
Familial Mediterranean fever—a not so unusual cause of abdominal pain

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Familial Mediterranean fever is a hereditary syndrome characterised by recurrent episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles. It is primarily diagnosed in people of Jewish, Arabic, Turkish or Armenian ancestry and is caused by mutations in the gene encoding for pyrin. Abdominal FMF attacks resemble the clinical presentation of ‘acute abdomen’, with severe abdominal pain and rigidity, but in FMF symptoms always resolve spontaneously. It is important to distinguish these regular pain episodes from small bowel obstruction due to adhesions to prevent life-threatening bowel strangulation. In most cases, colchicine will prevent new painful attacks. This seminar also discusses other causes of abdominal pain in FMF patients.

Key words: familial mediterranean fever; autoinflammatory syndromes; acute abdomen; colchicine; vasculitis.

CASE REPORT

A 24-year-old man of Turkish origin, living in the Netherlands, was referred to our University hospital because of unexplained abdominal pain. Since the age of 19, he

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suffers from episodes of severe abdominal pain, occurring about once every month. He abstains from eating or drinking during attacks because this increases the pain. Accompanying symptoms are often (though not always) high fever, mild diarrhoea, and sometimes chest pain. The pain resolves spontaneously within 2 or 3 days. Family history is negative, but his parents are cousins. On presentation to the emergency ward of a district hospital, which occurred regularly, physical examination was usually compatible with 'acute abdomen'. Laboratory evaluation during such an episode showed evidence of inflammation with increased serum concentration of C-reactive protein, but otherwise no abnormalities. Twice, laparotomy was performed because of suspected appendicitis or gastric perforation, which yielded a normal appendix, while biopsies showed microscopic evidence of haemorrhagic peritonitis. The patient met the clinical criteria for FMF and was started on colchicine 1 mg daily, with favourable effect. There was no evidence of amyloidosis. DNA analysis revealed that he was homozygous for a Met694Val mutation in the *MEFV* gene.

INTRODUCTION ON FAMILIAL MEDITERRANEAN FEVER (FMF)

This is a typical story for a patient with Familial Mediterranean Fever (FMF). FMF is a hereditary autoinflammatory disorder characterised by lifelong recurrent episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles (Table 1).^{1,2} In the majority of patients, these inflammatory attacks start before the age of 20.³ The onset of a typical FMF attack is acute, and the symptoms persist for only a short time (6–96 hours) before they resolve spontaneously. It is an autosomal recessive disease, which is most prevalent in people from the Mediterranean basin, including Sephardic Jews, Arabs, Turks and Armenians. Prevalence is estimated to be as high as 1 in 700 in Israel and 1 in 1400 in Turkey. There is often a delay of 5–10 years from the onset of symptoms before the correct diagnosis is made; major factors contributing to this delay were found to be patient's neglect of symptoms and physician's unawareness of FMF.⁴ Even in a region, where FMF can be encountered frequently, at least 11 FMF patients could be detected in a group of 59 children who had been given the diagnosis functional abdominal pain *per exclusionem*.⁵ The major long-term complication, which occurs in up to 40% of untreated patients with FMF, is AA type amyloidosis resulting in renal insufficiency.

FMF is caused by mutations in the *MEFV* gene, which encodes for the protein pyrin (or marenostrin).^{6,7} About 40 different mutations have been described until now, although just four or five mutations account for the majority of FMF cases. The function of pyrin was unknown at the time of discovery, but it has since been identified as

Table 1. Frequency of clinical features of FMF among 1558 patients, which include Jews ($n=515$), Turks ($n=601$), Arabs ($n=227$) and Armenians ($n=215$) (adapted from Ben Chetrit et al).²

Clinical feature	Frequency $n = 1558$ (%)
Fever	100
Peritonitis	94
Arthritis	54
Pleuritis	39
Rash	30

a cytoplasmic protein and member of a family of proteins that all contain a domain first described in pyrin, the so-called pyrin domain. These proteins are involved in regulation of inflammation, apoptosis and/or cytokine secretion. Pyrin is thought to indirectly regulate caspase-1 function, and therefore influence interleukin-1 β processing and apoptosis. Thus, FMF is caused by a disordered regulation of inflammation, resulting in excessive inflammatory attacks after 'trivial' stimuli.

