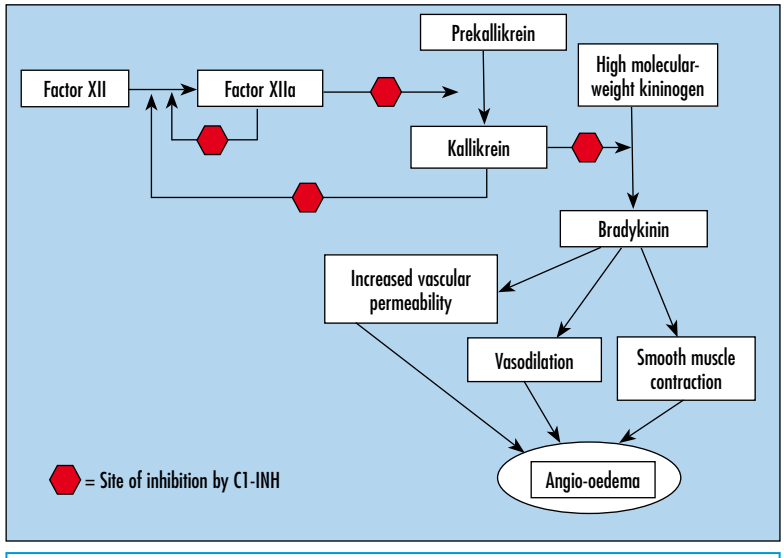
Diagnosis and treatment of hereditary angio-oedema attacks

Patients with hereditary angio-oedema will often present to the emergency department or hospital with cutaneous swelling, abdominal pain or laryngeal oedema. This article reviews the diagnosis and acute management of patients with hereditary angio-oedema.

Hereditary angio-oedema is a rare inherited disorder characterized by debilitating recurring episodes of oedema at various body sites, most commonly the skin and gastrointestinal tract and less frequently the upper airway. There are often significant delays in appropriate diagnosis and treatment of hereditary angio-oedema because of the variable clinical presentation of this disorder (Lunn et al, 2010). Gastrointestinal oedema, which is one of the most common presentations of hereditary angio-oedema, is often mistaken for acute abdomen, prompting unnecessary exploratory surgery (Agostoni and Cicardi, 1992; Lunn et al, 2010). Laryngeal oedema, which may be life-threatening, may be mistaken for an anaphylactic or allergic reaction, prompting administration of medications or procedures that are ineffective or that might even exacerbate the hereditary angio-oedema attack. In a survey of 313 patients with hereditary angio-oedema from five countries, 65% of respondents reported being given a wrong diagnosis, and about 20% underwent unnecessary surgery as a result of misdiagnosis (Lunn et al, 2010). These findings underscore the importance of increasing awareness of hereditary angio-oedema management among hospital physicians.

Figure 1. Bradykinin-forming pathway and sites of inhibition by C1 esterase inhibitor (C1-INH).



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Hereditary angio-oedema: a clinical overview

Hereditary angio-oedema is a rare, autosomal dominant, inherited disorder occurring in ~1 in 50 000 individuals that is caused by deficiency (type I) or functional impairment (type II) of C1 esterase inhibitor (C1-INH), a key regulator of the contact pathway (Nzeako et al, 2001). Within this pathway, C1-INH inactivates factors XIIa and XIIf and kallikrein, preventing the production of bradykinin, a key mediator of vascular permeability and swelling (Nzeako et al, 2001) (*Figure 1*). Deficiency or impairment of C1-INH therefore results in overproduction of bradykinin, which manifests as bradykinin-mediated angio-oedema.

About 90% of patients have symptom onset before the age of 20 years; the mean age at symptom onset is about 11.2 years (Bork et al, 2006a). Although there is no sex predominance in the incidence of hereditary angio-oedema, women generally have a more severe disease course and a greater frequency of episodes (Bork et al, 2006a).

