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Familial Mediterranean Fever in an Iraqi Family

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Familial Mediaterranean Fever (FMF) is a disease with recurring episodes of fever and abdominal pain, occuring in ethnic groups originating from the Mediterranean area. The nature of this disorder is still debatable, hence the different names given to describe what appears to be the same syndrome, i.e., Benign Paroxysmal Peritonitis,[1] Periodic disease,[2] maladie dite periodque,[3] Epanalepsie Mediterranean,[4] Familial Mediterranean Fever.[5] and recurrent Polyserositis.[6] Most of the patients previously reported have been Sephardic (less commonly Ashkenazi) jews while others have been Arminians,[7] Arabs,[8] Turks,[9] and Persians.[10]

Two types of F. M. F. are recognized: *Phenotype I*: The common variant, characterized by attacks of fever and short, self-limited peritonitis, pleuritis or arthritis. Mortality is high owing to amyloidosis affecting the kidneys. *Phenotype II*: The rarer variant in which amylodosis is the first or sole manifestation of the disease.[7]

This is a study of three children from an Iraqi family. (Figure 1) Suffering from F. M. F. Cyclophosphmide was used in the treatment of F. M. F. for the first time.

Case 1: a 12 year old girl, was admitted to the hospital with the complaints of recurrent episodes of fever over the preceeding 6 years and generalized oedema for three months. She had four sisters and three brothers, but there was no history of an allergic disorder in the family. The patients, medical history was unremarkable.

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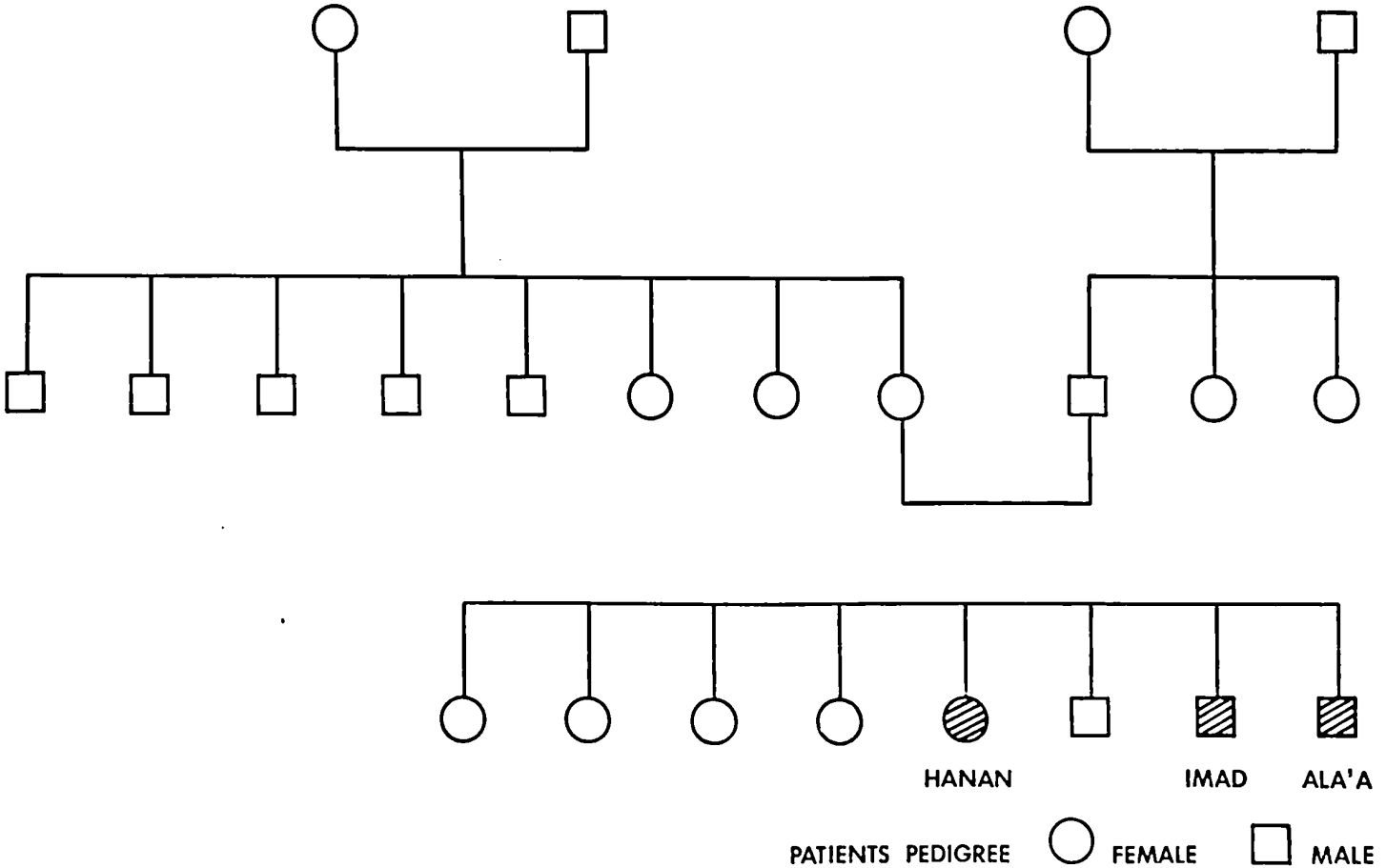

