
Autoinflammatory diseases as a cause of acute abdominal pain in the emergency department

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ABSTRACT

Autoinflammatory diseases (AIDs) usually present with acute abdominal pain and fever, both of which are also the main causes of referral in the emergency department. As some patients with acute abdominal pain may be discharged from the emergency department without a definitive diagnosis, it is not surprising that, due to their rarity, most cases of AID remain undiagnosed or are misdiagnosed as acute appendicitis. Indeed, the diagnosis of familial Mediterranean fever and autoinflammatory syndromes requires a high index of suspicion and careful assessment of clinical history. Age of onset and clinical features, in particular the self-limiting acute attacks, together with prodromal symptoms and trigger factors, are useful to suspect these disorders. In addition, discrepancies in laboratory tests that show an increase in acute phase reactants as well as diagnostic imaging, which usually fails to show specific abdominal disorders, may help in the identification of patients who require genetic testing to confirm a diagnosis of AID.

Introduction

Acute abdominal pain (AAP) is one of the most common causes of consultation in the emergency department and is a frequent cause of medical and surgical ambulatory visits. AAP accounts for around 7–10% of visits to an emergency department, and is often due to serious and life-threatening diseases necessitating surgical operation (1-3). Indeed, AAP was the second most common cause of complaint at admission to the emergency department, after limb pathological conditions, in a consecutive series of 2,623 adult patients from a 2013 Italian study (1).

In the primary care setting and in specialised ambulatory practice, AAP also represents a minor cause of consultation, usually due to benign and self-

limiting conditions (4). However, it should also be taken into account that approximately half the patients with AAP that are admitted to an emergency department do not require instant treatment or surgery, and instead can be managed at a later date by specialists and primary care physicians (5-7). This is even more important if we consider that approximately 20-40% of patients admitted to an emergency department with AAP remain without a clear diagnosis at discharge (1, 5-9).

The many possible causes of AAP are extremely heterogeneous and can be due to disorders of abdominal organs including the stomach, the small bowel and colon, and the hepatobiliary tract, or the retroperitoneal region such as the kidneys and aorta, the chest, oesophagus or the pelvic region. Epidemiological reports show a variable prevalence of causes of AAP according to the study design, age of population, geographical location, and definition of AAP. These studies report a high prevalence of urinary tract diseases (13–40%), intestinal occlusion (7–10%), acute appendicitis (1.3–28%), and acute diverticulitis (3–12%) (1, 7-9). However, many other infrequent or rare, harmless or life-threatening conditions have also been reported as a cause of AAP (Table I). It is noteworthy that almost all epidemiological studies refer to a prevalence of between 18–36% for non-specific or undifferentiated abdominal pain, as one of the main causes of admission to an emergency department for patients with AAP (1, 7-9). Non-specific or undifferentiated abdominal pain is probably underestimated if we consider that up to 25% of patients with AAP may have an unnecessary appendectomy (7). Interestingly, non-specific or undifferentiated abdominal pain also has the highest risk of recurrence and emergency department readmission, but the lowest rate of hospital admission (8).

Table I. Diagnosis of acute abdominal pain.*Common diagnoses of acute abdominal pain*

Abdominal	Appendicitis Acute diverticulitis Cholecystitis/cholelithiasis Peptic ulcer Intestinal obstruction Flare of chronic disease (IBS, IBD)
Extra-abdominal	Cardiac (myocardial infarction, angina, pericarditis) Pulmonary (pneumonia, embolus) Vascular (acute aortic dissection, mesenteric ischaemia) Pelvic (ectopic pregnancy, ovarian mass/torsion, pelvic inflammatory disease) Renal (calculosis, pyelonephritis) Pancreatic (acute pancreatitis, complications of chronic pancreatitis, neoplasia) Abdominal wall (hernia, herpes zoster, muscle strain)

Uncommon diagnosis of acute abdominal pain

Extra-abdominal	Systemic diseases (alcoholic/diabetic ketoacidosis, vasculitis, sickle cell crisis) Psychiatric (foreign body, depression) Toxic (heavy metal syndrome, narcotic withdrawal) Rare diseases (autoinflammatory diseases, porphyria)
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IBS: irritable bowel syndrome; IBD: inflammatory bowel disease.