ABDOMINAL ATTACKS IN FMF

Clinical presentation

Abdominal pain is the most frequent symptom encountered in FMF; 95% of patients report this as the main symptom during at least some of their fever episodes, while 50% cite such an 'abdominal attack' as the first symptom of their disease.⁸ Presentation of a typical abdominal attack will resemble that of 'acute abdomen'. Onset is sudden and acute, leading to rapid development of symptoms within 1–2 hours. The abdominal pain is usually diffuse throughout the entire abdomen, although in some cases it may be localized; it may be very severe in intensity. Patients prefer to lie still, as pain is aggravated on movement. This may be accompanied by any bowel activity, ranging from constipation (most often) to diarrhoea. Findings on physical examination will be compatible with 'acute abdomen' as well: distension of the abdomen, rigidity, direct and rebound tenderness, and reduced peristaltic sounds.⁸ The intensity of symptoms and signs of an inflammatory attack in FMF will decrease spontaneously after 12–24 hours, and usually, the attack resolves over the following 48 hours.⁸ Thus, after about 3 days the patient will be symptom-free again. The duration of remission is variable between patients and within patients and may last for weeks or months, or even longer.⁹ So-called incomplete abdominal attacks may occur. These differ from 'typical' abdominal attacks in one or two features, which may include absence of fever, minimal change in acute phase parameters, absence of 'true' peritonitis and/or localisation of the abdominal pain to a single specific abdominal area. It may be difficult to differentiate an 'incomplete' abdominal attack from other causes of abdominal pain, mainly because of its atypical presentation.^{3,10}

Laboratory and radiological evaluation

Laboratory examination during an FMF attack will reveal a vigorous acute phase response, including leukocytosis with a left shift, increased erythrocyte sedimentation rate and increased concentrations of C-reactive protein, fibrinogen and serum amyloid A protein.¹¹ Plain abdominal radiography may show dilatation of small bowel with air-fluid levels; in a study by Aharoni et al this was seen in 11 of 34 plain abdominal films made in symptomatic FMF patients.¹² On computed tomography (CT) scanning, the most common finding during an abdominal attack in FMF is non-specific mesenteric pathology, which may include engorged mesenteric vessels, thickened mesenteric folds and mesenteric and/or retroperitoneal lymphadenopathy.¹³ Minimal ascites, with or without focal peritonitis, splenomegaly and dilated small bowel loops may also be present on CT scanning (Table 2). No role for MRI in FMF has been defined yet.

On laparoscopy or laparotomy during an acute attack, it is possible to observe signs of peritonitis, including oedematous and hyperaemic peritoneal folds or greater

Table 2. CT findings in 14 patients with FMF during acute abdominal attack (adapted from Zissin et al).¹³

CT findings	No. of patients
Engorged mesenteric vessels and/or thickened mesenteric folds	12
Mesenteric and/or retroperitoneal lymphadenopathy	6
Ascites	6
Ascites with focal peritonitis	4
Splenomegaly	3
Dilated small bowel loops	2
Mural thickening of the ascending colon	1

omentum. Microscopic examination of omentum biopsies will reveal a sterile non-specific inflammation, which may be purulent or haemorrhagic and accompanied by signs of chronic recurrent peritonitis, such as peritoneal inclusion cysts.^{8,14} A sterile peritoneal exudate containing fibrin and polymorphonuclear cells is usually present in the peritoneal cavity.¹⁵ Fibrous adhesions may ensue (see below).

Diagnosis of FMF

FMF is a clinical diagnosis, and for diagnostic purposes, a set of clinical criteria was designed by Livneh et al¹⁰ (Table 3). However, this was validated in Israel in a population with a very high prevalence of FMF, and it is unknown whether they work as well in other populations.¹ The criteria include a beneficial response to colchicine. Additionally, DNA testing of the *MEFV* gene may be used as a confirmatory test.