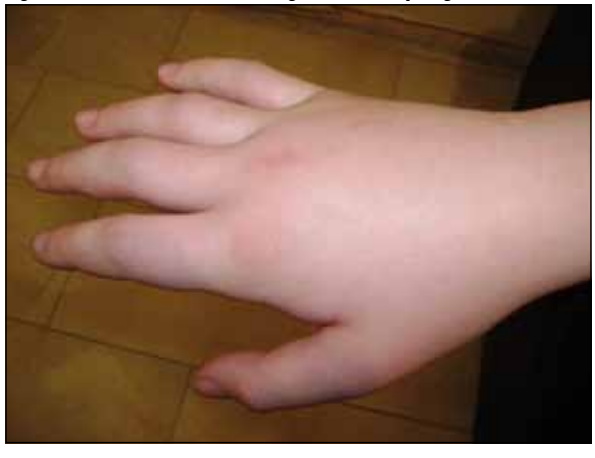
Hereditary angio-oedema presents as recurring and frequent episodes of cutaneous and gastrointestinal oedema and less frequent but potentially life-threatening episodes of laryngeal oedema (Bork et al, 2006a). Generally, these episodes last for 2–5 days before resolving spontaneously, resulting in significant debilitation and lost productivity (Nzeako et al, 2001; Lumry et al, 2010). The frequency and severity of attacks vary widely, even among members of the same family, and are unrelated to the degree of C1-INH deficiency or dysfunction. Known triggers of oedema include trauma, physical and psychological stress, medical, surgical or dental procedures, infections, menstruation, use of oestrogen-containing oral contraceptives, and angiotensin-converting enzyme inhibitors (Nzeako et al, 2001; Bork et al, 2003; Ricketti et al, 2007; Bouillet et al, 2008; Bowen et al, 2010). Often, no trigger can be identified.

Almost all hereditary angio-oedema patients have cutaneous manifestations that may persist for several days (Nzeako et al, 2001; Bork et al, 2006a). In about 75% of patients, cutaneous oedema of an extremity is the first presenting symptom of hereditary angio-oedema (Nzeako et al, 2001). Cutaneous oedema is non-pitting with ill-defined margins (Nzeako et al, 2001). Urticaria is not present, but one third of patients will develop erythema marginatum before or during an attack (Bork et al, 2006b). Unlike urticaria, this hereditary angio-oedema-related rash is not raised, pruritic, painful or warm and therefore can be distinguished from an allergic reaction or histamine-mediated angio-oedema (Nzeako et al, 2001). Cutaneous swelling usually occurs gradually and peaks at 24–36 hours, unlike allergic reactions, which are typically of rapid onset, another distinguishing feature of hereditary angio-oedema. Common sites of cutaneous oedema include the extremities, face, trunk, neck and genitals (Bork et al, 2006a) (*Figure 2*). Swelling can migrate from one site to another. Recurrent abdominal attacks occur in more than 90% of patients with hereditary angio-oedema (Bork et al, 2006a).

Gastrointestinal oedema and the resulting obstruction or constriction of the intestinal lumen can cause severe abdominal pain, frequently accompanied by vomiting and watery (secretory) diarrhoea (Nzeako et al, 2001; Bork et al, 2006b). Abdominal attacks of hereditary angio-oedema, particularly severe attacks, are frequently preceded by non-specific complaints of irritability, aggressiveness, fatigue or hunger (Bork et al, 2006b). The average duration of abdominal pain attacks is 3.3 days, with the majority lasting 2–4 days. The patient may vomit 10–20 times during the course of an attack and experience diarrhoea, increasing the risk of dehydration (Bork et al, 2006b). Abdominal pain is described by hereditary angio-oedema patients as crampy or colicky and is rated as severe to excruciating (8–10 on a 10-point severity scale) by the majority of patients (Bork et al, 2006b).

Frequent visits to the emergency department as a result of intense gastrointestinal pain may be mistaken for drug-seeking behaviour. Rarely, abdominal symptoms of hereditary angio-oedema may also be accompanied by severe circulatory symptoms including vertigo, hypovolaemic shock and loss of consciousness (Bork et al, 2005, 2006b). Laryngeal attacks occur infrequently compared with cutaneous and abdominal attacks, but about 52% of patients with hereditary angio-oedema experience laryngeal oedema at some point in their lifetime (Bork et al, 2006a). Laryngeal oedema may lead to upper airway obstruction and asphyxiation, which may be life-threatening. The risk of death from asphyxiation if a laryngeal hereditary angio-oedema attack is left untreated may be as high as 40% (Bork et al, 2000).