The underlying causes for AAP can involve many different medical and surgical specialties including internal medicine, gastroenterology, urology, gynaecology, abdominal, and vascular surgery. Therefore, expert assessment of patients with AAP is essential to properly drive the therapeutic management of these patients. This requires careful evaluation of symptoms and medical history, and the correct use and interpretation of diagnostic tests, in order to discriminate between medical and surgical diseases and to reduce the rate of non-specific abdominal pain.

Discrimination amongst these entities and the recognition of the underlying causes of AAP are sometimes difficult, if not impossible, to achieve if viewed only on their clinical presentation. However, features of AAP (*e.g.*, the onset, quality, time course, and location), and accompanying symptoms, such as fever, nausea or vomiting, and bowel changes, together with the clinical context and a thorough history and physical examination, are crucial to drive appropriate investigations and achieve an early diagnosis. Re-evaluation and short-term follow-up (within 30 days) of patients discharged with non-specific AAP have also been suggested as useful strategies to aid diagnosis; this approach was shown to be successful in up to 18% of patients (8, 10).

Depression has also been identified as a possible condition associated with repeat emergency department admission in patients discharged with non-specific abdominal pain, however, a substantial number of patients remain undiagnosed (11). It is likely that some patients, who present with AAP and overall symptoms that mimic more common causes of abdominal pain, have rare medical diseases. These patients may remain undiagnosed, be submitted to surgery, or misinterpreted as having acute appendicitis or bowel occlusion. Examples of these rare diseases include angioedema, porphyria, or familial Mediterranean fever (FMF).

In general, there is a low awareness of the existence of these rare causes of AAP among physicians, and likely among those working in the emergency department who are usually faced with life-threatening conditions. Therefore, guidelines and educational programs on rare medical disorders presenting as AAP are essential given that physicians may only diagnose diseases they know and that awareness of a disease may lead to a more frequent suspicion of it. Ideally, these will reduce the rate of patients misinterpreted with specific acute surgical conditions or discharged with the diagnosis of non-specific acute pain despite extensive investigation.

Among rare disorders presenting with

AAP, there are some that are frequently misinterpreted and erroneously treated, and are usually diagnosed after considerable delay (12, 13). FMF and autoinflammatory diseases (AIDs) are the main example of these diseases, which are usually diagnosed after many years, several emergency department admissions, and surgeries. Proper knowledge of the epidemiology of the causes of intermittent unexplained abdominal pain, and of the diagnostic tests usually performed to exclude more common causes, as well as genetic factors, which are at the base of the compromised immune system, may increase suspicion of these unusual causes of AAP and improve the outcome of these patients.

Familial Mediterranean fever and autoinflammatory syndromes

FMF is a hereditary, autosomal recessive, AID characterised by recurrent and self-limiting, short duration (1-3 days) episodes of AAP, fever, joint and chest pain, and rashes. Described initially in 1908, FMF has been recognised as a specific disease since 1955. In 1997, it was linked to a genetic disorder, the Mediterranean FeVer gene (MEFV), located in the short arm of chromosome 16 and to its encoding product Pyrin/Marenostrin.

FMF is considered the prototype of the autoinflammatory syndromes (AS), a heterogeneous group of diseases clinically characterised by recurrent febrile attacks in the absence of specific autoantibodies. Among the other AS (extensively reported in this issue), those more frequently correlated with recurrent abdominal pain are the TNF-Receptor-Associated Periodic Syndrome (TRAPS) and the Hyper-IgD with periodic fever Syndrome (HIDS).

Epidemiology

FMF is prevalent in the South-Eastern Mediterranean area and in people of this origin, in particular in non-Ashkenazi Jews, Arabs, Turks, and Armenians, where its prevalence is estimated between 1:200 to 1:1,400 (14). It has also been reported in patients from the South of Italy (15) and Greece, and in a few case reports from Japan (16, 17). The onset of FMF and AIDs usually

occurs before 20 years of age and rarely after 30 years of age, although cases diagnosed in patients >70 years of age have been described (17). The onset typically involves fever, AAP, and accompanying symptoms, which persist for a short time period (6-96 hours) before they spontaneously resolve.

Pathogenesis

The pathogenetic mechanisms of FMF and other AIDs will be clearly defined and discussed elsewhere in this issue. Although exact pathogenetic mechanisms of AIDs have still to be elucidated, it appears that, in FMF, mutations in pyrin cause excessive IL-1 β production in response to even banal stimuli (18) and, hence peritoneal inflammation. Serositis and peritonitis account for clinical features of the syndromes, including acute manifestations indistinguishable from those responsible for AAP.