Differentiating abdominal attack from other pathology in a known FMF patient

The inflammatory peritoneal exudate and recurrent peritonitis in FMF may lead to intraperitoneal adhesions. Adhesive small bowel obstruction is not uncommon in FMF

Table 3. Diagnostic criteria for diagnosis of FMF (Tel-Hashomer) (adapted from Livneh et al).¹⁰

Major criteria

1. Typical attacks with peritonitis (generalized)
2. Typical attacks with pleuritis (unilateral) or pericarditis
3. Typical attacks with monarthritis (hip, knee, ankle)
4. Typical attacks with fever alone
5. Incomplete abdominal attack

Minor criteria

1. Incomplete attacks involving chest pain
2. Incomplete attacks involving monarthritis
3. Exertional leg pain
4. Favorable response to colchicines

Requirements for diagnosis of FMF are ≥ 1 major criteria or ≥ 2 minor criteria. Typical attacks are defined as recurrent (≥ 3 of the same type), febrile ($\geq 38^\circ\text{C}$) and short (between 12 hours and 3 days). Incomplete attacks are defined as painful and recurrent attacks not fulfilling all the criteria for a typical attack.

patients, especially after previous (often unnecessary) abdominal surgical procedures. In a study of 355 children with FMF with a mean follow-up of 8 years, Ciftci et al identified 11 patients with adhesive small bowel obstruction, where adhesiolysis or resection of strangulated ileum or jejunum was necessary.¹⁶

It can be very difficult to differentiate between small bowel obstruction (a potentially life-threatening complication)⁸ and a severely painful, but otherwise harmless abdominal attack in FMF, which will resolve spontaneously. In the first case, surgical intervention must not be delayed, while in the second case this course of action might lead to further complications. The same is true for the differential diagnosis of acute appendicitis. In women, it can be difficult to differentiate an FMF attack restricted to the pelvic region from pelvic inflammatory disease.¹⁷ Such pelvic attacks are often precipitated by menstruation or pelvic instrumentation.⁸

The clinical course of the abdominal pain will often enable differentiation. In a typical FMF attack, signs and symptoms will peak within a few hours, remain stable for 12–24 hours and then gradually subside within an additional 6–12 hours, to resolve completely within 24–72 hours.⁸ In the case of small bowel obstruction leading to strangulation, or appendicitis, there will be a continuous progressive deterioration of the clinical picture. Most FMF patients are intimately familiar with the 'normal' pattern of symptoms during a typical abdominal attack, and close observation is warranted when the patient reports abdominal complaints which are experienced differently.⁸ In a small retrospective study of abdominal CT scanning in 17 known FMF patients with abdominal symptoms, Zissin et al were able to correctly identify two patients with appendicitis and one patient with complicated small bowel obstruction, while in the remaining 14 patients CT findings were compatible with mild peritonitis and acute surgical intervention could be correctly avoided (Table 2).¹³ Thus, the use of abdominal CT may be a promising tool for differential diagnosis in complicated cases.

Laleman et al report the use of fluoro-deoxy-glucose positron-emission tomography (FDG-PET) in a patient with suspected FMF and abdominal pain.¹⁸ FDG-PET demonstrated diffuse peritoneal uptake, fitting with diffuse peritoneal inflammation, but without local obstruction, appendicitis or other bowel diseases, such as Crohn's disease. The authors suggest that the use of FDG-PET during an FMF attack may be helpful for establishing the differential diagnosis, but its use is precluded by limited availability. Further research into its clinical applicability is warranted.

