Hereditary angioedema: causes, manifestations and treatment

Hereditary angioedema is a rare abnormality of the immune system that in severe cases can cause death by asphyxiation. The correct diagnosis and management of hereditary angioedema is vital and, for acute attacks, C1-esterase inhibitor concentrate is the therapy of choice.

Hereditary angioedema (HAE) is an inherited abnormality of the immune system that causes swelling, particularly of the face, and abdominal cramping. HAE is a rare disorder that is unfamiliar to physicians, and often remains undiagnosed, despite debilitating and life-threatening symptoms. Hence, death by asphyxiation as a result of laryngeal oedema still occurs today. Patients with HAE are deficient in C1-esterase inhibitor (C1-INH), and thus cannot be treated for angioedema in the same way as patients with histamine-mediated angioedema.

From a therapeutic perspective, the importance of making the diagnostic distinction between HAE and the more common angioedemas of different origins cannot be overstated. This article details the aetiology and pathophysiology of HAE, the manifestations of the condition, and how it should be treated, with a particular focus on acute attacks.

Prevalence and incidence of hereditary angioedema

The exact prevalence and incidence of HAE is unknown because there are hidden cases of the syndrome in the population, but it is estimated to affect between 1 in 10 000 and 1 in 50 000 of the worldwide population (Bork et al, 2000; Gompels et al, 2005). Often, patients will not be diagnosed with the condition until several years after the first presentation of clinical HAE symptoms. It is during this period that HAE sufferers are most at risk from death by asphyxiation associated with the condition, as physicians will be unaware that corticosteroids and antihistamines are an inappropriate form of treatment. It is therefore advisable that all chronic angioedema sufferers are tested for C1-INH activity, as well as all at-risk relatives of individuals diagnosed with HAE.

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C1-esterase inhibitor

HAE is caused by a genetic deficiency of C1-INH; patients have been shown to possess just 5–30% of normal C1-INH levels (Rosen et al, 1971; Quastel et al, 1983). Insufficient levels of C1-INH allow unrestricted activation of the classical complement pathway and other biochemical mediator systems. In the kinin-releasing system, C1-INH regulates conversion of prekallikrein to kallikrein. C1-INH deficiency results in increased activation of this pathway, causing an increase in kallikrein, which in turn increases bradykinin production.

It is this increased bradykinin concentration that is thought to cause clinical flares (Nussberger et al, 1998). Bradykinin is an important inflammatory mediator that has been implicated in alternative forms of angioedema.

There are two genetic types of HAE caused by C1-INH deficiency, which result in the same phenotypic expression. The inheritance is autosomal dominant (*Table 1*) with incomplete penetrance. All patients described to date have been heterozygotes, and have a clinical spectrum ranging from asymptomatic to severely affected.

Triggers and frequency of hereditary angioedema attacks

HAE attacks are often preceded by a prodrome (*Table 2*) – this may begin with a tight or prickling sensation in the skin, followed by a non-itchy, painless rash. Known initiators of attacks include physical traumas, for example dental procedures, and emotional distress (*Table 2*) (Landres, 2001). However, attacks frequently take place without warning and with no apparent triggering factor. Furthermore, the frequency of HAE episodes varies greatly among individuals, ranging from weekly episodes to intervals of more than a year between attacks (Nielsen et al, 1996). The age of the first clinical manifestations of the disorder also varies, from newborns to the elderly; however, two-thirds of patients experience their first bout of HAE in adolescence (Nielsen et al, 1996).

Symptoms of hereditary angioedema

Angioedema may develop in one or several organs or areas of the body. It usually develops in the subcutaneous tissues of the limbs, face, trunk or genitalia, but also commonly affects the mucous membranes of the

gastrointestinal tract (*Table 2*). The latter symptom can mimic peptic disease, biliary colic, appendicitis, acute abdomen or a perforated viscus, and is often misdiagnosed, precipitating unnecessary surgery. Rarely, the mucous membranes of the upper airways are affected (*Table 2*). Cutaneous lesions are non-pitting and typically resolve over 1–3 days. Severe abdominal pain with nausea and vomiting can occur in isolation or concurrently with cutaneous angioedema.

