Familial Mediterranean Fever (FMF) a study of thirty Iraqi patients

*** Makki H. Fayadh MRCP- FRCP ** Salah Aldeen Abdul Nabi M.B, Ch.B D.M C.A.B.M *** Jassem Muhsen FICS(GE&H) CABM****Basim A. Askir FICS(GE&H) CABM *****RaghadJ.AL-Akashi FICS(GE&H) CABM**

Familial mediterranean fever (FMF) also known as hereditary polyserositis , is an inherited disorder commonly found in Armenians , Turks, Arabs, Balkans and Jews originating from North African countries [(1)].

It is an autosomal recessive disorder, common amoung patients of Mediterranean origin [(2)], it's gene has been localized to the short arm of chromosome 16 with male to female ratio of three to two [(3)] . Homozygous incidence is calculated as 1:2000 ; and gene frequency as 1:45 [(4)].

There are differences in disease expression and heterogenicity has been reported in different populations [(5)] . FMF is characterized clinically by recurrent and self limited attacks of fever and polyserositis and it's devastating complication is the development of renal amyloidosis [(6)] . The symptoms of FMF often begins between the ages of 5-15 , although attacks some times commence during infancy and onset has occurred as late as age of 50 , the duration and frequency of attacks vary greatly in the same patient and their occurrence follows no set pattern .The usual acute episode last 1-2 days but some may be prolonged for 7-10 days ; the attack ranged in frequency from twice weekly to once a year but 2-4 weeks is the most common interval[(7)].

Severity and frequency of the attacks decrease with age or with development of amyloidosis [(8)].

Pregnancy is often associated with remission of attacks which resume after post partum , between attacks the patient typically feel entirely well [(4)] .

The symptoms are :-

temperatures as high as 39-40^0 accompany almost all attacks .Fever may occur without concomitant evidence of serositis but this is unusual .The fever preceded by chills and typically peak by 12-24 hours, diaphoresis frequently accompanies defervescence [(8)].

2- Abdominal pain :

typically manifest as abdominal pain which may be presenting symptoms in as many as 50% . The pain may be diffuse or localized and may range from mild bloating to acute peritonitis with board like rigidity , rebound tenderness and air fluid levels on upright radiograph ; the presentation may be confused with acute appendicitis, porphyria, intra abdominal adhesions caused by recurrent episodes of sterile peritonitis or due to previous surgery which may lead to small bowel obstruction in 3% of cases [(9)].

3- Chest pain :

most patients with abdominal attacks have referred chest pain at one time or another and 75% also develop acute pleuritic pain with or without abdominal symptoms in 30% , the attacks of pleurisies precede the onset of abdominal attacks by varying periods of time, chest pain is usually unilateral and is associated with diminished breathing sounds or transient pleural effusion [(7)] .

*** Dr.Makki H. Fayadh,the Gastroenterology and Hepatology teaching hospital,Baghdad**
**** Dr.Salah Aldeen Abdul Nabi,the Gastroenterology and Hepatology teaching hospital ,Baghdad**
***** Dr.Jassem Muhsen, the Gastroenterology and Hepatology teaching hospital,Baghdad**
***** Dr.Basim A. Askir, the Gastroenterology and Hepatology teaching hospital,Baghdad**
***** Dr.RaghadJ.AL-Akashi, the Gastroenterology and Hepatology teaching hospital,Baghdad**

4- Musculo skeletal :
non specific mild arthralagia is a common feature of febrile attacks and acute mono articular or oligoarticular arithritis may occur ,It's frequently observed among Israeli patients. Arthriitis usually affects large joints, the knee in particular and effusion are common .Arthritic episodes are typically short [10] . Protracted febrile myalgia is an uncommon dramatic manifestation that may occur despite colchicine therapy and require treatment with corticosteriods [11] .

5- Skin manifestation:
Erysipelas like skin lesions are commonly described , other skin lesions including Henoch-schonlein purpura-non specific purpura , diffuse erythema and angioneurotic oedema [2] .

6- Renal manifestation :
the most serious complication of FMF is systemic amyloidosis of the type AA, which relentlessly progress to renal failure and death which may occur at adolescence or even earlier. While substantial proportion of Turkish and Israeli patients develop amyloidosis, this complication has been very unusual among patients in U.S.A., in several well studied Armenian and Arabic kindred's, although renal complication thought previously to be due primarily to amyloidosis it may also caused by immunoglobulin deposit resulting in mesangial proliferative glomerulonephritis [12] .

Laboratory findings:
Polymorph nuclear leukocytosis 10000-30000/cc is almost invariable during the attack, elevated ESR is during the attacks and return back to normal between the attacks [7]. Plasma fibrinogen ,serum haptoglobin , ceruloplasmin and C-reactive protein are elevated during the episode [13] .

Diagnosis :
FMF is characterized by paroxysmal attacks of fever , peritonitis and pleurisy or arthritis. FMF is almost confined to population of Mediterranean origin and it is often familial ; the diagnosis is mainly clinical [14]. In individual appropriate ethnic background with typical recurrent , self limited attacks. Recently it has been reported that infusion of Metaraminol diluted in normal saline provokes acute signs and symptoms with a high degree of specificity for the disease. Chromosomal mapping studies that have determined the genomic location of FMF gene have also identified microsatellite DNA markers kindred's [3]. When the patient is first seen or when attacks are infrequent , a variety of acute febrile conditions must be excluded e.g. appendicitis , pancreatitis, cholecystitis, intestinal obstruction. Familial hyperlipidemia and porphyria associated with abdominal symptoms must also be considered [8].

