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REVIEW

Familial Mediterranean fever: clinical, molecular and management advancements

M. Lidar*, A. Livneh

Heller Institute of Medical Research, Sheba Medical Centre, Tel-Hashomer, affiliated with the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, *corresponding author: tel.: +972-3-530 21 56, fax: +972-3-530 21 14, e-mail: merav.lidar@sheba.health.gov.il

ABSTRACT

Familial Mediterranean fever (FMF), the most frequent of the periodic fever syndromes, is an autosomal recessive disease, predominantly affecting people of Mediterranean descent. The disease is caused by mutations in the MEFV gene, encoding the pyrin protein thought to be associated with the interleukin-1 related inflammation cascade. The condition manifests as attacks of serositis, commonly involving the abdomen, chest or joints, typically accompanied by fever and elevated acute phase reactants. Attacks subside spontaneously within one to three days, without residue. Continuous treatment with colchicine, at a daily dose of 1 to 2 mg, reduces attack frequency, duration and intensity in the majority of patients, and also prevents the development of secondary amyloidosis, the most dreaded complication of the disease. In this communication we review the current state of the art in the diagnosis and care of FMF patients, starting with the presentation of a typical case.

KEYWORDS

Diagnosis, familial Mediterranean fever, treatment

CASE REPORT

An 18-year-old male of Turkish descent was referred to the clinic for evaluation of recurrent abdominal pain and fever. He had recently undergone an appendectomy, during an attack of severe abdominal pain, accompanied by fever of 38.5°C and signs of peritoneal inflammation, localised to the right lower quadrant. Analysis of blood, drawn prior to surgery, revealed a leucocytosis of 15,000/μl with a left shift, normal platelet count and haemoglobin level. Blood chemistry was normal, except for an elevated fibrinogen (680 mg/dl, normal<400). Erythrocyte sedimentation rate was high (60 mm/h) as was the C-reactive protein (CRP; 15 mg/dl, normal <0.5). There was trace of protein on urinalysis. Given the clinical and laboratory findings, compatible with acute appendicitis, the surgeons were surprised when only a nonphlegmonous appendix, with minimal serosal irritation, and small amount of turbid peritoneal fluid were found on laparotomy. Their bewilderment increased when, after an uneventful recovery, the patient returned to the emergency room with the same clinical findings a month later. A thorough anamnesis at that time yielded the information that he has suffered from similar episodes, about twice yearly, since the age of 15. The episodes resolve within a day or two, and are alleviated by a cocktail of an NSAID and acetaminophen. He knows that abdominal pain 'runs in the family', as his father and two of his cousins suffer from similar episodes, as did an aunt who had later died of end-stage renal disease. Once attacks resolve, he feels completely well, he is an avid sportsman and experiences no limitations in his pursuits.

EPIDEMIOLOGY AND GENETICS

Familial Mediterranean fever (FMF), an autosomal recessive condition, affects more than 100,000 people worldwide, and as such, is the most common of the hereditary periodic fevers. The disease is most prevalent among non-Ashkenazi Jews, Arabs, Turks and Armenians, with carrier frequencies of 1:5 to 1:16, 1:5, 1:5, and 1:7, respectively. Yet, it is observed worldwide due to the extensive population movements of the 20th century.[1]

FMF is caused by mutations in the MEFV gene, which encodes for the pyrin protein, expressed primarily in the myeloid cell lineage. Pyrin belongs to a class of proteins involved in the regulation of apoptosis and inflammation.

Its N-terminal pyrin domain interacts with the ASC adaptor protein, regulating caspase-1 activation and consequently, IL-1β production.[2] Mutations interfere with the role of the pyrin domain, allowing an uninterrupted inflammatory cascade.

CLINICAL FEATURES

Abdominal pain is the most common presenting feature of FMF, eventually occurring in 95% of patients.[3] The abdominal pain may be diffuse or localised, and varies in intensity from mild, without overt signs of peritonitis, to the more typical severe pain, which necessitates bed rest. It is exacerbated by breathing and accompanied by signs of peritoneal inflammation. Attacks begin suddenly, usually without a recognisable precipitating event and last for 6 to 96 hours. Women of child-bearing age may note a tendency for attacks to occur around menstruation.

