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Familial Mediterranean Fever

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Abstract:

Familial Mediterranean Fever (FMF) or recurrent polyserositis is an inherited multisystem disease manifested by recurrent painful attacks affecting the abdomen, chest or joints, often accompanied by fever and sometimes a skin rash. FMF is a genetic condition, inherited in an autosomal recessive fashions. FMF could be described as a disorder of inappropriate inflammation of one or more of serusal membrane (serositis). The diagnosis of FMF is generally based on the clinical criteria although the direct analysis of MEFV gene is the only method to be certain of the disease. The goals of therapy are to reduce the morbidity and prevent complications of the disease, which is consists of taking colchicine, a neutrophil suppresisive agent. Since FMF is a genetic disease, it can be prevented only if the carriers of the defective gene are identified.

Key Words: Familial Mediterranean Fever, Clinical Presentation, Diagnosis, Treatment and Prevention.

Introduction:

Familial Mediterranean Fever (FMF) or recurrent polyserositis [1-2] is an inherited multisystem disease manifested by recurrent painful attacks affecting the abdomen, chest or joints. FMF is often accompanied by fever and sometimes a skin rash [3-6]. Despite its striking symptom pattern, FMF was first described as a distinct entity in 1945 [2]. It is the most common and best

understood of the hereditary periodic fever syndromes [7-8].

FMF, other names:FMF is also known by many other names, they include: Recurrent hereditary polyserositis, benign paroxysmal peritonitis, familial recurrent polyserositis, periodic fever, periodic amyloid syndrome, periodic peritonitis syndrome, Armenian syndrome, Reimann periodic disease and Siegel-Cattan-Mamou syndrome.

Etiology:

FMF is a genetic condition, inherited in an autosomal recessive fashion [1-8]. The underlying cause of FMF is a mutation in a gene known as MEFV (Mediterranean Fever) gene, which is located on the short arm of chromosome 16 [8-10]. The disease affects approximately 150/000 individuals [9] world wide with a prevalence that varies according to the populations studied. It is most prevalent in people of Armenian, Sephardic Jewish, Levantine Arabic and Turkish ancestry [3-4,6,8]. The estimated frequency of FMF within the affected populations range from 0.02 to 0.2% and the carrier frequency has been estimated to be as high as 1-5% 1. The FMF gene (MEFV) was cloned in 1997 [6,11] and the most frequent mutations (M 680 I, M 694 V, V 726 A, M 694 I and E 148 Q) are found in more than two thirds of cases [12-15].

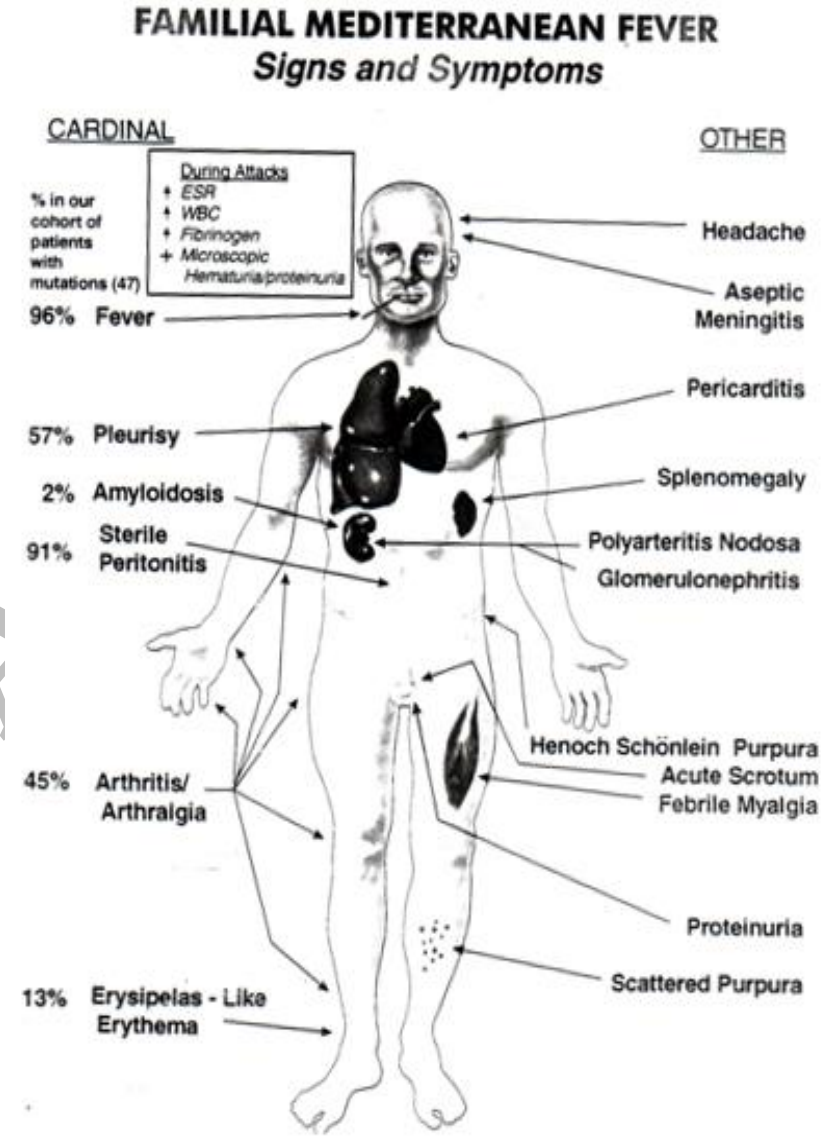
Pathophysiology:

