Background: We published the Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema (HAE; C1 inhibitor [C1-INH] deficiency) in 2004.

Objective: To ensure that this consensus remains current.

Methods: In collaboration with the Canadian Network of Rare Blood Disorder Organizations, we held the second Canadian Consensus discussion with our international colleagues in Toronto, Ontario, on February 3, 2006, and reviewed its content at the Fifth C1 Inhibitor Deficiency Workshop in Budapest on June 2, 2007. Papers were presented by international investigators, and this consensus algorithm approach resulted.

Results: This consensus algorithm outlines the approach recommended for the diagnosis, therapy, and management of HAE, which was agreed on by the authors of this report. This document is only a consensus algorithm approach and continues to require validation. As such, participants agreed to make this a living 2007 algorithm, a work in progress, and to review its content at future international HAE meetings.

Conclusions: There is a paucity of double-blind, placebo-controlled trials on the treatment of HAE, making levels of evidence to support the algorithm less than optimal. Controlled trials currently under way will provide further insight into the management of HAE. As with our Canadian 2003 Consensus, this 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of HAE was formed through the meeting and agreement of patient care professionals along with patient group representatives and individual patients.
PATIENT GROUP PERSPECTIVE
The HAE patient societies, including the CHAES/SAHC, have proposed establishment of comprehensive care clinics for the diagnosis, therapy, and management of HAE, including the development of home infusion and home care programs. Similar to the presentation by Hungarian-sponsored HAE workshops in their publication, we think it appropriate to share the patient perspective of HAE management to help administrators reflect on the development of comprehensive care clinics for HAE. The perspective of one Canadian patient with HAE is presented on the Canadian HAE Network Web site (http://www.haecanada.com, “Patient Perspective” section).

CLINICAL CHARACTERISTICS
HAE may present as recurrent angioedema (swelling) without urticaria (without hiving) and usually nonpruritic (without itch). Sometimes there is a nonpruritic serpentine erythematous rash. Distinguishing features of HAE are reviewed by Zingale et al and Bork et al. Swelling may affect any part of the body, including the extremities, face, trunk, gastrointestinal tract, genitourinary regions, or upper airways. Abdominal symptoms may mimic infantile colic, acute appendicitis, or other forms of acute abdomen, and symptoms may include nausea, vomiting, abdominal pain, and postattack diarrhea. In patients with known HAE and a strong indication that the abdominal attack may be HAE related, infusion with C1-INH replacement therapy can be used to differentiate acute abdomen from an HAE attack. Age of onset is variable, and patients may present at younger than 1 year with colic or rarely swelling. Laryngeal attacks are uncommon before the age of 3 years and tend to occur later than other symptoms. Attacks frequently worsen around puberty. Symptoms often worsen with estrogen-containing birth control pills or hormone replacement therapy. Untreated attacks tend to be prolonged, typically increasing during the first 24 hours and then slowly and spontaneously subsiding at more than 48 to 72 hours. However, some attacks may last longer than 72 hours as the swelling migrates from site to site. Attack triggers may include stress, minor trauma (such as dental procedures), menstruation, pregnancy, some drugs (eg, oral contraceptives, ACE-Is), or infections. However, triggers are often unidentified. Attacks tend to be periodic, sometimes coming in clusters, and often followed by several weeks of remission. Attacks may not respond to treatment with epinephrine, antihistamines, or glucocorticoids.

DIAGNOSIS
Indications for testing include clinical suspicion at any age or, if the family history is positive, test at any age. Tests may not be reliable in patients younger than 1 year (false-negative and false-positive testings may occur unless using genetic typing). Testing performed in patients before the age of 1 year should be confirmed after the age of 1 year. A serpiginous rash is sometimes seen with the prodrome of HAE, but clinical urticaria (hives) usually make the diagnosis of HAE unlikely. An algorithm approach to angioedema has been presented by Zingale et al. Figure 1 shows the HAE diagnostic algorithm.