Arthritis, typically involving a single knee or ankle, is another major disease manifestation, associated with local redness, swelling and tenderness.[3] Acute arthritic attacks tend to subside within the same time frame as described for abdominal attacks. Arthritis of upper extremity joints, protracted arthritis and a seronegative spondyloarthropathy have all been reported in association with FMF, in a small percentage of patients.[4,5]

Chest attacks, due to inflammation of the pleura, are reported by 30% of the patients. Usually they are unilateral and similarly to abdominal and joint attacks they resolve within hours to several days.[3]

A fourth disease feature, erysipeloid erythema, is described in 7 to 40% of patients.[3] It consists of erysipelas-like erythematous, shiny plaques, typically appearing on the shins.

FMF attacks are commonly accompanied by fever, often as high as 39°C, although not universally present in all patients or during all attacks in the same patient. Fever may at times be the only manifestation of an attack of FMF. Patients may describe recurring episodes of fever, without an obvious underlying cause or painful manifestation, each lasting a day or two, and resolving spontaneously.

Rare but distinctive attack manifestations of FMF include pericarditis (<1% of patients), acute orchitis (<5% of male patients) and protracted febrile myalgia (a steroid responsive condition, associated with paralysing muscle pain in the extremities, tenderness and, at times, a vasculitic rash and nephritis), entities which should be routinely enquired about when attempting to establish the diagnosis.

More than 50% of FMF patients experience premonitory symptoms, or a prodrome, heralding the FMF attack.[6] The prodrome may include discomfort at the impending attack site or various constitutional, emotional, and physical complaints, including irritability, dizziness, increased appetite, and altered taste sensation. A prodrome portends an attack in almost 100% of occurrences in affected patients and is thus a valid sign of an imminent attack. This time interval, which lasts 12 to 24 hours, may be used for prompt institution of preventive therapy prior to the impending spell, such as interferon-α (IFN-α).[7]

FMF patients markedly differ with respect to the features of their disease. The frequency of attacks, for example, may vary from several times a month to once every few years. The duration of the attacks ranges from several hours to several days. The site involved and the intensity in each site may also differ between patients and in the same patient in different attacks during the course of the disease.

Some patients may experience chronic manifestations in addition to the typical paroxysmal disease course. These may include features of spondyloarthropathy,[5] with pain and inflammation of central joints, fibromyalgia,[8] with diffuse bone, muscle and joint pain, as well as severe leg and/or foot pain on exertion,[9] sometimes associated with ankle swelling. An enlarged spleen, anaemia of chronic disease, and continuously elevated acute phase reactants may be found in 30% of inadequately treated patients.[10,11]

For the purpose of comparing patients, each exhibiting a diverse clinical spectrum, and in order to estimate disease burden, a severity scale was established. The scale is adjusted for two patient situations: colchicine-naive patients, usually in the process of undergoing a diagnostic evaluation, and colchicine-treated patients, under optimal control (*table 1*).[12]

LABORATORY ANALYSIS

Acute FMF attacks are associated with a nonspecific increase in inflammatory mediators, such as serum amyloid A, fibrinogen, ESR and CRP, as well as an elevation of the white blood cell count, typically returning to baseline levels in between attacks.[13-15] Urinalysis may detect haematuria and/or proteinuria, the significance of which is discussed subsequently. As mentioned previously, chronic subclinical inflammation, manifested by elevated CRP and serum amyloid A protein (SAA) levels during clinical quiescence, may be found in 30% of patients.[10]

Over the years, a myriad of cytokines, chemokines and other inflammation-associated proteins have been studied in FMF patients. These include IL-1, 4, 5, 6, 10, 12, 18 as well as TNF-α and γ, cytokine-associated receptors, complement proteins, adhesion molecules, growth factors, immunoglobulins and a large spectrum of antibodies.[11,16-26] The overall picture that emerges is that FMF is not an autoimmune disease. Rather, the cytokine/chemokine pattern is consistent with nonspecific inflammation. Unfortunately, these studies have not yielded FMF disease-specific or diagnostic laboratory tests.