Figure 2. Unilateral hand swelling in hereditary angio-oedema.



Diagnosis of hereditary angio-oedema

Patients with acute abdominal attacks, facial or cutaneous angio-oedema, or laryngeal oedema often present to the emergency department with symptoms. Thus, emergency department physicians are likely to be the first health-care professionals who encounter hereditary angio-oedema patients during an acute attack.

Acute abdominal attacks

When a patient presents to the emergency department with acute abdominal pain, a thorough medical history, family history, and review of current and recent medications can help raise clinical suspicion of an acute abdominal hereditary angio-oedema attack (*Table 1*). A history of cutaneous swelling or laryngeal angio-oedema supports the diagnosis of hereditary angio-oedema. Although hereditary angio-oedema is an inherited disorder, 25% of hereditary angio-oedema cases are caused by spontaneous mutations (Bowen et al, 2010), so absence of a family history does not necessarily rule out the diagnosis.

Physical examination, cross-sectional imaging studies of the abdomen and relevant laboratory tests can often confirm the diagnosis during the acute episode (*Table 2*). Physical examination may reveal characteristics of cutaneous angio-oedema or erythema marginatum, which may precede or accompany the abdominal symptoms (Bork et al, 2006b). Palpation of the abdomen may reveal diffuse abdominal tenderness with or without rebound. Bowel sounds may be hypoactive or hyperactive. Shifting dullness may be present, indicative of ascites (De Backer et al, 2001).

Table 1. Diagnostic features of hereditary angio-oedema

Recurrent episodes of cutaneous angio-oedema without urticaria or pruritus
Recurrent episodes of unexplained abdominal pain accompanied by frequent vomiting and/or diarrhoea
Onset of attacks in childhood or adolescence, increasing in frequency with puberty
Prolonged attacks (lasting 2–5 days)
Family history of angio-oedema and/or abdominal pain attacks
Episodes of erythema marginatum preceding unexplained abdominal pain or peripheral swelling

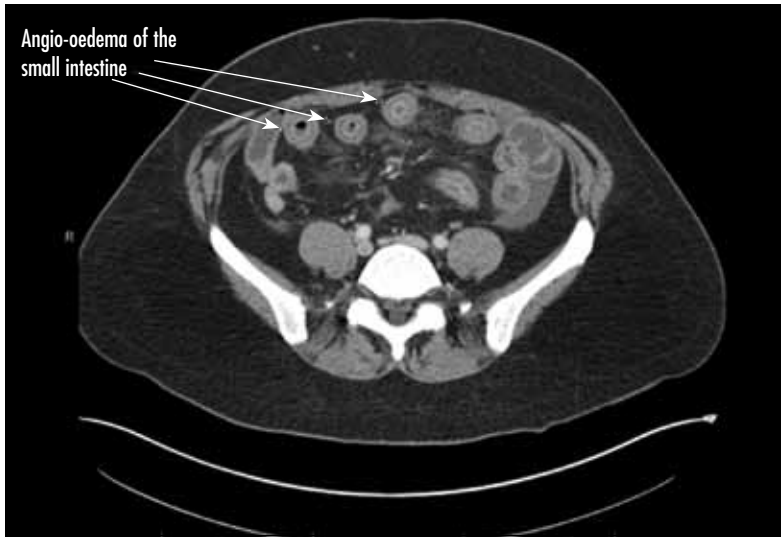
Contrast-enhanced abdominal computed tomography may reveal intestinal wall and mucosal thickening consistent with oedema, fluid accumulation in dilated small or large bowel loops, and ascites (De Backer et al, 2001) (*Figure 3*). Abdominal ultrasonography will usually reveal intestinal wall swelling and ascites and is therefore a useful tool to confirm the diagnosis of hereditary angio-oedema during an acute abdominal attack (Farkas et al, 2001; Pedrosa et al, 2009). Plain abdominal X-ray may show various degrees of obstruction with or without air–fluid levels, thumbprinting and dilated intestinal loops (Nzeako, 2010). Endoscopy of the gastrointestinal tract should be avoided in patients with suspected hereditary angio-oedema because of the risk of inducing laryngeal oedema. Exploratory surgery should be avoided in the absence of objective signs of a true acute abdomen, such as fever, leukocytosis or peritoneal signs (Nzeako, 2010).