Treatment and management

Colchicine prophylaxis

First-line treatment of FMF is colchicine. Its clinical efficacy as prophylaxis in FMF was established 30 years ago in three small randomized controlled double-blind trials.^{19–21} All three had a crossover design and recorded number of fever attacks as primary outcome measure. Zemer et al¹⁹ included 22 patients (18 of whom were men) of Sephardic Jewish origin and 13 patients were included in the final analysis. The treatment consisted of twice daily 0.5 mg colchicine or placebo for 2 months each, in random order. The patients had a total number of 67.5 attacks during 2 months of placebo versus 17.5 during colchicine (atypical attacks were counted as half; $p < 0.01$). Eleven of 13 patients had fewer attacks on colchicine.¹⁹ Dinarello et al²⁰ used an alternative crossover design with alternating 28-day cycles of colchicine and placebo in random order in each of their 11 adult patients. Initial

colchicine dose was three times daily 0.6 mg, but this dose would be reduced when gastrointestinal side-effects occurred, which in effect happened in all patients. In the final analysis, the most used dosage of colchicine was twice daily 0.6 mg. The study was terminated after 11 months when an interim analysis showed good results. The number of attacks for the total group of 11 patients was 38 in the placebo versus 7 in the colchicine courses ($p < 0.001$). Four of 6 patients who completed the trial benefited significantly from colchicine (defined in this study as a difference of at least 5 between total number of attacks on placebo versus colchicine).²⁰ Goldstein and Schwabe²¹ performed a study with two 90-day periods of colchicine 0.6 mg thrice daily versus placebo. Ten of 15 patients completed this study; 7 of these were of Armenian origin, and 8 were male. On placebo therapy the patients reported a total of 59 attacks versus 5 attacks in the colchicine period. In 7 of the 10 patients, no attacks occurred while on colchicine. No mention is made of any side-effects or dose reduction of colchicine, despite the relatively high treatment dose of 1.8 mg daily.²¹

Numerous clinical observational studies have corroborated the results of the initial trials. The accumulated experience tells us that colchicine provides significant improvement in up to 90% of patients, while in 60% of patients it will prevent attacks altogether.²² Optimal dosage should be determined in each individual patient, to gain a maximal effect with minimal side-effects (see below). General recommendation is to start colchicine in a dose of 1 mg daily (either 0.5 mg twice daily or 1 mg once a day³), and increase this slowly until remission is achieved, to a maximum of 2.5 mg/day.

Colchicine, fertility and children

Colchicine may affect male fertility by inducing oligospermia or azoospermia, but this is relatively rare.²³ Male FMF patients wanting to create progeniture should not be deterred from continuous use of colchicine. Colchicine does not seem to affect female fertility, frequency of miscarriage or teratogenicity,^{24,25} despite contrary results from in vitro studies. In fact, female fertility and outcome of pregnancy have improved in FMF patients using colchicine, due to a decreased incidence of peritoneal adhesions and of acute attacks which cause miscarriage and/or early delivery.²³ In Israel, pregnant female FMF patients on colchicine are offered amniocentesis with karyotyping.²³ However, there is no robust evidence that suggests that colchicine use throughout pregnancy carries a substantial teratogenic or mutagenic risk when used at recommended doses. Colchicine is detected in breast milk of women using the drug, but the dose ingested by the infant is less than one tenth of the therapeutic dose (per kg) in adults,²⁶ and clinical follow-up of children whose mother continued on colchicine while breastfeeding is favourable.²³ Thus, breast feeding is not contraindicated during colchicine use. In children, long-term colchicine use has been shown to be safe and without a negative effect on growth; rather, the cessation of FMF attacks and return to health will improve growth and development.²³

Alternatives to daily oral colchicine

Although oral colchicine remains the mainstay of treatment, alternatives to daily colchicine to suppress the periodic inflammatory attacks in colchicine-resistant patients are actively sought. Before the discovery of the benefit of colchicine, numerous other

therapies were reported to be effective (e.g. estrogen therapy²⁷ or low-fat diet²⁸) but none of these have withstood the test of time or thorough controlled investigation.

It would be desirable to have a drug available that is able to abort inflammatory attacks at the very onset of symptoms. Wright et al²⁹ report this effect of intermittent use of colchicine - starting at the earliest suspicion of an attack with a course of six tablets of 0.6 mg on the first day of (preliminary) symptoms, and two tablets on each of the two following days, distributed evenly over time. In a double-blind controlled study, they compared this with placebo in a total of 9 patients, and found that 21 of 28 attacks were aborted by colchicine (an aborted attack was defined by symptoms lasting less than 8 hours and absence of fever), while only 3 of 31 attacks were aborted when treated with placebo.²⁹ The only side-effect reported was diarrhoea.