Figure 1

The fever started at the age of 6 years, coming in attacks once a week. It usually lasted for 24 hours, sometimes for only a few hours, but occasionally for 48 hours. A typical attack started with rigor, being half an hour in duration, and was followed by fever as high as 40° C, and then by sweating. Towards the end of the attack a headache would occur, mostly frontal, with pain in the eyes lasting for 2 hours and usually associated with one attack of vomiting. The headaches were not relieved by analgesics, but by sleep. There was no blurring of vision.

Abdominal pain was always present, felt mostly in the epigastrium and sometimes in the right hypochodrium. Hot water bottles applied to the abdomen gave some relief. No cause could be found to precipitate the attack.

Three months before admission the patient developed puffiness of the eyes followed by swelling of the feet, distention of the abdomen and swelling of the neck below the chin. There was a burning, intermittant pain in the right loin and micturition became more frequent. Her appetite also became poor. The family doctor gave her prednisolone 40 mg/ daily, orally, which was tapered off within a month and she was off steriods for two months before admission.

Upon admission the patient was a well-developed girl with puffy eyes and considerable neck oedema, giving the appearance of a double chin. There was moderate oedema of the legs and sacrum. Weight was 39.0 Kg, blood pressure was 90/60, and temperature was 37° C. The abdomen was distended with ascitic fluid and the abdominal wall was also oedematous. No dots were seen upon repeated examination of the ocular fundi.[6] Examination of other systems revealed no abnormalities.

Urinary volume was 1050-1120 ml/day with protein content of 3.7-6.8 gm per day. Casts were present in the urine but no sugar. Blood urea was 21 mg/100 ml, serum sodium was 143 mEq/1. Serum potassium was 5.1 mEq/1.

Hb was 13.4 gm/100 ml, PCV 41 %, MCHC 33 %, WBC 5500/cmm, neutrophils 58 %; lymphocytes 38 %, monocytes 2 %, Eosinophils 2 %, and platelets were considered adequate on the blood smear. The stool examination showed giardia lamblia cysts. The erthrocyte sedimentation rate was 111 mm/hr, (Westergren). Serum Cholesterol was 450 mg/100 ml.

Estimation of serum proteins showed a total of 3.9 gm. On electrophoresis the following percentages were found: albumin 18, alpha-1 globulin 5, alpha-2 globulin 39, beta globulin 14, gamma globulen 24. Serum amylase was 142 Somogyi Units.

A plain radiogram of the abdomen and an ECG showed no abnormalities. In an EEG recorded between attacks, moderate high voltage sharp and slow waves were seen together with accentuated generalized spikes.

Rectal biopsy revealed fibrosis and chronic inflammation with hyline deposits in the small arterioles which took the amyloid stain. The renal biopsy specimen contained only few glomreruli but these also took up the amyloid stain and it was considered positive.