Table 2. Physical, imaging and laboratory findings during acute abdominal attacks of hereditary angio-oedema

Physical findings	History of cutaneous oedema without urticaria or pruritus
	Erythema marginatum (in 30% of cases of abdominal attacks)
	Abdominal tenderness with or without rebound
	Hypotension
	Dehydration
	No fever or leukocytosis
Imaging findings	Intestinal wall thickening
	Transient ascites
	Dilated intestinal loops
	Intestinal intraluminal fluid accumulation
	Visceral subcapsular oedema
Laboratory findings	Low C4 levels (normal range = 0.20–0.50 g/litre*)
	Low C1-INH functional activity (normal range = 70–130%*)
	Low or normal C1-INH levels (normal range = 0.15–0.35 g/litre*)
	Normal C1q levels (normal range = 50–250 mg/litre)

C1-INH = C1 esterase inhibitor. *Normal range values from Bork et al (2006b)

Figure 3. Abdominal computed tomography showing angio-oedema of the small intestine.



Laboratory testing should be conducted for patients presenting with angio-oedema to aid in the diagnosis. Assessment of complement markers, namely C1-INH antigen levels and functional activity, C4 levels and C1q levels in older patients, can be used to confirm the diagnosis of hereditary angio-oedema (*Table 2*). Hereditary angio-oedema is characterized by low (80–85% of cases) or normal (15–20% of cases) C1-INH levels, low C1-INH functional activity, low C4 levels and normal C1q levels (Bowen et al, 2010). Measurement of C4 level is a cost-effective initial test since levels are low 95% of the time in asymptomatic patients and almost always low during an attack. Low C1q level is found in acquired angio-oedema (acquired C1 inhibitor deficiency), thus distinguishing it from hereditary angio-oedema. These laboratory characteristics, along with clinical factors such as young age at onset, recurring episodes of abdominal pain and vomiting, and skin swelling, often with a positive family history of hereditary angio-oedema or similar symptoms, can help confirm the diagnosis.

Cutaneous oedema

Hereditary angio-oedema should be suspected in patients who present with symptoms of cutaneous angio-oedema without urticaria or pruritus that persist for more than a day. This absence of urticaria or pruritus is a key feature that distinguishes hereditary angio-oedema-associated cutaneous oedema from allergic angio-oedema. In most cases, patients also have abdominal involvement – cutaneous swellings in the absence of abdominal symptoms are rare, although abdominal and cutaneous symptoms are usually non-concurrent (Bork et al, 2006a). Lack of response or poor response to antihistamines, corticosteroids or adrenaline also supports the diagnosis. Diagnosis of hereditary angio-oedema can be confirmed with laboratory tests for C1-INH levels and functional activity, and C4 and C1q levels, as described above (*Table 2*) (Bowen et al, 2010).

Acute laryngeal oedema

Laryngeal oedema, regardless of aetiology, can be life-threatening and is therefore a medical emergency. However, knowing the aetiology of oedema in these cases is critical, since adrenaline, antihistamines and corticosteroids will not be effective in hereditary angio-oedema-related laryngeal oedema and can delay appropriate treatment. Signs and symptoms of laryngeal oedema as a result of hereditary angio-oedema may include voice changes, barky cough, dyspnoea, stridor, anxiety and agitation, rapidly progressive cyanosis and hypotension (Farkas, 2010). The diagnosis of hereditary angio-oedema can be confirmed as described above (*Table 2*).

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Emergency department or hospital management of the patient with hereditary angio-oedema

Unless a history of hereditary angio-oedema is immediately available, most patients presenting to the emergency department with angio-oedema will likely receive antihistamines, corticosteroids and, in some cases, adrenaline, as part of their management. A lack of response to these agents should act as a clue to the diagnosis of hereditary angio-oedema.

