Acute abdomen and angioedema: a classic presentation

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Abstract

Hereditary angioedema (HAE) is an infrequent disorder characterised by abnormalities in the levels and/or function of complement C1 esterase inhibitor (C1 INH). Clinical manifestations of HAE are due to recurrent episodic swelling of the subcutaneous or submucosal tissue. When swelling involves the gastrointestinal mucosa, patients may present with nausea, vomiting, diarrhoea, and severe abdominal pain. However, HAE is almost never suspected as a potential cause of acute abdomen. We describe a typical case of hereditary C1 esterase inhibitor deficiency in a 37-year-old woman presenting with recurrent acute abdomen and who had undergone negative surgical interventions before diagnosis was eventually established. Both the diagnostic and therapeutic approach to this rare condition is discussed in this report.

Keywords

Angioedema; C1 esterase inhibitor; abdominal pain; autosomal dominant; bradykinin; danazol.

Introduction

Acute abdominal pain is a common problem in the emergency room, with a broad differential diagnosis frequently requiring surgical intervention even when a definite diagnosis has not been established.

Hereditary angioedema (HAE) is an autosomal dominant, quantitative, or functional defect of C1 esterase inhibitor (C1 INH)[1]. The incidence of this disease is 1:50,000 to 1:150,000[2,3]. The gene responsible for the control of C1 INH synthesis is located on chromosome 11[4]. There are two types of HAE, and they have similar clinical manifestations. Type I HAE (85% of patients) is characterised by a low or unmeasurable level of C1 INH, while in type II HAE, C1 INH is normal but dysfunctional[5]. C1 INH deficiency allows activation of C1, with a decrease in the serum concentration of C2 and C4 complement components. The final result of this activation is a local release of vasoactive mediators which contribute to the increase in capillary permeability. The mediators of oedema include proteolytic fragments of C2 called C2 kinin and bradykinin. The production of bradykinin is increased in this disease, because C1 INH is a regulator of other plasma serine proteases besides C1, including kallikrein[6]. Patients with HAE have episodes of local oedema, localised on the face, extremities, upper airways, and gastrointestinal tract.
which usually last 1–3 days\textsuperscript{[7]}. Oedema of the intestinal wall may sometimes cause abdominal pain, imitating the clinical picture of the acute abdomen\textsuperscript{[8]}. We report the case of a patient with type I HAE. The only clinical manifestations were self-limited abdominal pain with diarrhoea with previous admission to the Intensive Treatment Unit for angioedema a few years prior to presentation.

**Case report**

A 37-year-old Caucasian woman presented to the emergency unit with a 1-day history of severe abdominal pain associated with diarrhoea. She presented earlier the same day to the emergency unit complaining of abdominal pain and diarrhoea. She was not able to wait and self-discharged against advice. She kept having abdominal pain with diarrhoea (20 episodes) over the next few hours. The pain got worse in the late evening and her abdomen started to distend, but gradually settled down and she went to sleep. She woke up early the next day with severe abdominal pain, distension (felt her abdomen was going to burst), a swollen neck and tongue with sore throat. The paramedics were contacted and she was brought directly to the emergency unit. On arrival, the patient was in discomfort, complaining of severe abdominal pain and distension with swollen tongue and sore throat. On physical examination, she had normal blood pressure of 152/69, pulse of 84, respiratory rate 28 and oxygen saturation 99% on air; she was apyrexic ($T \approx 37.2$). She had neck oedema with a swollen tongue. Her airways were not compromised and she had bilateral air entry on auscultation. Her abdomen was much distended with generalised tenderness and guarding with active bowel sounds. She was screaming in pain. Intravenous morphine and anti-emetic were given. Suddenly the patient became unresponsive and she was transferred to the resuscitation room. An anaesthetic team arrived, and fortunately the patient recovered quickly with $O_2$. Her airway remained uncompromised. Intravenous hydrocortisone and chlorphenamine were started as treatment for a possible allergic reaction. She had a previous history of appendicectomy (histology showed normal appendix), cholecystectomy and insulin-dependent diabetes. A chest x-ray was normal and an abdominal x-ray showed a dilated small bowel loop centrally located suggesting ascites (Figs. 1 and 2). She had blood tests for full blood count, urea and electrolytes, liver function tests and amylase, and urine dipstick with pregnancy test. All the investigations were within normal limits. The surgical team was contacted and they ruled out surgical abdomen and the patient was admitted to a medical ward with a diagnosis of angioedema secondary to possible allergic reaction. On arrival at the medical ward, the patient gave a history of admission to the Intensive Treatment Unit for respiratory problems secondary to neck swelling a few years previously and she was discharged with a diagnosis of anaphylactic reaction with unknown aetiology. In view of her recurrent episodes of angioedema and abdominal pain, the differential diagnosis at this stage was C1 esterase inhibitor deficiency. She was negative for anti nuclear antibody, anti neutrophil cytoplasm antibody and rheumatoid factor, with normal levels of IgG, IgA and IgM. She had C1 esterase inhibitor of 10 mg/dl (normal 16–33 mg/dl) and C4 <6 mg/dl (13–75 mg/dl). She was diagnosed with hereditary angioedema Type 1 C1 esterase inhibitor deficiency. The patient was referred to an allergist for further screening; she had two daughters and one of them was also found to have C1 esterase inhibitor deficiency. She is currently on a prophylactic dose of danazol (attenuated androgens) and her name is recorded in the emergency department with clear instructions about her condition and how to initiate treatment with C1 esterase inhibitor concentrate for further acute attacks of angioedema.