Clinical features

AIDs and FMF are characterised by recurrent unpredictable episodes of fever and abdominal pain indistinguishable from those of an acute abdominal emergency. The variable features of these attacks, in terms of severity and duration, and their erratic recurrence and remission, together with the rare incidence and low awareness, explain diagnostic delays of these disorders and the high rate of unnecessary laparotomies and appendectomies (19).

A number of epidemiological studies have shown that, prior to the diagnosis of FMF, the majority of patients are admitted to emergency units with AAP with up to half having undergone unnecessary abdominal interventions; for most FMF patients, a diagnosis is achieved following a significant delay (20, 21).

Typical clinical manifestations of FMF include fever, AAP, arthralgias and myalgia, chest pain, and rash. Fever occurs in almost all attacks and varies between 38°C and 40°C. It lasts for a maximum of 3 days, responds to NSAIDs and paracetamol but not to antibiotics, and resolves spontaneously.

More than 95% of patients with FMF complain of abdominal symptoms and are mainly represented by AAP. This is

often indistinguishable from appendicitis and/or peritonitis, especially when localised in the right lower quadrant. According to the location of involved peritoneum, the abdominal pain can be localised or diffuse, or mimic a renal colic or inflammatory pelvic disease. The involvement of the peritoneum both primarily by repeated acute episodes of peritonitis or secondary to useless surgical interventions (*i.e.* appendectomies, cholecystectomies or explorative laparotomies) can also be responsible for a higher rate of small bowel obstruction due to adhesions (22-24). This has to be taken into account in the differential diagnosis of acute abdominal attacks during the course of FMF, and in particular in patients with non-spontaneously resolving symptoms. In fact, in patients with bowel occlusion, the symptoms tend to worsen progressively over time while in FMF symptoms usually improve and resolve within 72 hours. However, abdominal pain in other AIDs, such as TRAPS and HIDS, is less frequent and dramatic and may persist for longer than in FMF (*i.e.*, for up to 3 weeks) (25-28).

Other less frequent abdominal symptoms include diarrhoea or constipation, which occur mainly in children and at the end of acute episodes. Diarrhoea or constipation may also result from gastrointestinal amyloidosis and vasculitis, which are long standing complications of FMF. Usual signs at physical examination look like those of peritonitis: distension of the abdomen, rigidity, rebound tenderness, and reduced peristaltic sounds. Abdominal complaints, other than AAP, such as vomiting, diarrhoea and splenomegaly are much more frequent in other AIDs, in particular in HIDS, which is more frequently associated with autoimmune disorders such as inflammatory bowel diseases (25, 27, 28).

Arthralgia, and less frequently arthritis, occur in two thirds of patients with FMF and involve medium-large joints such as the ankles and knees (29). In addition, cases of HLA-B27 negative sacroiliitis (30) and myalgia have been described.

Chest pain due to pleuritis and pericarditis have also been reported in approx-

imately half of the patients with FMF.

Other rare manifestation of FMF and AIDs may involve skin (*e.g.*, rash and erysipelas-like erythema), kidney, eyes, and the nervous system. These are much more frequent in other autoinflammatory conditions and will be extensively described elsewhere in this issue.

Despite the unpredictable course of FMF and AS, their attacks could be somewhat foreseen and likely prevented, because these may be triggered by several factors and preceded by prodromal symptoms. Clinical case series have identified a number of potential factors including infections, tiredness, emotional, physiological or physical stress, exposure to cold, and high-fat food consumption (31, 32). Even menstruation (33) and *Helicobacter pylori* infection have been suggested as potential predisposing triggers for FMF, although the latter is controversial (34, 35). However, among these factors only stressful life events have been confirmed in a case-crossover study (32). Prodromal symptoms are reported by around 50% of patients and recur in most attacks. These last a mean of 20 hours, and precede the attacks with predominant abdominal involvement manifesting with nausea, vomiting, constipation or diarrhoea, fatigue, anxiety, dyspnoea, lower back pain, myalgia, arthralgia, or headache (36). The possibility to foresee attacks of AIDs enables the prompt administration of a preventive therapy.