The patient was put on a low salt and high protein diet and she started to loose weight from the third day onwards. In a few days the oedema of the neck and ascites disappeared and leg oedema was much reduced. A low fat diet was tried but did not seem to alter the attacks. Cyclophosphamide in a dose of 2.5 mg/Kg/daily was given orally. There were no attacks during the first month of its trial but attacks reocurred thereafter. There was no change in protein-urea or serum protein levels.

Case 2: an 18 year old, was the product of a twin pregnancy. (His twin brother died at the age of 15 days of diarrhoea.) His illness started at the age of 9 yrs, with fever and abdominal pain, which had been diagnosed as appendicitis and an appendicectomy performed. The attacks of fever and abdominal pain were remarkably regular, occuring once a week. On occasions he had chest pain and leg pain. The attacks lasted 2-24 hours and severe were enough to confine him to bed. He could abort an attack by taking an analgesic such as asprin, but this was followed by a more severe episode 2-3 days later. He also felt hungry at the beginning of an attack. Constipation accompanied the attacks.

No oedema or other abnormal physical signs were detected upon examination. Blood pressure was 120/70. His urinary volume was 2000 ml per day, containing 0.42 gm of protein per 100 ml with 2-3 pus cells/HPF, 2-3 R. B. C. /HPF and occasional casts. Serum electrophoresis showed the following values: albumin 1.66 gm/100 ml. alpha-1 globulin 0.5 gm/100 ml., alpha-2 globulin 1.45 gm/100 ml,. beta globulin 1.3 gm/100 ml., gamma gobulin 1.03 gm/100 ml. Serum amylase was 230 Somogyi Units, ESR was 112 mm/hr (Westergrin). Blood urea was 23 mg/100 ml. The patient refused rectal and renal biopsies. Upon treatment with Indomethacin for two months, there was no improvement, but with cyclophosphamide in a dose of 2.5 mg/Kg/day for 3 months, there were no attacks for the first 6 weeks, though they then recurred.

The 3rd patient was the 15 year-old brother of Cases 1 and 2, a product of a normal pregnancy and delivery. His illnesss started at the age of 7 with fever and abdominal pain, for which his appendix was removed. The attacks came almost every week, on the same day, but occasionally they were delayed for as long as 3 weeks. The attacks consisted of fever and abdominal pain, sometimes with chest or leg pain. While the attacks were severe enough to confine him to bed, in between he looked and felt healthy. Analgesics like asprin or paractamol gave him some relief during the attack.

He had no abnormal physical findings. His weight was 39 kg and blood pressure, 120/70. Urinalysis did not reveal any abnormality. His total serum protein was 6.9 gm, albumin was 2.58 gm/100 ml, alpha-1 globulin was 0.67 mg/100 ml, alpha-2 globulin was 0.93 gm/100 ml. beta globulin was 0.94 gm/100 ml, and gammaglobulin was 1.7 gm/100 ml, Serum amylase was 200 Somogyi units.

He was put on Cyclophosphamide for 3 months. For the first 6 weeks he had no febrile attacks, but thereafter the illness returned to its periodicity.

Discussion

Sohar et al, 1967, put forward the following criteria for the diagnosis of F. M. F.:

1. Short attacks of fever recurring at varying intervals
2. Painful manifestations in the abdomen, chest, joints or skin, accompanying the fever
3. The absence of any causative factor or pathological finding in vivo or post mortem capable of explaining the picture
4. The presence of amyloid, clinically of enphropathic and anatomically of Periarticular type
5. Features of autosomal recessive inheritance
6. Preferance for people of Mediterranean stock, particularly sephardic Jews and Armanians

The first three criteria are obligatory for the diagnosis of the common variant of F. M. F., while when nephropathic and amyloidosis appears before the attacks of fever, F. M. F. phenotype 11 is diagnosed only if no associated disease is found and F. M. F. phenotype 1 has been established in one of the parents or siblings.

In the family studied the father was a Turk and the mother an Arab; other cases have been reported from Turkey.[9] Of the 55 cases reported by Ehrenfeld et al, 9 were emigrants from Iraq: of the 470 cases reported by Soher et al, 64 came from Iraq and in both cases all were Jews.