Tunca et al³⁰ published a pilot study on the use of interferon (IFN) alpha as an adjunct to daily colchicine at the onset of a fever attack, after they observed a cessation of attacks in a colchicine-resistant FMF patients during 6 months of IFN alpha treatment for his chronic hepatitis B.³¹ In an open-labelled, uncontrolled study, 7 FMF patients on daily colchicine who still experienced fever attacks used IFN alpha (3 million IU s.c.) at the earliest onset of a total of 18 attacks, which led to rapid resolution of symptoms, in a median of 3 hours time.³⁰ A formal double-blind trial by the same investigators failed to confirm the initial positive results.³² Calguneri et al³³ reported use of IFN alpha for 6 months in 7 colchicine-resistant patients, in a dose of 4.5 million IU s.c. three times a week. None of the patients experienced any attack during this period, in contrast to the mean number of 26 attacks per year before start of IFN alpha.

Lidar et al³⁴ have tried the addition of weekly intravenous colchicine at a dose of 1 mg to oral colchicine in an open-labelled study of 3 months in 13 patients with frequent FMF attacks despite high dose of oral colchicine. They found a significant reduction in number (mean 4.2–1.9 attacks per person) and severity of attacks, particularly abdominal and pleural attacks, without side effects.

However, daily use of colchicine is still recommended in all FMF patients because this is the only treatment that has been proved beneficial against development of amyloidosis, as follows below.

Colchicine and amyloidosis

Compliance to colchicine treatment should be strongly emphasized, even in the face of apparent unresponsiveness, as it has been shown to prevent the occurrence of the major long-term complication of FMF: amyloidosis. This was nicely demonstrated by Zemer et al³⁵ in a follow-up study of 960 FMF patients during 4–11 years after they were recommended to start colchicine (1–2 mg daily). All patients were free of proteinuria at the onset of the follow-up. Persistent proteinuria, taken as a sign of amyloidosis, developed in only 4 of 906 patients who adhered to the prophylactic schedule while it occurred in 16 of 54 who admitted non-compliance.³⁵ This latter percentage exactly corresponded to the incidence of amyloidosis in a historic control group without treatment. Colchicine also seemed to stop further deterioration of renal function in 73 of another group of 86 FMF patients with proteinuria at the onset of the study. In 24 FMF patients who had already developed nephritic syndrome or uremia, colchicine did not cause improvement, suggesting that amyloidosis had developed to far to be resolved in these patients.³⁵ This same group demonstrated in a subsequent study of 68 FMF patients with amyloidosis in a follow-up of 5 or more years that the therapeutic dosage of colchicine for amyloidosis in

FMF is > 1.5 mg/day, and that this is only effective in the first stages of amyloidosis before overt deterioration of renal function.³⁶

Since the introduction of colchicine, the incidence of amyloidosis in FMF has dropped dramatically. Amyloidosis was previously observed in 30–50% of FMF patients and in areas with a high prevalence of FMF, where colchicine is not routinely available, such as Armenia, amyloidosis is still common.

Management of abdominal attack

During an abdominal attack, conservative management is the mainstay. Colchicine is ineffective for the full-blown acute FMF attack. Diclofenac (75 mg administered intramuscularly) may be used for pain relief.³ Other agents (e.g. reserpine, steroids) have only limited efficacy. Many patients become familiar with their disorder and deal with the inflammatory attacks at home, without consulting a doctor, once they know the diagnosis and its consequences.

When a FMF patient presents with an atypical course of an abdominal attack, close observation is warranted to exclude complications, such as adhesive small bowel obstruction and strangulation (see above). Elective laparoscopic appendectomy has been suggested in FMF patients to prevent unnecessary emergency surgery,³⁷ but this has not been recommended by others, because any surgical procedure may provoke an attack and add to the formation of adhesions.³

OTHER CAUSES OF ABDOMINAL PAIN IN FMF

Colchicine toxicity

Crampy abdominal pain, diarrhoea and nausea due to hyperperistalsis are frequent side effects of colchicine;^{38,39} these adverse effects are most pronounced with maximum therapeutic doses. Gastrointestinal intolerance is used in clinical practice as a parameter of dose titration and may serve as a warning to protect patients from toxic doses.