Laryngeal oedema

Laryngeal oedema typically occurs if the oral cavity has been traumatized (e.g. dental surgery), but it can occur spontaneously. It can cause an immediate life-threatening emergency, especially if the patient is initially misdiagnosed (Bork et al, 2000, 2003; Bork and Barnstedt, 2003). Indeed, laryngeal oedema is almost always the cause of HAE-related fatalities. The patient's condition can worsen rapidly following the trigger event, with the time between onset of symptoms and complete airway obstruction occurring in as little as 20 minutes, although the average period is 8 hours (Bork et al, 2003). The unpredictability of laryngeal oedema necessitates the initiation of treatment without delay. Hospitalization is always advised – close observation is mandated at all times should the patient require emergency intubation or tracheotomy to ensure adequate airways. It is important to note that HAE sufferers do not respond to drugs typically prescribed for urticaria or non-hereditary forms of the disorder, such as steroids, antihistamines or epinephrine.

Table 1. Genotypes and phenotypes of hereditary angioedema caused by C1-esterase inhibitor deficiency

Genotype	Phenotype	Description
Common form	1	85% of hereditary angioedema cases Autosomal dominant quantitative disorder Mutant gene causes discernibly suppressed serum C1-esterase inhibitor levels (5–30% of norm) as a result of abnormal secretion or intracellular degradation
Variant form	2	15% of hereditary angioedema cases Autosomal dominant disorder Point mutation causes synthesis of dysfunctional C1-esterase inhibitor in ample amounts. Synthesis of normal C1-esterase inhibitor is thereby decreased, and both are rapidly metabolized

Treatment of hereditary angioedema with C1-INH concentrate

Minor incidences of cutaneous angioedema do not require intervention, while attacks that affect the abdominal cavity may require adjunctive intravenous hydration and narcotics for pain relief (Landres, 2001). For acute cases, which may include oedema of the abdominal organs, larynx, glottis and face, the therapy of choice is C1-INH concentrate (Bork et al, 2005).

C1-INH is available as Berinert P (ZLB Behring, Marburg, Germany) and Cetor (Sanquin, Amsterdam, The Netherlands). Cetor is licensed in The Netherlands. Berinert P is currently licensed in Germany, Austria,

Table 2. Distinguishing factors for hereditary angioedema *vs* other frequent forms of recurrent angioedema

	Hereditary angioedema (C1-INH deficiency)	Angioedema associated with chronic urticaria	Angioedema associated with ACE inhibitor use
Developmental and medical history	Family occurrences First manifestation in first or second decade of life No history of urticaria Abdominal colics Increased incidence of autoimmune diseases	Usually no family history History of urticaria Normally no abdominal pain	No family history First manifestation usually after fourth decade
Triggering factors	Trauma (50%), especially dental Emotional stress Co-existing illnesses Often no obvious trigger	In most cases no trigger factors Aspirin	ACE inhibitors
Prodromes	Appear in 50% of cases, e.g. reticulate erythema	None	None
Symptoms	Cutaneous angioedema Abdominal pain Acute airway obstruction	Cutaneous angioedema Urticaria Abdominal pain (rare) Acute airway obstruction (rare)	Cutaneous angioedema Acute airway obstruction Gastrointestinal symptoms
Laboratory studies	Low C1-INH plasma activity Low C1-INH plasma concentration (type 1) Normal or elevated but dysfunctional (type 2)	Normal	Normal
Treatment	Acute attacks: Emergency procedures if necessary; C1-INH concentrate; fresh frozen plasma Prophylaxis: Danazol, stanozolol, tranexamic acid	Emergency procedures if necessary Corticosteroids Antihistamines	Emergency procedures if necessary Immediate discontinuation of ACE inhibitors

ACE = angiotensin-converting enzyme; C1-INH = C1-esterase inhibitor.

Switzerland, France, Hungary, Argentina and Japan. Neither is licensed in the UK although both products are available on a named patient basis. UK and Canadian guidelines for the use of C1-INH have been published (Bowen et al, 2004; Gompels et al, 2005).