The fever in all these patients was remarkably regular, occuring on the same day of the week, though on different days for the three patients; in all of them it lasted no longer than 24 hours. Although this periodicity was regarded as an essential feature of the disease by Reimann, 1948, Sohar et al, 1967, in their extensive study stated categorically that there was no periodicity. Nor was heredisity a constant feature in the series of Ehenfeld et al, but they stated that the most common regular interval in their patients was seven days, as it was in our patients.

The abdominal pain occurred in our patients at the same time as the fever, and a headache occurred towards the end. The abdominal pain started in the epigastric region and spread to involve the two hypochondriac regions. These were tender and the muscles felt moderately rigid. This picture suggested an acute abdominal condition if seen for the first time; hence the elder brothers underwent laparotomy.

Abdominal pain was present in 95 % of Sohar et al cases and 98 % of Errenfeld et al series. Chest pain, which was experienced by our three cases, was present in 38 % of the Ehrenfeld cases and 40 % of Sohar's. Joint pains were reported to be 35 % in Ehrenfeld's and 75 % in Sohar's series.

No hepatomegaly was found in our cases. It is said not to exist by Sohar and colleagues, but Ehrenfeld et al detected it in 27 % of their cases. The spleen, on the other hand, was palpable in 40 % of Ehrenfeld's and most of Sohar's cases.

Skin manifestations, e. g. erysepilas-like erytheme, regarded as characteristic by Sohar et al. (1967) being found in 50 % of their cases and 7 % of Ehrenfeld (1961), were absent in ours.

Repeated examinations of the first patient's eyes did not reveal any dots, though these were present in 50 % of Ehrenfeld's cases, being porcelain white or yellowish lesions with a punched out appearance.[11]

In Case 1, the EEG showed moderate high voltage sharp and slow waves with accentuated generalized spikes. Generalized irregular activity and non-specific diffuse theta activity of 5 to 6 c.p.s. has been reported previously.[12]

The white cell count done between attacks was normal but rose to 13,000 during them. The ESR was as high as 111 mm/hour (Westergren) during the attacks, and the blood fibrinogen was raised to 820 mg for Case 1. Plasma fibrinogen is raised in 88 % of and FMF cases and is considerably raised in nephrotic syndrome or uraemia.[13]

After 6 years of recurring febrile episodes she developed gradual swelling of the face, neck. and ascites and moderate oedema of the legs. This was associated with heavy proteinurea, cylindruria, and hypercholesterolaemia. The serum albumin was reduced and alpha-2 globulin was increased. These findings were similar to Ehrenfeld,s.

The gammaglobulin level was within normal limits; Sohar et al found it to be normal or increased in their patients.[17] These findings were consistant with the diagnosis of nephrotic syndrome, a known complication of amyloid disease in FMF. The presence of amyloidosis in this case was established by renal and rectal biopsies. The incidence of anyloidosis in FMF was found to be 4 out of 55 (7 %) in Ehrenfelds et al patients, all of whom developed nephrosis. The 2nd case had proteinuria, and changes in serum proteins suggestive of nephrotic syndrome, but no oedema. Unfortunately, the presence of amyloidosis was not established as he repeatedly refused rectal and renal biopsies.

Amloidoisis is the usual cause of death in FMF. Heller et al. recognized 4 stages: 1. Preclinical, when there is renal involvement not manifest clinically; 2. Proteinuria only; 3. Nephrotic syndrome; and 4. Ureamia.

The illness of the lst case seems to fit into stage 3 and the 2nd case, stage 2. Amloidosis is considered to carry a bad prognosis and most patients die within 5 years.[14] It is not related to the severity of the attacks or their frequency.[5] The appearance of amyloidosis does not seem to alter the attacks of FMF, which may continue until death occurs. Corticosteroids do not affect the course of amyloidosis in FMF, in fact they may make it worse.

The three patients were also treated with indomethacin (25 mg twice a day) for a month with apparently no appreciable effect. On the other hand, although cyclophosphamide aborted the febrile attacks initially, it did not materially affect the picture of the illness afterwards.

Summary

In an Iraqi family of 8 children, 3 (2 boys and one girl) presented with Familial Mediterranean Fever. The girl developed amyloidosis

and nephrotic syndrome; one boy had proteinurea. Therapeutically neither indomethacin nor cycphosphamide had alasting effect on the illness.

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