Table 1. *Familial Mediterranean fever disease severity score*

Subgroup	Severity	Number of features	Features
Patients either not yet taking colchicine or not responding to colchicine therapy	Severe	2 or more	1. ≥2 attacks per month 2. Involvement of more than 1 attack site in >25% of attacks 3. Involvement of more than 2 attack sites during the disease course
	Moderate	1 or more	1. 18-24 attacks/year 2. Attack duration ≥4 days, on most attacks
	Mild		Neither severe nor moderate disease
Patients under optimal colchicine therapy*	Severe	3 or more	1. Involvement of more than 1 attack site in >25% of attacks 2. Involvement of more than 2 attack sites during the disease course 3. ≥2 mg/d colchicine (or less if intolerant) 4. ≥2 pleuritic attacks during disease course 5. ≥2 erysipeloid-erythema attacks during disease course 6. Age of onset ≤10 years
	Moderate	2	
	Mild	0-1	

*Attack-related features (e.g. frequency, site affected, etc.) refer to disease activity prior to colchicine treatment.

GENETIC ANALYSIS

Although over 80 mutations in the MEFV gene have been described, the majority of cases are caused by four mutations clustered on a single exon: M694V, V726A, M680I and M694I, the prevalence of which varies according to the population studied. In Turks, who constitute the largest ethnic group with FMF in the Netherlands, M694V would, in all probability, be the leading MEFV mutation (51% according to the Turkish FMF study group) followed by M680I (14%) and V726A (9%). Overall, around 80% of FMF patients have an identifiable MEFV mutation; 57% have two mutations, 26% have a single mutation, while 16% have no identifiable mutation.[27,28] A comparable distribution is found in all ethnic groups in which FMF is prevalent. Currently, the underlying mechanism for the expression of FMF in heterozygous or MEFV mutation-free patients is unclear.

The role of the exon 2, E148Q mutation, as a disease-causing mutation is controversial. This non-founder mutation is found in populations in which FMF is distinctly rare, such as the Japanese,[29] Chinese and Punjabi Indians.[30] Additionally, E148Q homozygotes are rarely found in the FMF population.[27] Yet, despite the slim penetrance of this mutation, most FMF experts refer to it as a mild disease-causing mutation. This mutation appears in 3 to 18% of the major ethnicities which are at risk for FMF.[27,31,32]

DIAGNOSTIC CRITERIA

Despite the cloning of the MEFV gene and the ongoing identification of new mutations, the diagnosis of FMF remains a clinical one for several reasons, the most notable of which is mentioned above, namely, the lack of identifiable MEFV mutations in at least 20% of patients with clinically proven FMF. The importance of making the diagnosis of FMF in patients without identifiable mutations is underscored by the observation that when M694V homozygotes, who tend to suffer a more severe disease course, are excluded, patients who bear no MEFV mutations are phenotypically similar to patients with recognisable mutations. The Tel Hashomer criteria (*table 2*) form the basis of the clinical diagnosis.[33] Clinical criteria are combined with results of MEFV mutation analysis and a therapeutic trial,[34] monitored by clinical response and SAA levels,[35] in a diagnostic algorithm (*figure 1*), which goes through the information and investigations, by the order in which they are usually processed in an office visit of a new patient suspected of having FMF.

THERAPY

Colchicine, an alkaloid, originally extracted from plants of the genus *Colchicum*, has been used in the treatment of gout since the first century CE. In 1972, Goldfinger first described its effectiveness in preventing FMF attacks, by reporting his experience with colchicine in five patients.[36] The use of colchicine in FMF over the past three decades has dramatically changed the course of the disease in two aspects. First, a daily dose of 1 to 2 mg renders most patients asymptomatic, and in others, reduces attack frequency and/or duration. Only 10% of patients are colchicine resistant and continue to suffer attacks at the same intensity as before. Second, reactive amyloidosis, the most feared complication of FMF (discussed subsequently), is almost completely prevented in patients adherent to their colchicine therapy, including the 10% of patients who fail colchicine attack prophylaxis.

The initial colchicine dose in patients with normal renal function and without proteinuria is 1 mg/day. If patients continue to suffer frequent attacks, the dose can be increased by 0.5 mg/day up to a total of 2 mg/day. For compliance purposes, we suggest taking up to 1.5 mg in a single, consolidated daily dose.

