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

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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 among patients of Mediterranean origin (2), its 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 heterogeneity 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\(^\circ\) 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 previous episodes of sterile peritonitis or due to previous surgery which may lead to small bowel obstruction in 3% of cases (5).

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).

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4- Musculo skeletal:
non specific mild arthralgia is a common feature 
of febrile attacks and acute mono articular or 
oligoarticular arthritis may occur ,It’s frequently 
observed among Israeli patients. Arthritis 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 corticosteroids (11).

5- Skin manifestation:
Erysipelas like skin lesions are commonly 
described , other skin lesions including Henoch- 
Schonlein purpura-non specific purpura , diffuse 
erthema 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 
etnic 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 mediterranean 
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 
intolerance to the drug . 
A wide spread use of colchicine has resulted in 
dramatic decrease in the incidence of amyloidosis.

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 mediterranean 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 live 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%).

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/mm³ (56%).
- 13 patients have WBC count below 10 000 cell/mm³ (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/mm³ which was found in 64% of cases while it was over 80.9% in a Turkish study (8), the ESR was 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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