FMF could be described as a disorder of inappropriate inflammation. That is, an event that in a normal situation causes a mild or unnoticeable inflammation, might cause a severe inflammatory response in someone with FMF. The symptoms of FMF are due to inflammation of one or more of the serosal membranes (serositis). Episodes of FMF are associated with inflammation of sheets of tissue covering the organs (serosal membranes) inside the abdominal cavity (peritonitis), the chest cavity (pleurisy) and joints (arthritis) [2]. The exact pathogenesis of FMF is not known [11,16-18]. During an attack, large numbers of neutrophils move into the affected area and causing painful inflammation and fever 7,16. The MEFV gene produces a protein called pyrin (because of the predominance of fever) or marenostrin (by the French consortium) [2,6,9]. This protein is expressed mostly in neutrophils [19-20] in serosal cells lining the peritoneal and pleural spaces or in synovial cells. Therefore, these areas of the body are at risk of FMF related symptoms. The protein was not expressed in lymph nodes, spleen, thymus or bone marrow. In fact, the precise function of pyrin is still uncertain. The pyrin protein may function as an inhibitor of a chemotactic factor (C5a) [21-24], perhaps interlukin 8 (IL 8) [25] or suppressor cells[26-27]. Patients with normal pyrin may have the ability to deactivate the target chemical factor when it is produced in response to an inflammatory stimulus. Patients with FMF, however lack this ability [6,11,28-29], resulting in uninhibited activity of the chemotactic factors and episodes of inflammation in the peritoneum, pleura or joints with associated fever. Presumably, these inflammatory episodes lead to excess production of amyloid A (AA) protein with subsequent deposition in the kidneys. Exactly what causes pyrin in FMF to lose its ability to control neutrophils in some situation is not know.

Clinical presentation:

The recurrent acute attack of FMF typically begin in childhood although the disease may be evident even in infancy [2,15-16,30-31]. The pain usually is located in the abdomen, chest, joints or less commonly in the area surrounding the testis and sometimes in two or more of these areas at the same time (Fig 1) [2,7,9,16]. An FMF attack is nearly always accompanied by fever, but it may not be noticed in every case. Some people experience chills prior to the onset of fever [2,7,16]. The attacks usually last 48-96 hours, with the peak intensity occurring within the first 12 hours [7,15-16]. The time interval between attacks ranges from days to months or even longer 9. Between attacks, most victims are completely without symptoms. It is not entirely clear what brings on an attack, however people with FMF often report mild physical trauma, physical exertion or emotional stress just prior to the onset of symptoms [16].

FIG. 1



Sex: In adults, FMF is more prevalent in males, with a male to female ratio of 1.5-2:1 [32].

Age of onset: [2, 15-16, 30-31]

Younger than 10 years: occurrence of 60-70%.

Younger than 20 years: occurrence of 80-95%.

Older than 20 years: occurrence of 5-10%.

Older than 40 years: rare occurrence.

Fever: Temperature rises rapidly to 38-40°c [2]. Temperature increase may occur before the other manifestations. In mild attacks, fever may be the only manifestation. Sometimes the disease may present as pyrexia of unknown origin (PUO) [33-34].