Treatment :-
Colchicine is recommended as daily prophylactic therapy in patients with familial mediterrian Fever to prevent febrile paroxysms.
The drug is known to be a potent inhibiter of mitotic activity and might therfore be expected to have a significant adverse effects on tissues that undergo rapid turnover [15].
Colchicine therapy have shown that prophylactic colchicine 0.6 orally 2-3x a day prevents or substantially reduced the acute attacks of FMF in 75-90% of patients [12].Treatment failures are often associated with noncompliance and or intorlance to the drug .
A wide spread use of colchicine has resulted in dramatic decrease in the incidence of amylodosis.

Patient and methods:
This is prospective and retrospective study conducted in a private gastroenterology clinic involving thirty patients with a diagnosis of familial Mediterranean fever.
The aim of the study is to know the demographic and clinical characteristics of the disease. They have been studied according to their race , sex, age of presentation , duration of the illness before the diagnosis , residency , their family

history , previous surgical interventions, laboratory investigation and clinical features .
Most of these patients have been submitted to all investigations which include upper and lower endoscopy, plain abdominal X-Ray, Barium contrast studies, ultrasound and laboratory investigations of other differential diagnosis of familial mediatrianin fever .
The criteria of diagnosis depend on the clinical features characterized by sporadic , paroxysmal attacks of fever and serositis with intervening asymptomatic periods that may range from as short as one week to many months, or response to colchicine trial therapy which may include less than one attack per six months to less than one attack per three months [15] or depend on both clinical features and colchicine trial therapy.
We don't have the facility of gene study neither other supportive laboratory investigations.

Results:
This study included thirty patients
18 patients are male (18/30=)60%)
12 patients are female (12/30=)40%)
This study has showed the following :
Age incidence :
- Nine patients (30%) of cases the onset of the disease was in the first decade of life .
- In Fifteen patient (50%) of cases the onset of the disease was in the second decade of life.
- While Six patients (20%) of cases the onset of the disease was in the third decade of life.

Family history :
Out of 30 patients ; 20 patients have positive family history for the disease (66%)

Residence :
- 21 patients live in the middle of Iraq (21/30=70%)
- 8 patients live in the north of Iraq (8/30 = 27%)
- 1 patient lives in the south of Iraq = 3%)

Duration of illness before diagnosis :-
- 20 patients were diagnosed before 5 years after starting their illness (20/30=66%).
- 5 patients were diagnosed after 5 years of starting their symptoms (5/30=17%).
- 5 patients were diagnosed after 10y of starting their symptoms (5/30=17%).

Surgical intervention:
Only 5 patients have been submitted to surgical intervention
(abdominal surgery) (5/30=17%).

Laboratory findings: ESR:
- 11 patients had elevated ESR below 40 mm/h (36%).
- 19 patients had elevated ESR above 40 mm/h (19/30 (64%).

WBC count and neutrophilia:
- 17 patients have elevated WBC count above 10 000 cell/mm (56%).
- 13 patients have WBC count below 10 000 cell/mm^3 (44%).

Criteria for diagnosis : Based upon:
- Response to colchicines therapy trial only (9) patients (30%).
- Clinical feature only 4 patients (13%).
- Clinical feature & colchicine therapy 17 patients (58%).

Discussion :
In this study the male to female ratio is 3/2 which is similar to other study (3).
Most patients with FMF experience their first attack in early childhood. In (65%of cases) , the initial attack was before the age of 10 years , and in 90% before the age of 20 [17]; in another study the onset of the disease in most of patients (51.3%) was before the age of 10 years and none of patients was experienced his first attack after the age of 20 years [18] . In this study the first attack in 30% was experienced before the age of 10 and in 80%before the age of 20 years , these may be explained on the basis of lack of awareness of this disease in children among pediatricians and general practioners. After the age of 10 and because of the chronicity of the disease , the patients family seeks the attention of the specialist In this study the family history was positive for the disease in 66% of patient while it was in 82.8% in a Turkish study [12].

This may be due under diagnosis of the disease rather than incomplete penetrance [19]. Despite the fact that the disease is familial , in about 50% of cases a family history may not be identified [12].
Almost all the patients lived in the middle & North of Iraq.
The duration of illness before the diagnosis ranged from 3-14 years.
The most important laboratory findings in this study is [1] elevated WBC count > 10000/mm^3 which was found in 64% of cases while it was over 80.9% in a Turkish study[8] fratthe ESRwas more than 40mm/hour in >75% patients [18] ,this may be due to the fact that the disease run a milder course and seems to bear a better prognosis in Arabs ,Druzes and Iraqi jews [12].
A number of diagnostic criteria have been proposed for the diagnosis of FMF but most physicians have gone directly to a colchicine trial if a patient is suspected of having FMF [19], the clinical criteria for the diagnosis in combination with classification tree format have been proposed ; in one reports , these criteria had a sensitivity as high as 95% and specificity as high as 99% for the diagnosis [19] in this study those whose diagnosis was on the basis of colchicine trial alone are 30% , while those whose diagnosis was made on the basis of the clinical features of the disease and response to colchicine trial are 58% while those whose diagnosis was on the basis of clinical feature alone were 12%,this may be due to the fact that unawareness of the disease or milder atypical course and lack of other important genetic or laboratory investigation .
Almost all patient are responding dramatically to colchicine treatment, control of pain , milder & significant decrease in frequency of the attacks, this is consistent with other study done in Turkey [12].

Surgical intervention:

About 17% of patients were submitted to abdominal surgery while surgery due to bowel obstruction due to previous adhesion resulting from recent sterile peritonitis or previous surgery is in 3% of the cases [9].

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