Table 2. *Criteria for the diagnosis of familial Mediterranean fever*[*]

Major criteria

Typical attacks

1. Peritonitis (generalised)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)

Minor criteria

1-3. Incomplete attacks involving 1 or more of the following sites:
   1. Abdomen
   2. Chest
   3. Joint
4. Exertional leg pain
5. Favourable response to colchicine

Supportive criteria

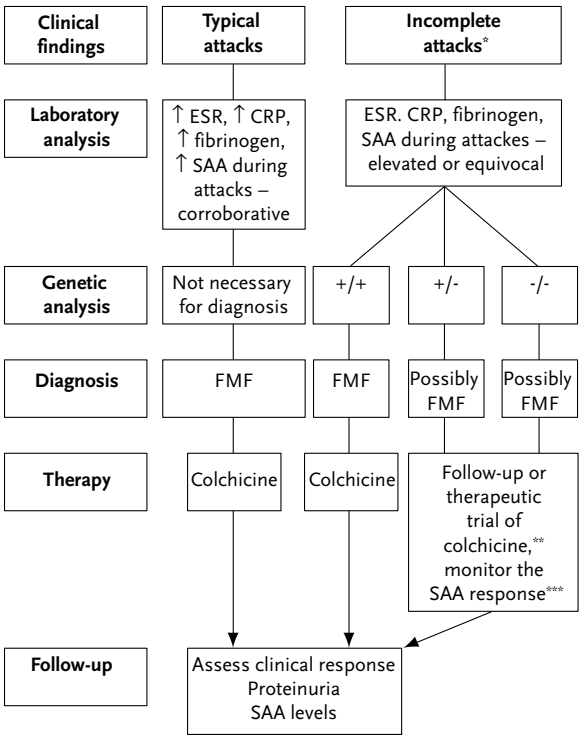
1. Family history of familial Mediterranean fever
2. Appropriate ethnic origin
3. Age <20 years at disease onset

4-7. Features of attacks
   4. Severe, requiring bed rest
   5. Spontaneous remission
   6. Symptom-free interval
   7. ransient inflammatory response, with 1 or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen

8. Episodic proteinuria/haematuria
9. Unproductive laparotomy or removal of 'white' appendix
10. Cosanguinity of parents

[*]**The requirements for diagnosis of familial Mediterranean fever are ≥1 major criteria, or ≥2 minor criteria, or 1 minor plus ≥5 supportive criteria, or 1 minor criterion plus ≥4 of the first 5 supportive criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (rectal temperature of 38°C or higher), and short (lasting between 12 hours and 3 days). Incomplete attacks are defined as painful and recurrent attacks that differ from typical attacks in 1 or 2 features, as follows; 1) the temperature is normal or lower than 38°C; 2) the attacks are longer or shorter than specified (but no shorter than 6 hours or longer than a week; 3) no signs of peritonitis are recorded during the abdominal attacks; 4) the abdominal attacks are localised; 5) the arthritis is in joints other than those specified. Attacks are not counted if they do not fit the definition of either typical or incomplete attacks.**

Figure 1. *Diagnostic algorithm*



ESR = erythrocyte sedementation rate; CRP = C-reactive protein; SAA = serum amyloid A protein; FMF = familial Mediterranean fever.
[*]**Typical and incomplete attacks are defined in *table 1*.**
[**]**Therapeutic trial with colchicine denotes evaluation of patient response to colchicine. If attacks continue, the colchicine dose is increased gradually to 2 mg/day. If attacks subside, colchicine is discontinued. Resumption of attacks serves to validate the diagnosis of FMF.** [***]**SAA levels during remission and their response to colchicine administration.**

The most frequent side effects of colchicine therapy are gastrointestinal: cramp, abdominal pain and diarrhoea. These may be avoided by commencing treatment at a subtherapeutic dose of 0.5 mg/day, and gradually increasing the daily dose by 0.5 mg increments, in divided daily doses. In more difficult cases, oral desensitisation, similar to that used in cases of allergic reactions, may be attempted. An optional desensitisation protocol is as follows: 1 ml of a 1 mg ampoule of colchicine diluted in 1000 ml of 5% glucose is given initially, after which the dose is doubled daily, until 0.25 mg is tolerated, at which point an oral tablet is commenced.[37] Most patients, however, tolerate an initial dose of 1 mg/day without perturbations.