Peritoneal symptoms: Nearly all patients with FMF experience abdominal pain which is the most common complaint, with about 50% citing such episodes as the first symptom[2,7,9,16,35-36]. The hallmark of FMF is the recurrent acute attacks of febrile peritonitis. The pain can range from mild to severe and may be diffuse or localized[2,7,9,16]. The pain may mimic appendicitis, cholecystitis or renal colic and the patients have frequently underwent surgery before diagnosis of FMF[2,7,37]. Most patients experience either constipation or intact bowel habit during attacks, yet in 20% of the patients diarrhea may occur [2,9]. The other uncommon abdominal manifestations include ascites, mechanical obstruction, paralytic ileus, bowel infarction, bleeding and inflammatory bowel disease (IBD)[9,38-39].

Pleural and pericardial symptoms: The frequency of these attacks varies among ethnic groups, with 25-80% of patients reporting pleuritic episodes [2,7,16]. The pain is usually on one side of the chest. Pericarditis may develop and present with chest pain [2]. Tamponade and constrictive pericarditis are very rare. Sometimes acute or recurrent pericarditis or pleuritis may be the presenting manifestation of FMF[2,40]. Myocardial infarction and pulmonary hemorrhage has been reported secondary to vasculitis in these patients [41-43].

Synovial symptoms : These symptoms also vary, from 25-85% in reported series [2,7,35-36]. The acute episode may resemble gout. The pain is usually confined to one joint at a time and often involves the hip, knee, ankle and wrists [2,7,16]. Between attacks, the joints are normal. Arthritis symptoms tend to last several days longer than abdominal symptoms. The course of arthritis is generally benign [44], however in some peoples, the recurrent joint pain becomes chronic arthritis and sacroilitis has been reported also [45-47]. Sometimes the disease may present with recurrent polyarthritis [5,48]. Joint involvement can be the earliest manifestation of FMF [5,49]. In these situations the disease may be misdiagnosed for systemic JRA [2,5,49-50]. Temporomandibular joint arthritis is a rare manifestation of FMF, which improves with intra articular corticosteroid injection [51-52].

Myalgia: Up to 25% of patients with FMF report muscle pain [7]. These episodes typically last less than two days and tend to occur in the evening or after physical activity[2,7]. Three clinical patterns of myalgies have been identified[53]: 1)spontaneous pattern, 2) exercise induced pattern, 3) protracted febrile myalgia syndrome (PFMS). Rare cases of muscle pain and fever lasting up to 6 weeks have been reported [54]. These episodes do not respond to colchicine and

sometimes require steroid therapy. Protracted febrile myalgia is an uncommon dramatic clinical manifestation of FMF that may occur despite colchicine therapy and requires treatment with corticosteroid[55-57].

Cutaneous manifestation: An erysipelas like rash, most often occurs on the front of lower leg or top of foot[2,7,58]. The rash appears as a red, warm, swollen area, about 10-15cm in diameter [9]. Rash and fever may be the only manifestations of an attack of FMF. Recurrent urticarea also has been reported as an infrequent skin manifestation of FMF [59-60].

Scrotal attacks: Inflammation of the tunica vaginalis testis (scrotal swelling) may mimic torsion of the testis: It is usually unilateral and is self-limited and lasts from few hours to 5 days [7,61-62]. Scrotal swelling may be the only presenting feature or the first manifestation of FMF in male patients [63].

Pelvic symptoms: An FMF attack, when restricted to pelvic region, simulates acute pelvic inflammatory disease (PID)9,64. In these cases, attacks are frequently precipitated by menstruation or pelvic instrumentation [64]. Many of the attacks lasts between several hours and up to 24 hours. The use of female sex hormones, prompted by the observation of freedom from attacks in some patients during pregnancy and lactation, has proved beneficial in some patients unresponsive to the usual treatment with colchicine has been occasionally tried in an attempt to control this form of FMF65-66. The awareness of the possibility of pelvic attacks is important to avoid unnecessary surgery in these patients.

Vasculitis: An increased incidence of Henoch-Schonlein Purpura (HSP) and polyarteritis nodosa (PAN) is reported in FMF, even in childhood [8,67-72]. Behcet's disease also occurs more often [73].

Hepatic involvement: Acute hepatitis and recurrent hyperbilirubinemia have been reported in the course of FMF which are responsive to colchicine [74-76].