Colchicine intoxication is a rare, but serious and potentially lethal complication. In general, the severity of the reaction correlates with the dose administered and a high case-fatality rate is associated with an oral dose above 40 mg in adults, but there is considerable individual variability and lethal toxicity has been described with doses as low as 7 mg orally.³⁸ Risk factors for colchicine intoxication³⁸ are intravenous use, use of loading doses, use in elderly patients, prior maintenance colchicine use, excretory organ failure (renal or hepatic dysfunction) and drug interactions (especially cimetidine and other cytochrome P-450 inhibitors and cyclosporine).⁸

Clinical presentation of intoxication starts with a gastrointestinal phase characterized by diffuse abdominal pain, nausea, vomiting and severe (haemorrhagic) diarrhoea, which may develop into paralytic ileus. This is accompanied by volume depletion and hypotension.^{38,39} From 24 to 72 hours after ingestion, multiorgan failure may develop, including bone marrow depression, renal failure, adult respiratory distress syndrome, heart failure and disseminated intravascular coagulation.³⁸ If the patient survives this second phase, recovery will set in thereafter, typically accompanied by alopecia. The hair loss is usually reversible, but permanent alopecia has been described.³⁸

Management of colchicine intoxication is mainly supportive and symptomatic. Because of the rapid distribution of colchicine and its high binding affinity, haemodialysis and plasma exchange are ineffective.³⁸ There is no specific antidote available; immunotherapy with anticolchicine antibodies is still in development.

Amyloidosis of the gastrointestinal tract

As mentioned above, type AA systemic amyloidosis is a serious complication of FMF. This type of amyloid fibrils may be deposited in many organs, including the kidneys, adrenals, intestines, spleen, liver, stomach, thyroid gland, heart and lungs.⁸ Clinically, the kidneys are the most significant organs involved, as amyloidosis will eventually impair renal function and lead to kidney failure.

Microscopic evidence for amyloid depositions in the gastrointestinal tract can be found early in the course of FMF. Nevertheless, amyloidosis of the intestines will only result in clinical symptoms in a minority of patients and often only after many years of asymptomatic amyloid deposition, when the entire wall of the small intestine is affected.⁴⁰ These symptoms may include constipation or intractable diarrhoea and severe malabsorption, especially in the case of bacterial overgrowth and bile acid deconjugation due to decreased mobility of the small intestine.⁸ However, it may be difficult to differentiate amyloidosis-induced diarrhoea from colchicine-induced diarrhoea.⁸

Another possible manifestation of amyloidosis in the intestinal tract is ischemic enterocolitis,^{41,42} which may result in fibrosis, mucosal ulceration or colonic obstruction or perforation. Clinical, radiological and histopathological features of amyloid-associated ischemic enterocolitis may mimic those of Crohn's disease, except for the absence of transmural lymphoid aggregates and granulomas.^{42,43} Spontaneous rupture of an amyloid spleen, resulting in acute abdomen, as is sometimes described in AL type amyloidosis,⁴⁴ is rarely seen in AA type amyloidosis,⁴⁵ and has never been described in FMF.

In recent years, the incidence of clinical manifestations of extra-renal amyloidosis is increasing and associated with longer survival in patients with renal amyloidosis due to hemodialysis and renal transplantation,⁸ although the overall incidence of amyloidosis has declined due to the use of colchicine. It is not yet known whether colchicine also has a beneficial effect on gastrointestinal amyloidosis, as is seen in renal amyloidosis. Often, the dose of colchicine optimal for anti-amyloidogenic effect (2 mg per day) cannot be tolerated by patients with gastrointestinal amyloidosis, which aggravates the diarrhoea.

