he concluded that the disease is due to a single autosomal recessive gene. Among families studied, consanguineous marriage was as high as 20%. Males make up 60% of patients with FMF and this may be due to decreased penetrance in females. In a more recent study, Armenian[6] analysed the inheritance pattern of 150 patients and detected a lower proportion of affected offsprings than expected. He also found that the disease is more severe in familial cases. This suggested to him that the inheritance pattern may be polygenic and that the penetrance varies from one family to the other. Gazit et al.[7] studied the HLA antigens in cases of FMF and no difference was found between affected and non-affected members in the same ethnic group. The age of onset of the disease has been described as early as the first year of life to as late as 52 years of age. Two-thirds of the patients manifested the disease by the first decade of life and 90% before the end of their second decade[5].

The series by Barakat et al.[4] reports a mean age of the onset of the disease as 13.8 years. The disease is not manifested at birth, nor is there any prodromal symptom or sign during the period of latency before the onset.

The disease appears as paroxysms of fever and serosal inflammation. Depending on the serosal membranes involved, the attack appears as peritonitis, pleuritis or synovitis. During the life span of the patient all types of serosal surface inflammations may be encountered. Fever (which ranges from 38.5–40°C) begins abruptly, peaks in 12–24 hours and subsides rapidly leaving the patient with no residual illness. Chills may precede the fever. Spontaneous defervescence is accompanied by diaphoresis. In 2% of the patients fever is the only manifestation and this makes the diagnosis very difficult unless there is a family history, or later attacks with other features of FMF. The fever does not respond to antipyretics. The largest number of patients (94–95%) present with features of peritonitis[5]. The patient with the peritoneal attack presents with abdominal pain which starts in one quadrant and then spreads to the whole abdomen. The initial site is usually very tender. Physical signs like distension, rebound tenderness, board-like rigidity and absence of peristalsis are common. The abdominal radiographs show oedematous small bowel loops with air-fluid levels. These findings may simulate findings of intestinal obstruction. Vomiting may also be present. In 6–12 hours the symptoms and signs decrease, and disappear by 24–48 hours. Attacks of variable intensity with mild abdominal discomfort and slight temperature elevation may occur. Many of the patients have undergone laparotomy during an abdominal attack. Peritoneal erythema and a few millilitres of cloudy sterile peritoneal fluid are found during these operations. Occasional organisation of the exudates may result in fibrous adhesions with the complication of intestinal obstruction as reported in 2 out of 470 cases by Sohar[5].

The patient with the pleural attack presents with acute febrile pleuritis with guarding and splinting of the chest wall. Signs of pleural effusion or rub are present and resolve in 48 hours. The chest films show unilateral effusion and the pleural fluid contains many PMNS but no organisms. Seventy-five percent of patients with peritoneal type of attacks develop pleuritic pain, while only 40% of patients suffer attacks limited to the chest[5].

The synovial attack occurs in two forms. The first is an acute attack lasting 1–7 days and the second is a chronic form which may last for as long as a year. The acute type is more common. This type of attack affects 33.7% of Arab patients as reported by Barakat[4]. Usually one joint is affected at a time. The large joints of the lower extremities are commonly involved. The knee, ankle and hip are involved with sudden intense pain and tenderness. Fever is present as well joint effusion, hotness and redness. Two to three days later the attack subsides and the joint is left with no residual damage. The synovial fluid contains 200–1000000 cells/ml, most of which are PMNS. Mucin clot is always present. The proteins are high and the fluid is sterile. The attacks are self-limited and do not respond to intra-articular or systemic steroids. There is total reversibility of the attack. On the other hand, the chronic FMF synovitis is a monoarticular arthritis with swelling but less redness and hotness. Muscle atrophy in the affected limb accompanies it and may be severe. Attacks may last for months. Complete functional and anatomic recovery is the rule. Osteoporosis can complicate this form of chronic arthritis[5].

The skin is also involved in FMF. Erysipelas-like rash is one of the manifestations of FMF. Red, well demarcated patches measuring 15–50 cm usually appear on the lower extremities below the knee[5]. Tenderness, hotness and swelling are present at the site of the involvement. Fifty percent of patients with FMF develop this rash at one time during their illness[5].

The disease is not periodic and recurrences are irregular. Remissions of months or even years are common. Attacks may be precipitated by prolonged physical activity like walking, marching or standing. Remissions are known to occur during the second and third trimesters of pregnancy[5].

AETIOLOGY OF FMF

Though the disease is a genetic disorder the pathogenesis remains unclear. Several experts have different theories, the most important are as follows :

1. The leukocyte function theories :

The PNM leukocyte is the important cell in inflammation and is responsible for the release of pyrogens and proteolytic enzymes which, in their turn, activate the complement and the kinin system. Moreover, colchicine, an inhibitor of PNM metabolism and stabiliser of lysosomes, is beneficial in this disease. Consequently, people have studied various functions of the PNM in FMF. Chemotactic activity, which increases during febrile episodes in FMF, is suppressed by colchicine treatment[8]. However, studies have shown that the phagocytic activity and pyrogen release is normal in patients with FMF and remains unchanged after colchicine treatment[6,7].