Amyloidosis: FMF is associated with high levels in the blood of serum amyloid A (SAA)[2,7]. Amyloidosis may affect the GI tract, liver, spleen, heart and testis, but effect on the kidneys are of greatest concern. The frequency of amyloidosis varies among different ethnic groups [2].

In the appropriate ethnic group, proteinuria, followed by the development of nephrotic syndrome (NS) and finally death due to renal disease, inevitably occurs. Amyloid nephropathy without preceding attacks may be the presenting event in some patients with a family history of FMF. Chronic renal failure due to amyloidosis has been reported in patients as young as 10 years [77]. Once renal amyloidosis develops, progress to end-stage renal failure is almost inevitable within 3-12 years78. Some patients with otherwise typical FMF may develop gross hamaturia, oliguria and acute renal failure without previous proteinuria[79-80]. Renal vein thrombosis may occur in 1/3 of patients [81-82]. The frequency and severity of attacks of disease seems to have no relation of developing amyloidosis. In fact a few of people with FMF have been described who have amyloidosis, but apparently no other FMF related symptoms. Goiter and hypothyroidism also have been reported even in children due to amyloidosis[83].

Neurologic manifestations: Headaches occur frequently during attacks of FMF [84]. Aseptic meningitis 84-86 (with increased cerebrospinal fluid protein and variable number of leukocyte in the fluid), pseuodutumor cerebri [87] and cranial

nerve involvement [88] also has been reported, which are responsive only to colchicine therapy.

Opthalmic manifestations: Optic neuritis has been reported as a rare clinical manifestation of FMF [89-90]. Fundoscopy may reveal retinal colloid bodies in some patients [2].

Reproductive system: FMF, amyloidosis and colchicine may affect the reproductive system of male and female patients [91]. Untreated women with FMF have up to 30% incidence of infertility due to ovulatory dysfunction and peritoneal adhesions [92-93]. In males, progression of the disease may induce testicular impairment and consequently affecting spermatogenesis [6,94]. Colchicine treatment improves the prognosis of patients with FMF and increase their reproductive ability [91].

Physical findings:

Physical findings depend mostly on the serosal surface involved.

Temperature: Temperature as high as 40oc can occur, but rapidly returns to normal in most cases within 12 hours [2].

Abdomen: A board like or surgical abdomen occurs with typical findings, ie, abdominal tenderness with distention and decreased bowel sounds 9. Splenomegaly is common in response to the inflammation [2,35]. Recurrent jaundice has been reported during attacks [74-76].

Chest: Patients wit pleural or pericardial involvement have chest pain. The pleurisy is usually unilateral, and examination often reveals diminished breath sounds and a friction rub [7].

Joints: Show typical inflammatory changes with warmth, erythema or swelling [44,47].

Skin: A well demarcated, erythematous, warm rash with swelling, particularly bellow the knee ranging from 15-20 square centimeter may be seen [9].

Muscles: May be tender in patients with painful myalgia [55-57].

Female genitalia: Painful, tender, enlarged ovaries may develop, mimicking PID [9,64].

Males genitalia: Unilateral, erythematous and tender swelling of the scrotum occurs in scrotal attacks [61-63].

Amyloidosis: Usually is asymptomatic. Hypertension is reported in upto 35% of patients. Renal vein thrombosis may develop and presents with relative symptoms or signs [81-82].

Laboratory studies:

Results of routine blood test performed during the acute attacks are non specific. In all attacks, the blood findings include leukocytosis, elevated ESR, elevated acute phase reactants, including CRP, fibrinogen, haptoglubin, C3, C4 and serum amyloid A (SAA) [2,16,19,95-97]. Proteinuria may present [98-99]. Hematuria occurs in 5% of patients, most probably secondary to PAN or glumerulonephritis[7,9,80,100-101]. Analysis of joint fluid reveals 200 to 1/000/000 white blood cell/mm3 [44,102], with a predominant neutrophils and an elevated total protein concentration. Laboratory abnormalities return to normal after the resolution of the attack [9].

Imaging studies:

The findings during an acute attack are as expected in patients with peritonitis, pleuritis and arthritis, ie, air fluid levels [7,9], pleural effusion 103 and synovial effusion [104]. CT is a useful technique for the early diagnosis of destructive arthritis [46] and acute abdominal attack [105].