Laboratory tests and imaging

Laboratory tests during an FMF attack reveal an increase of acute phase reactants, leukocytosis, increased erythrocyte sedimentation rate, and increased concentrations of C-reactive protein, fibrinogen, and serum amyloid A protein. However, these laboratory parameters, similar to the clinical picture, are not specific and are not able to discriminate between abdominal pain due to a FMF attack or from that of acute appendicitis. However, a preliminary study found that microalbuminuria and urinary beta-2 microglobulin levels were significantly higher in patients with acute appendicitis compared with an attack of FMF, and may be helpful

to differentiate these conditions (37). Another promising test is procalcitonin. In patients with AAP, both the acute phase reactants and procalcitonin levels are increased. However, high levels of procalcitonin (>0.5 ng/ml) have been found more frequently in patients with acute appendicitis (62%), compared with those with FMF (11%) (38). Like all patients presenting with AAP, patients with FMF and AS usually undergo diagnostic imaging investigations in addition to biochemical tests. Plain abdominal radiography may show some features typical of acute peritonitis, such as dilatation of small bowel with air-fluid levels, but this sign has been observed in less than half of patients with FMF attacks (39).

Likewise, a computed tomography (CT) scan during an abdominal attack in FMF may reveal thickened mesenteric folds, mesenteric and/or retroperitoneal lymphadenopathy, engorged mesenteric vessels in less than one third of patients, or mild peritoneal fluid or ascites in the same proportion, as well as focal peritonitis, dilated small bowel loops, and splenomegaly (40, 41).

Although these are non-specific signs of mesenteric involvement, a precise diagnostic role of magnetic resonance imaging (MRI) or abdominal and intestinal ultrasound in FMF has not yet been defined. However, diffusion-weighted MRI has been successfully used to suspect the presence of FMF complicated by renal impairment but it does not play a significant role in the emergency department (42). On the contrary, ultrasonography can easily and quickly detect abdominal organs and peritoneal cavity in the emergency setting. The sonographic detection of an enlarged spleen (length >11 cm and/or width >4 cm) seems to have a very high specificity and positive predictive value (100%) to suspect the presence of FMF when this finding was combined with a previous appendectomy (43). Moreover, intestinal ultrasound has high specificity in the detection of acute appendicitis, and is also useful in revealing lymphadenitis and signs of acute peritonitis during attacks of FMF (44, 45).

Given the fact that a large proportion of patients undergo appendectomy during

FMF attacks, there is also the possibility to suspect an AID by revealing macroscopic and microscopic signs of peritonitis. Macroscopic signs during an acute attack are oedematous and hyperaemic peritoneal folds or greater omentum, while microscopic examination may reveal a sterile purulent or haemorrhagic non-specific inflammation, along with signs of chronic recurrent peritonitis, such as peritoneal inclusion cysts and fibrous adhesions (46, 47).

Diagnostic pathway

The final diagnosis of FMF and AIDs is ultimately clinical, may be corroborated by laboratory tests and imaging diagnostic examinations, but requires a high index of suspicion and awareness. This has been shown in a prospective study carried out in Turkey where FMF has a higher prevalence compared with other European countries. In this study, 100 consecutive patients with AAP admitted to an emergency unit were screened for FMF with results showing a frequency of 2% of cases, a prevalence of FMF that was significantly higher compared with previous reports (21).

It is therefore possible to suggest a diagnostic pathway for patients admitted to an emergency department in order to reduce the diagnostic delay of FMF and AIDs and for patients discharged with unspecific AAP.

A high suspicion should be reserved for young patients admitted to an emergency department with AAP and fever, in particular if they originate from the Mediterranean basin and have previous appendectomy or history of similar self-resolving acute attacks, with prodromal symptoms and triggers. Clinical signs and laboratory tests show results suggestive of acute inflammation. The use of urinary beta-2 microglobulin and procalcitonin in this setting could be useful but should be interpreted with caution due to the scarce evidence in the literature. Diagnostic imaging still plays an important role in confirming the presence of acute conditions, such as acute appendicitis, mesenteric lymphadenitis, and small bowel occlusion, taking into account that the latter may also be a severe complication of autoinflammatory conditions. The main

diagnostic procedures are ultrasound and CT. An algorithm with sequential positioning of ultrasound followed by CT scan for dubious or indeterminate results is currently suggested and adopted as the best strategy to improve diagnosis of acute conditions of the abdomen and to spare the use abdominal CT in children and adults (9, 48).

In the absence of specific abnormal findings suggesting acute conditions (e.g. appendicitis, diverticulitis, peritonitis coupled with intestinal perforation or ovary torsion), this clinical context may be highly suggestive of an AID and deserves, if met with the formal diagnostic criteria, DNA testing of the MEFV gene to confirm the diagnosis. This point, along with treatment, will be discussed in another section of this issue.

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