When a patient presents to the hospital emergency department with acute angio-oedema of any aetiology, the mnemonic 'A-B-C-D' steps of emergency medicine should be initiated immediately, particularly if head and neck involvement is apparent. Step A comprises a thorough airway assessment to ensure that the airway is secured early, if necessary by endotracheal intubation, especially if oropharyngeal or laryngeal angio-oedema appears to be massive or progressive. Complaints of tightness in the throat, difficulty clearing saliva or difficulty swallowing indicate a need for very close monitoring and urgent treatment (Gower et al, 2011). The presence of stridor, hoarseness, cyanosis or hypoxaemia signals the immediate need for intubation (Farkas, 2010). Localization of oedema may make endotracheal intubation difficult. In such cases, surgical intervention (e.g. cricothyroidotomy, percutaneous tracheostomy or surgical tracheostomy) may be necessary. Oropharyngeal or nasopharyngeal intubation may be helpful in unconscious patients (Farkas, 2010). Frequent reassessment is essential until signs of abating angio-oedema are noted.

Step B is the assessment and management of any breathing difficulty. When non-hereditary angio-oedema swelling is suspected (often as a result of presence of concomitant urticaria or wheezing as a result of bronchoconstriction), or when the patient has no history of hereditary angio-oedema, appropriate urgent management using antihistamines, corticosteroids, inhaled beta-2-agonists or racemic adrenaline, or injected adrenaline should also be administered while appropriate investigations are initiated. In the case of angio-oedema known to be hereditary angio-oedema, further emergency department management involves the administration of appropriate therapy to abort the acute attack (discussed below). Those with evolving or severe laryngeal angio-oedema should be transferred to the intensive care unit for close monitoring and management.

Step C refers to an assessment of the patient's circulation through pulse and blood pressure measurements, with aggressive intravenous fluid resuscitation and electrolyte replacement as necessary. Step D refers to drugs, such as analgesics, for control of abdominal pain. Specific drugs used for treatment of acute hereditary angio-oedema attacks are covered in detail below. Upon resolution of the acute attack, an appropriate treatment regimen to prevent future attacks should be initiated and continued following hospital discharge.

For patients known to have hereditary angio-oedema, prompt treatment of symptoms at an early stage minimizes the need for supportive treatments or overnight hospital stay.

Treatment of acute hereditary angio-oedema attacks

Given that bradykinin is the primary mediator of oedema in hereditary angio-oedema (Kaplan and Joseph, 2010; Bouillet et al, 2011), current agents available for the acute treatment of hereditary angio-oedema are designed to prevent the generation or activity of bradykinin (*Table 3*). Treatment should be initiated as soon as possible after symptom onset.

The standard of care in Europe for the acute treatment of hereditary angio-oedema has been plasma-derived C1-INH concentrate. In Europe, licensed plasma-derived

Table 3. Current options for the treatment of acute attacks of hereditary angio-oedema

Product (manufacturer)	Indication (EU)	Dosage and administration (for acute attacks)	How supplied
Plasma-derived, pasteurized C1 esterase inhibitor (Berinert, CSL Behring)	Acute treatment of hereditary angio-oedema in children and adults	20 U/kg administered via intravenous injection	500 U vial or infusion
Plasma-derived, pasteurized, nanofiltered C1 esterase inhibitor (Cinryze, ViroPharma Incorporated)	Acute treatment of hereditary angio-oedema in adolescents and adults; also approved for pre-procedural prevention of hereditary angio-oedema attacks	1000 U administered via intravenous injection, second dose to be given if insufficient response after 1 hour	500 U vial
Recombinant human C1 esterase inhibitor (Ruconest, Pharming)	Acute treatment of hereditary angio-oedema in adults	50 U/kg (for body wt <84 kg) administered via slow intravenous injection; 4200 U (for body wt ≥84 kg)	2100 U vial
Icatibant (Firazyr, Shire)	Acute treatment of hereditary angio-oedema in adults	30 mg by subcutaneous injection	30 mg (3 ml) solution for injection in prefilled syringe
Ecallantide (Kalbitor, Dyax)*	Under European medicines agency review for acute treatment of hereditary angio-oedema	30 mg by subcutaneous injection as three injections of 10 mg (1 ml) each	10 mg/ml vial as solution for injection

*Not approved in European Union

C1-INH products include pasteurized C1-INH concentrate (pdC1-INH, Berinert, CSL Behring) and the recently approved pasteurized, nanofiltered C1-INH product (nfC1-INH, Cinryze, ViroPharma Incorporated). While pdC1-INH is approved for the acute treatment of hereditary angio-oedema attacks, nfC1-INH is approved for acute treatment as well as pre-procedural prevention of hereditary angio-oedema attacks in adolescents and adults.