Diagnosis:

The clinical symptoms of FMF are non specific and difficult to distinguish from similar symptoms arising from completely different diseases, ie FMF is easily mistaken for appendicitis [2,7,37]. Therefore the diagnosis of FMF requires a high index of suspicion 1,35-36 and is based on the clinical criteria [9,106] of acute, reversible serosal attack and positive family history for FMF (Table 1) [7]. When available, until recently, the only diagnostic laboratory test for this disease was the documentation of C5a-inhibitor deficiency in serosal or synovial fluid1, a laborious assay that requires an invasive procedures. FMF should be suspected for any patient who:

1) Has had at least four episodes of abdominal pain or chest pain or both, lasting from 24-72 hours.
2) Without symptoms between attacks.
3) Does not have any other condition that would explain the symptoms.
4) Has positive family history of FMF.
5) Responds to colchicine.

The direct analysis of the MEFV gene for FMF mutations is the only method to be certain of the diagnosis [2,16,106-109]. However it is not yet possible to detect all MEFV gene mutations that might cause FMF. Thus if DNA analysis is negative, clinical methods must be relied upon.

If the colchicine eliminates or decreases the number of attacks, the diagnosis of FMF is confirmed; because colchicine does not help any other diseases with similar symptoms. However, if colchicine is not effective, FMF can not be ruled out. Accurate diagnosis of FMF is important not only for genetic consultation and avoidance of unnecessary colchicine therapy, but also for prevention of avoidable laparatomies and also for early colchicine therapy [1,37,95]. The diagnosis of amyloidosis may be made expediently and safely by rectal or bone marrow biopsy [110].

Differential Diagnosis

Similar symptoms of periodic fever and inflammation can be seen in familial Hibernian fever and hyperimmunoglobulinemia D syndrome (Table 2) [16,111-118].

Table 1. Criteria for diagnosing familial Mediterranean fever*

Major Criteria:	Typical attacks (≥3 of the same type, rectal temp. ≥38°C, at tacks lasting 12 hr to 3 d):
	Peritonitis
	Pleuritis (unilateral) or pericarditis
	Monarthritis (hip, knee, ankle)
	Fever alone
Minor Criteria:	Incomplete attacks (typical attacks with 1 or 2 of the following exceptions: 1) temperature < 38oC, 2) attacks lasting 6-12 hours or 3-7 days, 3) no signs of peritonitis during abdominal attacks, 4) localized abdominal pain, 5) arthritis in joints other than hip, knee or ankle) involving 1 or more of the following sites:
	Abdomen
	Chest
	Joint
	Exertional leg pain
	Favorable response to colchicine
Support criteria	Family history of FMF
	Appropriate ethnic origin
	Age < 20 yr at disease onset
	Features of attacks:
	Severe, requiring bed rest
	Spontaneous remission
	Symptom-free interval
	Transient inflammatory response, with 1 or more abnormal test result (s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
	Episodic proteinuria/hematuria
	Unproductive laparotomy or removal of white appendix
	Consanguinity of parents

* An FMF diagnosis require ³ 1major criteria, or ≥ 2 minor criteria, or 1 minor criteria plus ≥ 5 supportive criteria, or 1 minor criteria plus ≥ 4 of the first 5 supportive criteria.

Table 2. Clinical differentiation of three hereditary periodic fever syndromes

	Familial Mediterranean Fever	Hyperimmunoglobulinemia D Syndrome	Familial Hibernian Fever
Typical Ethnicity	Jewish, Armenian, Arab, Turkish	Dutch, other European	Irish
Prevalence	As high as 1:100	88 cases reported	24 definite cases (one family)
Inheritance	Autosomal recessive;gene is MEFV,on 16p 13.3	Autosomal recessive; gene unidentified but is not MEFV	Autosomal dominant; gene unidentified but is not MEFV
Age at Onset	90% by age 20	96% by age 10	Usually childhood
Length of Attacks	1 to 3 days	3 to 7 days	Variable: 1 day to several weeks
Abdominal Involvement	Peritonitis; constipation more frequent than diarrhea	Severe pain and vomiting; diarrhea more frequent than constipation	Pain; diarrhea or constipation; sometimes peritonitis
Pleuritic Involvement	Frequent	None reported	Frequent
Rheumatologic involvement	Monarticular arthritis	Oligoarticular, symmetric arthritis or arthralgia	Arthralgias common
Cutaneous Involvement	Occasional, with erysipeloid erythema, usually below knee	Common, with erythematous macules or papules	Common, with tender erythematous patches
Lymphadenopathy	Uncommon	Very common (cervical, axillary, inguinal)	Common
Conjunctivitis	Uncommon	Uncommon	Frequent
Myalgias	Febrile myalgia uncommon	Uncommon	Frequent
Scrotal pain	Rare episodes in childhood	None reported	50% of males
Amyloidosis	Common, perhaps especially in association with M694V MEFV mutation	None reported	1 case reported
IgD	Elevated in 13%	Exceeds 100 IU/ml (14mg/dl)	Elevated in 10%
Treatment	Oral colchicine to prevent attacks and amyloidosis	No known prophylaxis; arthritis may respond to NSAIDs or steroids	Steroids often effective, NSAIDs less so
Prognosis	Good (with colchicine to prevent amyloidosis)	Disease has no apparent effect on longevity	Disease has no apparent effect on longevity