Berinert P and Cetor are available as pasteurized virus-inactivated concentrate (Agostoni et al, 2004) that is stable at 4°C for 3 years. Berinert may also be stable at room temperature for up to 6 months, although storage under these conditions is not recommended (Schulte and Hofmann, 2004). C1-INH has been proven to be effective (Visentin et al, 1998), safe (Juers and Groener, 2004) and well tolerated. It is administered intravenously (500–1000 U), and halts most attacks within 2–3 hours, although it can take as little as 30 minutes (Visentin et al, 1998). The relatively long half-life of C1-INH (approximately 33 hours; Kreuz et al, 2004) also allows the treatment of patients who cannot tolerate prophylaxis with androgens or for whom androgens are contraindicated (Bowen et al, 2004; Gompels et al, 2005).

Alternative means of acute intervention include the infusion of fresh frozen plasma (FFP) – although because of viral safety concerns, FFP should only be administered when C1-INH concentrate is unavailable (Longhurst, 2005).

Home therapy for hereditary angioedema using C1-INH concentrate

For the majority of patients who only suffer from infrequent HAE attacks, C1-INH infusion is customarily given in hospital, typically in the accident and emergency department. However, for the small but critical proportion of patients who have frequent attacks, or for whom access to a hospital is difficult, interest in home therapy is growing, and it has been successfully implemented in various European locations (Vidler, 1999; Longhurst and O'Grady, 2004). The advantages of home therapy are apparent, as there is often a delay in treatment associated with hospital admission; accident and emergency physicians may be unfamiliar with the condition, and C1-INH concentrate may not routinely be held in hospital stock. Delayed treatment increases the risk of severe adverse incidents in HAE patients, including death.

Expert panels in the UK and Canada have published consensus documents on the management of HAE, which recommended offering patients the option of home therapy (Bowen et al, 2004; Gompels et al, 2005). In any case, whether infused at hospital or elsewhere, as C1-INH concentrate can be difficult to obtain at short notice, practitioners are strongly recommended to ensure that patients have a supply at home (Bowen et al, 2004; Gompels et al, 2005).

KEY POINTS

- Hereditary angiodema is caused by deficiency of C1-esterase inhibitor (C1-INH), causing episodic angioedema, subcutaneous swellings or abdominal pain.
- Angioedema commonly affects subcutaneous or submucosal tissues.
- Laryngeal oedema is life-threatening and requires urgent treatment with C1-INH concentrate.
- Abdominal pain may mimic a variety of serious abdominal complaints.
- C1-INH concentrate results in onset of symptom relief within 30–180 minutes.
- Home therapy with C1-INH concentrate should be offered, particularly for patients with frequent or life-threatening attacks.
- Long term prophylaxis with attenuated androgens or fibrinolytics is usually effective.

Therapeutic options for prophylaxis

Prophylaxis for HAE patients is important for its short- and long-term management and short-term prophylaxis is essential for patients undergoing dental surgery or tonsillectomy. C1-INH is the treatment of choice for major procedures or severely affected patients. For long-term prophylaxis, attenuated androgens such as danazol and stanozolol are effective in the majority of cases (Cicardi et al, 1997; Bork et al, 2000). Androgens are associated with a number of side effects, however, including menstrual irregularities, elevated cholesterol, arterial hypertension and liver disease (Cicardi et al, 1997). They may virilize the female fetus and affect growth, therefore are unsuitable for pregnant women and children. Hence, in paediatric HAE patients, the antifibrinolytic agents tranexamic acid and e-aminocaproic acid are used for first-line long-term prophylaxis.

Optimal prophylaxis is especially vital for HAE patients who have frequent, severe or rapid onset of attacks. If prophylaxis is ineffective, where available, such patients should be prioritized for C1-INH home therapy (Bowen et al, 2004; Gompels et al, 2005).

Conclusions

HAE can lead to recurrent intra-abdominal oedema, often requiring hospital attendance, and laryngeal oedema, which may lead to asphyxiation (Bork et al, 2000). Hence the correct diagnosis of HAE is essential, as patients do not respond to the therapies typically prescribed for other types of angioedema. The preferred therapy for acute attacks of HAE is C1-INH concentrate, a supply of which should be kept at home by all patients. Recommendations (Bowen et al, 2004; Gompels et al, 2005) suggest that home therapy for HAE should be made widely available for patients, since the delays associated with hospital administration can occasionally prove fatal. Prophylactic treatment can reduce the incidence and severity of acute HAE attacks. Attenuated androgens are the most effective oral long-term treatment for this purpose.

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