The pdC1-INH concentrate has been shown to relieve attacks at facial, abdominal and laryngeal sites when administered at a dose of 20 U/kg, with a mean time to onset of relief of 0.46 hours (Craig et al, 2009, 2011).

The efficacy of nfC1-INH as acute treatment was studied in a randomized, double-blind, placebo-controlled, parallel-group study of 71 subjects with acute hereditary angio-oedema attacks (nfC1-INH, *n*=36; placebo, *n*=35). Treatment with nfC1-INH within 4 hours after the onset of an hereditary angio-oedema attack resulted in a greater than two-fold decrease in the time to beginning of unequivocal relief of the defining symptom of the hereditary angio-oedema attack compared with placebo (median 2 h for nfC1-INH *vs* >4 h for placebo, *P*=0.048). The time to complete resolution of the hereditary angio-oedema attack was also significantly shorter in the nfC1-INH arm (median 12.3 h *vs* 31.6 h, *P*=0.001) (Zuraw et al, 2010).

Although pdC1-INH and nfC1-INH are plasma-derived products, there have been no reports of virus transmission with these products. Pasteurization and nanofiltration purification steps have helped keep this risk to a minimum; nevertheless, a theoretical risk exists. Recombinant human C1-INH (rhC1-INH, marketed as Ruconest in Europe by Pharming) is approved for acute treatment of hereditary angio-oedema in 30 European countries, including the UK. Pooled results of two randomized, saline placebo-controlled, double-blind trials involving 41 patients demonstrated that rhC1-INH at doses of 50 U/kg or 100 U/kg provided initial relief of symptoms in less than 4 hours in >90% of patients (Zuraw et al, 2010). This product is manufactured by expressing the human C1-INH protein in the milk of transgenic rabbits. Although the risk of hypersensitivity reactions has been found to be small, the product is contraindicated in patients with a history of rabbit allergy (Zuraw et al, 2010). Presently, rhC1-INH is not approved by the Food and Drug Administration for use in the United States.

Icatibant (Firazyr, Shire), a bradykinin B2 receptor antagonist, is administered as a single 30 mg subcutaneous injection and is available in a prefilled syringe. Icatibant has been shown in clinical trials to reduce the time to onset of symptom relief *vs* placebo, with a median time to onset of symptom relief of ~2 hours (Cicardi et al, 2010; Lumry et al, 2011b). Icatibant was approved for use in Europe in July 2008 and in the United States in August 2011. It is approved for use only in adults with hereditary angio-oedema. To date, no paediatric data are available on this agent.

Ecallantide (Kalbitor, Dyax), a plasma kallikrein inhibitor that is administered subcutaneously, has also been shown to provide rapid symptom relief in patients with hereditary angio-oedema (Cicardi et al, 2010; Levy et al, 2010). In December 2009, this product was approved by the Food and Drug Administration for use in the United States for treatment of acute hereditary angio-oedema attacks in patients aged 16 years or older; however, it is not yet approved for use in Europe. Rarely, anaphylactoid reactions have been reported.

Short-term prophylaxis before medical procedures

Medical, dental and surgical procedures, particularly those that involve manipulations of the neck and throat, can often trigger acute attacks in hereditary angio-oedema patients (Bowen et al, 2010; Bowen, 2011). These patients may require prophylaxis to reduce the risk of an attack during or after the procedure or surgery.

According to the 2010 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema, prophylaxis may not be necessary before minor manipulations, provided an adequate supply of acute medication is immediately available for the management of acute attacks (Bowen et al, 2010; Bowen, 2011). However, for major manipulation and those requiring intubation or extubation, and for patients with a history of oedematous attacks during minor manipulations, pre-procedural prophylaxis with C1-INH should be considered.