Treatment:

The goals of therapy are to reduce morbidity and to prevent complications of the disease. Treatment of FMF at this point consists of taking colchicine, a neutrophil-suppressive agent. Studies have shown that 75% of FMF patients achieve complete remission of their symptoms and about 95% shown marked improvement with colchicine [9,11]. Colchicine is so effective in preventing attacks of FMF and the development of amyloidosis that the most important aspect of medical care is to make the correct diagnosis and to institute therapy.

Colchicine therapy:

The first effective therapy for FMF with colchicine was reported in 1972 [2,119]. In adults usually colchicine is institute with 0.6mg bid. In patients who do not respond to twice a day, administer colchicine 3 or 4 times per day [2,7,120]. In children the optimal effective dosage of colchicine is about 0.02-0.03 mg/kg/24 hr (maximum of 2 mg/24 hr)[15]. It has been shown that children younger than 5 years of age may need colchicine as high as 0.07mg/kg/24hr [121]. The largest series evaluating the long term efficacy of colchicine was published in 1991 [122]. This report described the outcome with the prophylactic use of colchicine in 45 patients with FMF treated for 15 years. The dosage of colchicine administered varied from 1 to 3 mg daily, with most patients taking 1 to 1.5 mg. In this study 72% of patients had good response to colchicine, 15% had a partial response and 13% failed to respond. In another study of 21 colchicine non-responders eleven cases were in fact non compliant [123].

In patients who do not respond to oral colchicine, the use of intravenous colchicine [124], interferon-alpha 1[25-126], thalidomide [127,] tumor necrosis factor (TNF) or alpha blocker prazosin[128] may be effective. The colchicine will stabilize the proteinuria in patients with amyloid nephropathy and also prevent amyloidosis[8,129-130]. Colchicine is not likely to be effective in patients who already have chronic renal failure, since irreversible glumerular injury is probably present. The treatment of FMF attacks in patients who cannot use colchicine is an important problem. There are insufficient data about the use of immunosuppressive agents in the treatment of FMF attacks, however colchicine 0.05 mg/day and azathioprine 2 mg/kg/day have successfully controlled the attacks [131]. Long-term colchicine therapy is quite safe, highly effective with only mild and infrequent side effects [121,132-133].

Compliance with taking colchicine daily may be hampered by its side effects, which include diarrhea, nausea, abdominal cramps and gas passing [9].

Allogeneic bone marrow transplantation has been suggested as a modality for treatment of FMF [134].

Given its genetic nature, there is no cure for FMF, nor is there likely to be in the near future, thus colchicine therapy should be continued for life [131].

Episodes of prolonged myalgia with fever and severe pain may need treatment with prednisolone (1mg/kg/day) or NSAID for as long as 6 weeks [7,53-55]. Patients who develop seronegative spondyloarthropathy should be treated with NSAIDS135 and those with chronic destructive arthritis may need arthroplasty [45].

Colchicine use in children: The safety of prolonged colchicine administration in children considered as a major issue, since the majority of FMF cases begin in the first decade of life. There has been a theoretical concern over whether colchicine delays the normal growth process in children [121]. One series followed

children on prolonged colchicine therapy and found their height and weight curves to be clearly within the normal range [121,136]. Most investigators consider colchicine to be not only acceptable but absolutely indicated in children with FMF, whose growth and development could otherwise be retarded by frequent, debilitating FMF attacks[121,136].