2. The immune system theories :

Investigators have not been able to detect autoantibodies or LE cells in FMF patients[9]. Reimann reported that levels of C1– estrase and total complement were decreased in these patients[10]. Mantzer found that the chemotactic inhibitor in synovial fluid of FMF patients is subnormal in activity, and that this allows inflammation to occur in response to sporadically released C5a, a potent inflammatory mediator in synovial fluid[11]. However, the role of the immune system on the aetiology of FMF remains unclear.

3. The role of the sympathetic system :

In 1976 Hayashi reported a Japanese patient with recurrent peritonitis who benefited from reserpine prophylaxis and whose attacks were induced by infusion of noradrenaline[12]. Barakat et al. followed this by demonstrating that small daily doses of reserpine decreased the frequency of attacks in 60% of 22 FMF patients[13]. This led him to study the effects of catecholamine release in the pathogenesis of FMF[2]. He found that inducing endogenous catecholamine release by infusion of metaraminol precipitated a disease-like attack in all prediagnosed patients, while none of the controls developed any symptoms[2]. Metaraminol is a sympathomimetic agent that acts directly on adrenergic receptors, and indirectly by releasing noradrenaline and inhibiting its uptake[14,15,16]. Thus it would appear that sympathetic system stimulation plays a role in the pathogenesis of FMF. Barakat[2] also found that pretreatment with colchicine prevented the induction of attacks by metaraminol. This preventive effect is thought to be due to inhibition of the transport of catecholamines in neuronal axons by colchicine. He proposed that FMF symptoms may be due to abnormal catecholamine metabolism. Further testing of this interesting theory is necessary and the clinical utilisation of this provocative diagnostic test is promising.

PATHOLOGY OF FMF

Cytologic examination of synovial aspirates, peritoneal and pleural fluids demonstrate exudates of PNMS. In addition; vascular dilation, oedema and exudates of PNMS and mononuclear cells are seen on synovial membranes, peritoneum and pleural biopsies. Remarkable reversibility of these pathologic findings are well documented after resolution of the attack. Few reports of obliteration of pleural cavities, and peritoneal intra-abdominal adhesions have been noted[5].

Twenty-five percent of patients develop amyloidosis of the perireticular type involving the intima and media of vessels. The kidneys, adrenals and spleen are mainly involved with relative sparing of the heart and liver[5]. The amyloid deposited is of the AA type, the major constituent of secondary immunoglobulin variety[5].

COMPLICATIONS OF FMF

Due to the difficulty and delay in diagnosis of FMF, many patients undergo multiple surgical procedures and are given many drugs, including narcotics. These procedures and drugs are associated with significant morbidity in FMF patients.

In afflicted Arabs and Jews there is a high incidence of amyloidosis leading to renal failure and death[5]. Armenian patients studied in California seem to escape this complication and have a milder course and longer life expectancy[9]. There is no relationship between the appearance of amyloidosis and the time of onset, type or number of attacks. At one extreme there are patients who may show no signs of amyloidosis despite hundreds of attacks over many years, on the other hands some may manifest amyloidosis before they have experienced an attack. It is thought by Sohar and his co-workers that FMF and amyloidosis are two independent phenotypic expressions of a single pleiotropic gene[5]. In his series of 470 cases of FMF, 125 of them (26.5%) developed amyloidosis, and it was the cause of death in 67 out of 68 autopsied cases[5].

The major clinical presentation of amyloidosis is nephropathy with proteinuria, nephrotic syndrome and terminal uraemia. The uraemia phase is accompanied by hypertension in 50% of the cases[5].

Anaemia, splenomegaly, malabsorption and autonomic or peripheral neuropathy may also occur in amyloidosis related to FMF. Amyloidosis can exist for several years before death of the patient. The average duration from onset of proteinuria until death is 7 years. Recurrence of amyloidosis in transplanted kidneys has been reported[17].

TENTATIVE DIAGNOSTIC TEST FOR FMF

In 1984 Barakat et al.[2] reported on the development of a provocative test in establishing the diagnosis of this disease using metaraminol infusion. This provocative test needs to be carried out on a larger number of patients with FMF to confirm its specificity and sensitivity. If Barakat's observation becomes widely accepted, this will make the diagnosis of FMF easier and could lead to the discovery of a biochemical basis of this disease.

TREATMENT OF FMF

Colchicine, an extract of the Colchicum autumnal plant was introduced for the treatment of gout in the 6th century AD. In 1952 Mamou and Cattan reported that a single dose of colchicine given IV shortened the duration of an attack of FMF[18]. Many investigators refuted this observation. In 1972 Goldfinger reported the value of colchicine as a prophylactic drug for FMF[19]. Many double-blind studies followed proving the efficacy of colchicine in preventing FMF. On a dose of 0.6 mg three times daily, patients experienced a marked reduction in the frequency and severity of their attacks[20]. This effect is thought to be secondary to suppression of biochemical function of the PNM. It may interfere with lysosomal degranulation and phagolysosomal formation. Colchicine may affect the PNM in vivo, interfering with margination, locomotion, chemotaxis and generation of kinins[20].

At the cellular level, colchicine is an inhibitor of microtubules which are necessary for lysosomal and phagosomal activation of the PNM[21]. Proponents of the theory that catecholamine metabolism is abnormal in FMF, suggest that the action of colchicine is due to prevention of transaxonal transport of catecholamines in neurons[2,13].

Initially, because of the youth of many of the patients and the long term treatment plan, there was