Diagnosis of amyloidosis requires tissue biopsy, preferentially of the involved organ (usually rectal biopsy or renal biopsy); an alternative to obtain tissue is fine-needle aspiration of abdominal fat pad, although one small study suggests that this might not be very sensitive in FMF.⁴⁶ The tissue sample is then stained with Congo Red to detect amyloid deposits. Further classification of the type of amyloid can be done by immunohistochemistry with specific antibodies.⁴⁷

Disorders associated with FMF and accompanied by abdominal pain

Several inflammatory diseases have been found in association with FMF, some of which may be accompanied by abdominal pain. Such associations may complicate clinical interpretation of the symptoms and may thwart diagnosis.

An increased prevalence of inflammatory bowel disease in FMF was reported in two studies. Cattani et al⁴⁸ described 3 patients with concomitant FMF and either

Crohn's disease or ulcerative colitis in a group of 300 FMF patients from 173 families of non-Ashkenazi Jewish descent; eight other persons in these families studied had inflammatory bowel disease without FMF. Crohn's disease was diagnosed in 7 of nearly 5000 FMF-patients from the FMF-registry in Tel Hashomer, Israel.⁴⁹ While Cattani et al⁴⁸ found that the patients with inflammatory bowel disease in the FMF families were more severely affected, Fidler et al⁴⁹ report similar severity on comparison with a Crohn's disease control group, although the prevalence of amyloidosis was increased. This association of Crohn's disease with FMF is interesting in the light of the recent findings of *NOD2* gene mutations as a susceptibility factor in Crohn's disease. The *NOD2* (or *CARD15*) protein belongs to a family of proteins involved in inflammation and apoptosis and is (indirectly) related to the pyrin domain family. The defects underlying Crohn's disease and FMF are thus thought to be located in closely related areas of inflammation and might have a modifying effect on each other. It remains to be seen whether FMF patients with concomitant inflammatory bowel disease do have specific *NOD2* gene mutations. However, questions might be raised about the diagnosis of inflammatory bowel disease in some FMF patients, in the light of the similarity between ischemic enterocolitis due to amyloidosis and Crohn's disease⁴² and based on the fact that not all FMF-cases were confirmed by demonstration of transmural granulomas and lymphoid aggregates in biopsies,^{48,49} while proteinuria due to amyloidosis was more prevalent in this group.

A number of types of vasculitis, which may be accompanied by abdominal symptoms, have been associated with FMF as well,^{8,50} although it could be questioned in some cases, whether vasculitis is a manifestation of FMF, rather than an associated disorder.

Behçet's disease (found in 16 of 4000 FMF patients⁵¹) is an episodic inflammatory disorder of unknown pathogenesis, with a broad clinical picture that may include oral and genital aphthous ulcers, pustulosis, erythema nodosum, arthritis, central nervous system involvement and pathergy (hyperreactive skin lesion evoked by a needle prick).⁵² Abdominal pain and diarrhea are common as well; this type of abdominal pain is usually more prolonged than the short abdominal attacks seen in FMF. A second type of vasculitis, reported more frequently in FMF patients, is Henoch-Schönlein's purpura (4–7% of FMF patients^{15,53,53}) often in a severe form; gastrointestinal symptoms in Henoch-Schönlein's purpura may include colicky abdominal pain, nausea, vomiting, diarrhoea or constipation and frequently stools with blood or mucus are observed.⁸ Thirdly, the systemic necrotizing vasculitis, polyarteritis nodosa (PAN), is found in 1% of FMF patients^{53,54} and may lead to abdominal symptoms ranging from vague non-specific pain to bowel infarction and perforation due to ischemia.⁸

Three case reports have been published on patients who developed peritoneal mesothelioma after years of abdominal FMF attacks.^{55–57} The development of malignancy was suggested to be linked to the chronic recurrent peritonitis, but questioned by others.⁸

ABDOMINAL PAIN IN OTHER AUTOINFLAMMATORY SYNDROMES

FMF is part of an expanding group of hereditary disorders known as familial autoinflammatory syndromes, which are commonly characterized by recurrent

episodes of fever and inflammation.¹ Abdominal pain and other signs of abdominal distress are also frequently seen in the TNF-receptor associated periodic syndrome (TRAPS)⁵⁸ and the hyper-IgD and periodic fever syndrome (HIDS).⁵⁹