**Discussion**

C1 esterase inhibitor deficiency, a deficiency of the inhibitor of the first component of complement, is a rare disease with an estimated incidence of 1:50,000 to 1:150,000. It is a classic, although rare, medical cause of acute abdomen mimicking a surgical emergency. In a large series, 34% of 235 patients had undergone a surgical abdominal intervention before the diagnosis was established\textsuperscript{[9]}. It was initially described as a hereditary disease (hereditary angioedema; HAE) in 1888, and the acquired form (acquired angioedema; AAE) was reported in 1972. The clinical presentation of HAE and AAE is similar but the pathogenesis and specific laboratory findings are different\textsuperscript{[9,10,12,13]}. The hereditary form is transmitted as an autosomal dominant trait and at least two distinct hereditary forms have been described. The classic form or type I, representing 85% of HAE,
is caused by diminished C1 INH concentration, whereas type II is caused by a mutation of the gene resulting in normal or even elevated concentrations of a functionally inactive C1 INH. The abnormal gene is located on chromosome 11\[^{14}\]. A third form of HAE with normal C1 INH activity and C4 level has recently been described. This is probably an X-linked disease as no affected males have been identified. A deficiency of another inhibitor of the complement or kallikrein-kinin system is supposed to be the underlying abnormality in this particular form.

AAE is mostly associated with lymphoproliferative or autoimmune diseases with the formation of immune complexes. This condition is much rarer than the hereditary form\[^{9,10}\]. Two pathogenic mechanisms are supposed to play a role in the acquired deficiency of C1 INH. In type I, the binding of immunoglobulins to C1 INH is hypothesised to result in the accelerated consumption of C1 INH. When synthesis cannot keep up with consumption, the level becomes abnormally low. In type 2, the deficiency is caused by autoantibodies against C1 INH, resulting in inactivation of C1 INH but normal C1 INH concentrations\[^{9}\].

C1 esterase inhibitor belongs to the serine protease inhibitor family, which includes alpha-1-antitrypsin and antithrombin. Its major functions within the human body include direct inhibition of activated kallikrein, inhibition of activated Hageman factor (factor XII of the coagulation cascade), and prevention of C1 complement autoactivation. C1 complement is a heteropentameric protease and is made up of one C1q, two C1r, and two C1s subunits. C1 esterase inhibitor prevents autoactivation of C1 complement by causing dissociation of the C1q subunit and forming an inactive C1r2–C1s2–(C1 INH)2 complex. This complex is unable to cleave and activate C4 and C2 complement components, the usual substrates of activated C1 (Fig. 3). Decreased C1 INH activity allows activation of increased quantities of Hageman factor, which cleaves prekallikrein to the active enzyme kallikrein. Increased kallikrein activity leads to the cleaving of high molecular weight plasma kininogens, resulting in excessive release of various kinins, especially bradykinin. The large quantity of bradykinin released during acute attacks of HAE or acquired angioedema (AAE) is thought to be responsible for most symptoms by

Fig. 1. Chest x-ray showing normal lung.
directly causing increased vascular permeability (oedema and swelling), vasodilatation (congestion), contraction of non-vascular smooth muscle (cramps and spasms), and pain (Fig. 4). Autoactivation of complement component C1 (especially C1r and C1s) resulting from decreased C1 INH activity also initiates activation (and consumption) of complement components C4 and C2, which results in decreased serum levels during acute attacks. Levels of C4 and C2 may be normal during symptomatic quiescence. Decreased C1 INH also results in loss of the direct inhibitory effect on kallikrein activity, thus further promoting bradykinin generation.

The clinical picture does not allow a differentiation between the hereditary and the acquired form, although the age of onset of symptoms is clearly different. In HAE, symptoms are present before the age of 30 years in nearly all the cases, whereas the onset of AAE is after the fourth decade of life\textsuperscript{14}. In our case, the age of onset clearly suggests HAE. The typical presentation

Fig. 2. Abdominal x-ray showing dilated single small bowel loop.
Fig. 3. Role of C1 esterase inhibitor.