As previously mentioned, the majority of patients experience a prodromal phase prior to the full blown FMF attack.[6] Institution of preventive therapy during this time interval may curtail the impending attack. Therapeutic options include a transient increase in the oral colchicine dose or the addition of a nonsteroidal anti-inflammatory drug (NSAID). If these simple measures fail, administration of IFN-α may be attempted. Although not studied in the prodromal phase proper, IFN-α was found to shorten attack duration and result in a depressed inflammatory response in some patients when administered in the early stages of the attack.[7]

TREATMENT OF RESISTANT CASES

About 10% of FMF patients suffer frequent attacks, despite compliance with colchicine therapy and are therefore deemed nonresponders. Reasons for nonresponsiveness remain a puzzle. Yet, an abnormality in colchicine consumption by mononuclear cells suggests that these patients sustain an additional genetic defect.[38] Therapeutic options for this important group of patients are unsatisfactory as proposed agents have only been studied in individual cases or in small, nonrandomised

trials. Nonetheless, patients suffering frequent or disabling attacks, on a maximal tolerated dose of oral colchicine, may be offered a therapeutic trial with 1 mg weekly intravenous colchicine, in addition to the regular oral regime.[39] Alternatively, efficacy of TNF inhibitors has been shown in several case reports, with significant improvement in attack parameters for both etanercept and infliximab.[40-42] Thalidomide, an anti-inflammatory agent with anti-TNF properties, was also efficacious in a small group of patients, albeit, disquieting due to side effects such as peripheral neuropathy and teratogenicity.[43] A fourth option might be IFN-α, which was successful at halting 18/21 FMF attacks in an open label trial,[44] although results were less encouraging in a larger placebo-controlled trial in which it was no more efficacious than placebo.[7]

REACTIVE AMYLOIDOSIS

Reactive (or secondary) AA amyloidosis is the most devastating complication of FMF. It is caused by the extracellular deposition of amyloid fibrils, consisting of β-pleated sheet configured polymers of the N-terminal fragments of the acute phase protein, SAA.[45] As amyloid slowly accumulates in various organs and tissues, organ dysfunction ensues, most prominently in the kidneys. The most common and perhaps the exclusive presenting feature of renal involvement due to AA amyloidosis is proteinuria, gradually progressing into nephrotic syndrome and/or renal dysfunction. Before the advent of colchicine therapy, amyloidosis was reported to occur in about 75% of FMF patients over the age of 40 years.[3] Ethnicity affects the prevalence of amyloidosis, with a high prevalence found in untreated North African Jews, Armenians and Turks. The explanation may reside in the increased prevalence of the M694V mutation in these ethnicities, a mutation that has also been generally recognised as a risk factor for development of amyloidosis in most ethnic origins other than Turks,[46,47] Additional factors which may increase the risk for developing amyloidosis are the SAA1 α/α genotype, male gender, joint attacks and a positive family history of amyloidosis.[48,49]

As proteinuria is the earliest sign of amyloidosis in FMF, patients should have a general urinalysis bi-yearly. If persistent proteinuria is revealed, the colchicine dose should be increased to 2 mg/day and histological confirmation obtained, by rectal (which is easier to attain and may show involvement prior to clinical symptoms) or by renal biopsy. Should proteinuria progress despite colchicine dose escalation, a therapeutic trial with the investigational compound eprosidate,[50] or with an anti-TNF preparation,[40-42] should be considered. Implication of TNF antagonists in FMF amyloidosis is inferred from case reports and retrospective analysis showing regression of proteinuria in non-FMF related reactive amyloidosis.[51] Also, angiotensin-converting enzyme inhibitors and cholesterol-lowering statins are typically added to the therapeutic regime, although their benefit in this patient population has not been evaluated. FMF patients with end-stage renal disease requiring dialysis therapy or renal transplantation should continue receiving colchicine, 2 mg/day, or less, if suffering from diarrhoea, in order to mitigate attacks and prevent amyloidosis in other organ systems as well as recurrent graft amyloidosis in the latter group.[52]

DIFFERENTIAL DIAGNOSIS

To the astute clinician, the diagnosis of FMF is generally straightforward, based on clinical criteria of recurrent attacks at typical sites. However, the episodic nature of the disease as well as its clinical manifestations, which mimic a myriad of disease states (*table 3*), coupled with, unfortunately, the lack of awareness of FMF on the part of physicians, contribute to the average diagnostic delay