In HIDS, the clinical presentation of abdominal pain is usually less dramatic, and often the pain is more crampy than fitting with full-blown serositis. Other frequent symptoms and signs are (cervical) lymphadenopathy, headache, myalgia, arthralgia and a erythematous skin rash.⁵⁹ The fever episodes generally last somewhat longer than in FMF, usually 4–days, and they start within the first year of life.¹ Characteristically, a continuously high concentration of immunoglobulin D (IgD) and IgA is detected in serum. Inheritance pattern of HIDS is autosomal recessive. HIDS is caused by mutations in the gene encoding for mevalonate kinase, an enzyme in the isoprenoid pathway.^{60,61}

TRAPS is usually distinguished by inflammatory episodes of longer duration; attacks of 14–21 days are often seen, although episodes of a few days may occur.^{62,63} Apart from abdominal distress, the high spiking fever during such episodes may be accompanied by myalgia, arthralgia, migratory erythematous skin lesions and ocular involvement, including conjunctivitis and periorbital edema.¹ The genetic mutations in TRAPS are found in the gene encoding the type I TNF-receptor;⁶⁴ it is autosomal dominantly inherited.

Unnecessary laparotomies, intraperitoneal adhesions and small bowel obstruction are complications of both HIDS and TRAPS, as seen in FMF. Abdominal pain is more rarely reported in the clinical spectrum of cryopyrin-associated periodic syndromes, which are characterized by joint or skin manifestations, among other features.^{65–67}

SUMMARY

Familial Mediterranean fever is a hereditary syndrome characterized by recurrent episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles. It is primarily found in people of Jewish, Arabic, Turkish and Armenian ancestry. Causative mutations are located in the *MEFV* gene, which encodes for the protein pyrin.

Abdominal FMF attacks present clinically as an 'acute abdomen' with severe abdominal pain and rigidity, which resolve spontaneously within 3–4 days. It is important to distinguish these attacks from small bowel obstruction due to adhesions, a serious complication of FMF. In the case of a FMF attack, surgery will be of no help and will only increase the risk of adhesions, while in adhesive small bowel obstruction, surgical intervention should not be delayed in order to prevent life-threatening bowel strangulation. Distinction can be made on close observation of the clinical course, while abdominal imaging by CT may be helpful.

FMF is effectively treated by use of oral colchicine in more than 90% of patients. However, abdominal pain and diarrhoea are frequently observed side-effects of colchicine use, and may also represent the first phase of colchicine intoxication. Abdominal pain in FMF patients may also be caused by one of the associated types of vasculitis, such as Behçet's disease or Henoch Schönlein's purpura.

Recurrent episodes of fever and abdominal pain are also seen in other autoinflammatory syndromes, especially TNF-receptor associated periodic syndrome and hyper-IgD syndrome.

Practice points

- abdominal attacks in FMF are characterized by signs of 'acute abdomen', but will resolve spontaneously within 3–4 days
- FMF is a hereditary syndrome characterized by lifelong recurrent episodes of fever and serositis (mainly peritonitis)
- FMF is especially prevalent in people from the Mediterranean, including Sephardic Jews, Arabs, Turks, and Armenians
- diagnosis of FMF is based on a set of clinical criteria, and may be confirmed by DNA analysis of the *MEFV* gene
- treatment of FMF consists of colchicine
- the recurrent peritonitis may lead to peritoneal adhesions and small bowel obstruction
- it is important to differentiate between small bowel obstruction and the abdominal FMF attack
- the first phase of potentially life-threatening colchicine intoxication is characterized by diffuse abdominal pain, nausea, vomiting and (haemorrhagic) diarrhoea

Research agenda

- the exact function of pyrin, the mutated protein in FMF, needs to be determined
- detailed controlled studies are necessary to define the best method of pain relief in FMF
- the precise mechanism of action of colchicine needs to be determined
- further development of a diagnostic tool to distinguish an abdominal FMF attack from other causes of 'acute abdomen' is warranted
- other therapies to prevent and combat inflammatory attacks and to prevent amyloidosis should be sought for

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