Fig. 4. Contact activation pathway leading to bradykinin formation.
consists of episodic attacks of non-painful, non-pruritic and non-erythematous angioedema without urticaria lasting 1–3 days before resolving spontaneously\textsuperscript{[9,10,13]}. The predilection areas are the extremities, but the whole body can be involved. Acute abdominal pain, with colic, nausea and vomiting are reported in 70% of cases. These abdominal attacks mostly subside within 24 h. Watery diarrhoea may be present; ascites is rarely reported, but is a common finding during surgical exploration at the time of an abdominal attack. In our case, the abdominal x-ray showed a centrally located dilated bowel loop suggestive of ascites. Abdominal symptoms are caused by angioedema of the bowel wall and fluid leakage. The absence of inflammatory signs (e.g. normal C-reactive protein level) is a typical feature and may be a clue to the diagnosis in cases like ours, presenting as acute abdomen\textsuperscript{[9]}. Airway obstruction caused by angioedema is a dreaded complication occurring in approximately 10% of cases\textsuperscript{[9]}. Attacks may be induced by trauma or local pressure and occasionally by emotional stress, but a precipitating factor is frequently not found.

A diagnosis of C1 INH deficiency must be suspected in cases of recurring acute abdominal pain, particularly when classic laboratory investigations are normal despite the impressive clinical picture. A simple screening consists of the measurement of C2, C3 and C4 during the attack. The C4 concentration is almost always decreased during attacks and is usually low between attacks. The concentrations of C3 and C1q are normal in patients with HAE, regardless of the clinical status of their disease. If C4 levels are below normal, the determination of other complement factors and C1 INH is indicated. Diagnosis is based upon the finding of low titres of C4 and C2, a decreased total haemolytic complement (CH\textsubscript{50}), normal C3 levels and decreased C1 INH activity (less than 40% measured by a functional assay)\textsuperscript{[9,13,16]}. Normal or near-normal values of C2 and C4, and occasionally of C1 INH, can be found in symptom-free periods. C4 levels are also normal during attacks in cases of type III C1 INH deficiency\textsuperscript{[15]}. Keeping in mind that patients can have C1 inhibitor (C1 INH) that is antigenically present but is non-functional, functional tests may be useful.

The treatment of choice for acute attacks of HAE or AAE is intravenous purified C1 INH concentrate 1000–1500 units per hour. This treatment is less effective in AAE because of the rapid catabolism of C1 INH by the autoantibody, and higher replacement doses are frequently required\textsuperscript{[9]}. Fresh frozen plasma, which contains C1 INH, is not recommended for severe exacerbations because it may occasionally worsen symptoms, as it also contains C4 which acts as ‘fuel on the fire’. High doses of tranexamic acid or epsilon-amino caproic acid (1 g every 3–4 h) may give satisfactory results when administered early during the attack\textsuperscript{[11]} especially with AAE. The mechanism of action of these antifibrinolytic drugs is not known. Plasmin, the key enzyme of fibrinolysis, which is blocked by these drugs, is supposed to play a role in the release of vasopermeability mediators such as bradykinin and others. Acute exacerbations of HAE or AAE typically do not respond to antihistamines, glucocorticoids, or epinephrine.

Prophylactic treatment should be offered to patients with frequent attacks or life-threatening presentations. Danazol and stanozolol, attenuated androgens, increase the synthesis of C1 INH and are the most effective prophylactic treatment\textsuperscript{[9,10]}. They play no role in the treatment of the acute attack because they require several days to become effective. Epsilon-amino caproic acid and tranexamic acid are less effective but safer preventative drugs than androgen derivatives, and are considered as the first choice preventative treatment for AAE.

Knowledge of this rather rare cause of unexplained episodic abdominal pain is essential to prevent unnecessary surgical interventions, and to be prepared for the life-threatening obstruction of the upper airway caused by laryngeal oedema, which occurs in approximately 10% of cases before diagnosis.

**Conclusion**

Hereditary angioedema should be suspected in adults with episodic abdominal pain for which common causes have been convincingly excluded. Quantitative and functional C1 INH assays should be performed when the disease is suspected. Acute attacks of angioedema should be treated with intravenous purified C1 INH concentrate, where available. Clinicians should keep this disorder in mind in their differential diagnosis of unexplained, episodic abdominal pain. Both the diagnostic and therapeutic approach to this rare condition should be known by emergency physicians for two reasons: (1) it may present as an acute abdominal emergency resulting in unnecessary surgical intervention; (2) it may cause life-threatening upper airway obstruction as a result of laryngeal oedema.
Teaching point

Hereditary angioedema should be considered in the differential diagnosis of unexplained, episodic abdominal pain in young patients. Diagnosis and therapeutic approach should be known in order to prevent unnecessary surgical exploration.

References