Colchicine use during pregnancy and lactation: FMF has been associated with a higher than normal rate of miscarriage and infertility [6,91-93,137]. The prospective, long term, studies in women with FMF on colchicine therapy found that all of their infants were healthy. Colchicine therapy has never been associated with an increased risk of abnormalities in infants of mothers on colchicine therapy [6,138]. Thus colchicine therapy is recommended for pregnant patients with FMF [139]. A Separate issue is the safety of colchicine in nursing mothers. One report [139] serially measured the colchicine concentration in serum and breast milk of mothers on colchicine therapy. The concentrations in breast milk were low and similar to those in serum. These findings and the other clinical experiences suggest that nursing is safe in women with FMF who continue to take colchicine [139].

Colchicine toxicity: Colchicine is an alkaloid that may interfere with microtubule formation, thereby affecting mitosis and other microtubule-dependent functions [6,133,140]. Colchicine and its metabolites are excreted through the urinary and biliary tracts [132], thus it is a relatively safe and effective medication when used in appropriate dosage in patients with normal kidney and liver function.

Early recognition of colchicine toxicity is important because it can be fatal if undiagnosed and not managed properly. Gastrointestinal side effects include: diarrhea, nausea, abdominal cramps and gas passing [122] or mucosal injury which is characterized by hyperplastic crypts, villous atrophy pattern with increased mitotic rate [141]. The most common reported adverse effects of colchicine toxicity include: bone marrow suppression[142-145] (usually occurs on day 3 to 5 post exposure, with anemia, thrombocytopenia, leukopenia, agranulocytosis and pancytopenia), acute renal failure, rhabdomyolysis [146] and neuromyopathy [144,147-148] (muscle and peripheral nerve toxicity). Severe colchicine toxicity results in multiple organ failure, convulsions, coma and death [133].

Colchicine induced toxicity are usually reported in patients with renal failure or liver disease, thus dose reduction is recommended in patients with renal or hepatic disease and in the elderly [133,148]. Potentially, effective treatment with anti colchicine unfortunately is unavailable, therefore treatment of colchicine induced toxicity is supportive, with a rapid gastric decontamination with lavage and active carbone and appropriate hydration [149]. Patients usually rapidly improve with either colchicine dose reduction or discontinuation.

There is a theoretical risk that colchicine use could damage chromosomes in sperms and eggs or in an embryo during pregnancy or it might reduce fertility[150]. However, studies looking at reproduction in men and women who have used colchicine have not shown any increased risks [151-152].

Patient education: Patients and even parents need to understand the importance of strict compliance with daily colchicine therapy.

Out patients care: A urinalysis should be performed in every visit, if proteinuria is present, assess the patients carefully for compliance, and increase the daily dose of colchicine. If hematuria occurs with prolonged abdominal or muscle pain, suggests, the development of PAN.

Mortality and Morbidity

Amyloidosis:

The most serious and life threatening complication of FMF is amyloid nephropathy [2,7-8,19,79] which include: Nephrotic syndrome, renal vein thrombosis and renal failure. Left untreated, amyloidosis often leads to kidney failure, which is the major long term health risk in FMF. Colchicine is effective in preventing, delaying or reversing renal complications with amyloidosis [153-154]. Dialysis and renal transplant might became necessary in patients with advanced kidney disease [11,78].

Appendectomies:

Many undiagnosed FMF patients had appendectomies due to the severity of the peritoneal episodes [2,9,37].

Chronic arthritis:

About 5% of patients may develop chronic episodes of arthritis that sometimes leads to a destructive arthritis of the hip or knee and may necessitate joint replacement [45-47]. About 10% of patients with chronic arthritis may develop a seronegative spondyloarthropathy [47].

Fertility and pregnancy:

About one third of female patients are infertile and 20-30% of pregnancies result in fetal loss.

Prevention:

Since FMF is a genetic disease [1-4], it can only be prevented if carriers of the defective gene can be identified. This is not currently possible, because at the moment there is no diagnostic test to identify the carriers of the defective gene. Since now the gene of FMF has been cloned [8-10], it may soon be possible to develop tests that will allow people in high risk group to find out if they carry the gene.

Prognosis:

Patients who are compliant with daily colchicine probably can expect to have a normal lifespan[11,121,155]. For those individuals who are diagnosed early enough and take colchicine consistently, the prognosis is excellent. Most will have very few, if any, attacks of fever and polyserositis and will likely not develop serious complications of amyloidosis [2,7,155]. Even with amyloidosis, the use of colchicine, dialysis and renal transplantation, should extend a patient survival beyond age 50 years [8,77,127-128,156].

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