Table 3. *Differential diagnosis of familial Mediterranean fever*

Abdominal attacks (recurrent peritonitis)
Appendicitis
Diverticulitis
Cholecystitis
Pyelonephritis
Pelvic inflammatory disease
Pancreatitis
Recurrent abdominal attacks (without peritonitis)
Peptic disease
Renal colic
Endometriosis
Menstruation pain
Irritable bowel syndrome
Chest attacks (recurrent pleuritic chest pain)
Pulmonary embolism
Pleuritis (idiopathic, infectious, autoimmune)
Pericarditis (idiopathic, infectious, autoimmune)
Joint attacks (recurrent synovitis)
Gout
Pseudogout
Spondyloarthropathy
Juvenile idiopathic arthritis
Febrile attacks (recurrent)
Lymphoma
Infections (malaria, relapsing fever)
PFAPA (periodic fever, aphtous stomatitis, pharyngitis, adenopathy)
Systemic conditions (recurrent febrile attacks involving ≥2 systems)
Inflammatory bowel disease
Hyper IgD syndrome
TNF receptor associated periodic syndrome
Acute intermittent porphyria
Behçet's disease
Systemic lupus erythematosus
Adult Still's disease

of ten years.[53] Apart from regional and systemic diseases, detailed in *table 3*, hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS), deserve special mention. These diseases, together with FMF and the rare cryopyrin-associated periodic syndromes (CAPS), constitute the bulk of hereditary periodic fevers.

TRAPS is a dominantly inherited disorder, caused by mutations in the TNF receptor and characterised by recurrent attacks of abdominal pain associated with disabling myalgias, erythematous migratory rash, conjunctivitis and periorbital oedema.[54,55] The disease was originally described in patients of Irish/Scottish ancestry but was later identified in other ethnicities worldwide. The age of onset, abdominal involvement, rash, myalgias and propensity for amyloidosis resemble FMF. However, TRAPS attacks tend to be longer than FMF attacks (up to several weeks as opposed to an average of three days in FMF). Myalgia and localised, painful erythema, which are the hallmark of TRAPS, are less common in FMF and migration of the rash and eye involvement are not features of the latter.

HIDS is an autosomal recessive disease, caused by mutations in mevalonate kinase.[56] It is mainly found in patients of Dutch and Western European origin, and should be differentiated from FMF, especially in these populations. HIDS typically appears in the first year of life with attacks consisting of spiking fever accompanied by abdominal pain, cervical lymphadenopathy, hepatosplenomegaly, arthralgias and skin rash. Attacks tend to dissipate within four to six days only to recur periodically in intervals of several weeks.[57] While hepatosplenomegaly may be found in FMF, peripheral lymphadenopathy, diffuse rash and oligo-polyarthritis are not attributes of the disease. Moreover, HIDS is associated with a marked elevation of serum immunoglobulin D and is only rarely (less than 1%) complicated by amyloidosis, further distinguishing the syndrome from FMF.

CASE INTERPRETATION AND CONCLUSION

Our case depicts a young adult with short episodes of severe abdominal pain, associated with fever, which resolve spontaneously, only to recur after a variable asymptomatic period. Peritonitis as the underlying cause of the clinical picture was observed in the episode ending in appendectomy, which was comparable with the other attacks. This scenario in itself fulfils the criteria for the diagnosis of FMF. His age, ethnic origin, history of explorative laparotomy and family history are corroborative details which strengthen the diagnosis in the present case and serve to affirm it in atypical presentations. Also, FMF attacks are typically associated with an inflammatory response, as depicted. Genetic analysis was not given, intentionally, as it is noncontributory in a typical case, such as this one. Moreover, even with negative results on mutation analysis, the diagnosis of FMF is definite in this case. However, in atypical presentations, homozygosity on mutation analysis serves to confirm the diagnosis, while heterozygosity typically warrants a therapeutic trial with colchicine. Therapy with colchicine serves a dual purpose of ameliorating attack frequency and severity as well as preventing secondary amyloidosis.

Of note, the frequency of appendectomy in FMF patients is double the reported rate in the general population (40% *vs* 12 to 25%), while the rate of noninflamed appendectomies is extremely high (up to 80%), undoubtedly due to the overlapping clinical presentation of the two diseases (unpublished observation). Reliance on clinical parameters, namely a change from the regular diffuse involvement to right lower quadrant abdominal pain, has been shown to be the best predictor of an inflamed appendix in FMF patients. Had the history of previous attacks, not dissimilar from the index one, been elicited from the patient, the unnecessary appendectomy could have been avoided.

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