The only C1-INH product approved for pre-procedural prevention of hereditary angio-oedema attacks in adults and adolescents is nfC1-INH. The efficacy of nfC1-INH was evaluated in a retrospective review of 91 medical procedures in which this agent was used prophylactically (Lumry et al, 2011a). Hereditary angio-oedema attacks reported within 72 hours and adverse events occurring within 7 days of the prophylactic dose were reviewed retrospectively. In this analysis, 41 subjects received nfC1-INH for 91 procedures (e.g. dental work, surgery, interventional diagnostic procedures). A single 1000 U dose of nfC1-INH was administered within 24 hours before the procedure; two doses were administered for four of the procedures. Two hereditary angio-oedema attacks were reported, and both resolved after a second dose of nfC1-INH. Adverse events were reported by seven subjects within 7 days of the first nfC1-INH dose; none were deemed to be related to prophylaxis with nfC1-INH (Lumry et al, 2011a).

Although pdC1-INH is not indicated for pre-procedural prevention of hereditary angio-oedema attacks, the efficacy of this agent in the pre-procedural setting has been evaluated in 51 adult and paediatric hereditary angio-oedema patients undergoing minor or major surgery

(Rusicke et al, 2010). All patients received 500–1000 U of pdC1-INH concentrate (Berinert) 1 hour before surgery. No acute hereditary angio-oedema attacks or incidents of laryngeal oedema were observed during or after any of the 71 surgical procedures monitored. In contrast, Bork et al's (2011) retrospective review suggested that pdC1-INH given in a dose of 500 or 1000 U before surgery could reduce, but not prevent, the risk of laryngeal angio-oedema in a dose-dependent fashion.

Pregnant or lactating patients

There is now published evidence in humans that, when administered prophylactically throughout pregnancy or as treatment for acute attacks during pregnancy, plasma-derived C1-INH appears to be safe and effective (Gorman, 2008; Bowen et al, 2010; Czaller et al, 2010). Thus, emergency department physicians and other physicians caring for pregnant patients in whom a hereditary angio-oedema attack is suspected or confirmed should use C1-INH for treatment or prophylaxis in this group of patients. Interestingly, normal labour and delivery does not appear to trigger hereditary angio-oedema attacks, and thus prophylactic administration of C1-INH concentrate during labour and delivery is not routinely recommended unless a patient reports a history of worsening of attacks with progression of pregnancy (Bouillet et al, 2008; Bouillet, 2010). However, this drug should be available for use if necessary during labour and delivery.

Conclusions

Both diagnosed and undiagnosed patients with acute hereditary angio-oedema attacks often present to the emergency department or hospital with cutaneous, abdominal or upper airway symptoms of hereditary angio-oedema. Recurring unexplained abdominal pain and vomiting or cutaneous angio-oedema without urticaria or pruritus should prompt an evaluation for hereditary angio-oedema. The diagnosis can be confirmed with laboratory assessments of C4 levels and C1-INH levels and functional activity. In older patients, C1q levels should also be checked to exclude acquired angio-oedema.

Patients who present to the hospital with an acute hereditary angio-oedema attack should be managed with one of the several agents currently available for this indication such as pdC1-INH (EU and US), nfC1-INH (EU), rhC1-INH (EU only), icatibant (EU and US), or ecallantide (US only). Treatment should be administered as soon as possible after onset of symptoms. Patients with hereditary angio-oedema may also require prophylaxis with C1-INH before certain medical and surgical procedures. Prompt diagnosis and appropriate management of hereditary angio-oedema in patients who present with symptoms to the emergency department or hospital can help reduce the mortality, morbidity and burden associated with this rare disorder. BJHM

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KEY POINTS

- Hereditary angio-oedema is a rare inherited disorder that presents as recurring and frequent episodes of cutaneous and gastrointestinal oedema and less frequent but potentially life-threatening episodes of laryngeal oedema.
- There are often significant delays in the appropriate diagnosis and treatment of hereditary angio-oedema as a result of the variable clinical presentation of this disorder.
- Diagnosis of hereditary angio-oedema should be based on patient and family history and laboratory assessment of complement levels, specifically C4 level, C1 esterase inhibitor (C1-INH) level, C1-INH function and C1q level.
- Current agents available for the acute treatment of hereditary angio-oedema are designed to prevent the generation or accumulation of bradykinin and include pasteurized C1-INH concentrate, pasteurized, nanofiltered C1-INH, recombinant C1-INH, icatibant and ecallantide.
- Patients with hereditary angio-oedema may also require prophylaxis with C1-INH before certain medical, dental and surgical procedures.

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