DIAGNOSTIC TESTING
If C1-INH deficiency is clinically suspected, we recommend screening with serum C4 and C1-INH proteins. C4 is normal between swelling events in only 2% of cases, so a normal C4 level should make one question the diagnosis of HAE. If there is a low index of suspicion, it may be more cost effective to screen with C4 alone (it is not necessary to screen with CH50 or C3). If serum C4 and C1-INH antigenic protein levels are both low and AAE not suspected, then the diagnosis is compatible with type 1 HAE (we suggest repeating testing once to confirm). If AAE is possible (ie, no family history and later onset of symptoms, such as age older than 40 years), then serum C1q antigenic protein testing is required, and if levels are low, the diagnosis is highly compatible with AAE (C1q antigenic protein is reduced in 75% of AAE but normal in HAE). If the C4 level is normal or low and the C1-INH antigenic protein level normal but clinical suspicion is strong, HAE is NOT ruled out. We recommend obtaining a C1-INH functional assay. If the C1-INH functional activity is low with normal or elevated C1-INH antigenic protein and normal C1q levels, this finding is compatible with type 2 HAE. Testing should be repeated at least once more to confirm the diagnosis. If C4 antigenic protein and C1-INH functional assays are both normal, types 1 and 2 HAE can be ruled out. However, this does not rule out the recently described types of HAE—sometimes called type 3 HAE or estrogen-dependent angioedema, with normal C1-INH protein and function occurring mainly in women—including HAE due to mutations in the coagulation factor XII gene and other defects yet to be identified. The same is true for ACE–1-related angioedema. If C4 and C1-INH protein levels are normal, these tests should be repeated during an acute attack (Fig 1).

Genetic testing is not necessary to confirm the diagnosis of types 1 and 2 HAE and similar to other autosomal dominant disorders, approximately 25% of patients may represent de novo mutations. However, genetic testing may be necessary to investigate type 3 and C1-INH functional assays vary, and we recommend standardizing the functional assays and establishing specialized laboratories capable of accurately measuring C1-INH function and establishing an international set of reference patient samples to facilitate independent quality assurance programs for laboratories claiming to test for HAE. (For example, one of our authors, E. Wagner, surveyed Canadian laboratories testing for HAE, with results of the survey summarized in http://www.haecanada.com - diagnosis section Canadian testing facilities.) Physicians are reminded that patient sample handling for complement testing must be strictly adhered to obtain reliable results (http://www.haecanada.com – diagnosis section – sample handling).
Hereditary Angioedema
Bruce L. Zuraw, M.D.

A 19-year-old woman presents to the emergency department with light-headedness, severe abdominal pain, and intractable nausea and vomiting that began 12 hours earlier. The patient reports previous episodes of abdominal pain and swelling of her hands and feet that have been attributed possibly to food allergies, which have recently become more frequent. There is no associated urticaria. Her only medication is an oral contraceptive that was started 3 months earlier. She notes a history of similar episodes in her father. She is afebrile, with a blood pressure of 75/40 mm Hg, a pulse of 120 beats per minute, and diffuse abdominal tenderness with guarding and rebound tenderness. How should her case be evaluated and treated?

The Clinical Problem

Hereditary angioedema, initially described by Osler in 1888, is an autosomal dominant disease caused by a deficiency in functional C1 inhibitor. Hereditary angioedema is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema typically involving the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, or larynx (Fig. 1). Its prevalence is uncertain but is estimated to be approximately 1 case per 50,000 persons, without known differences among ethnic groups. Symptoms typically begin in childhood (often as early as 2 or 3 years of age), worsen around puberty, and persist throughout life, with unpredictable severity. Untreated patients have attacks every 7 to 14 days on average, with the frequency ranging from virtually never to every 3 days. There is considerable variation in the severity of hereditary angioedema, even within a kindred. Results of observational studies suggest that minor trauma and stress are frequent precipitants of episodes of swelling, but many attacks occur without an apparent trigger. Pregnancy has a variable effect on disease severity, but attacks are rare at the time of delivery. Patients with hereditary angioedema have an increased frequency of autoimmune diseases, especially glomerulonephritis.

Attacks of hereditary angioedema usually follow a predictable course. Many attacks are preceded by a prodrome (usually a tingling sensation), and approximately a third are accompanied by erythema marginatum, a nonpruritic, serpiginous rash. The swelling classically worsens slowly but relentlessly over the first 24 hours, then gradually subsides over the subsequent 48 to 72 hours. The arms, legs, hands, feet, and abdomen are the most common sites of swelling. Oropharyngeal swelling is less frequent, but over half of patients have had at least one episode of laryngeal angioedema during their lifetime. Attacks may start in one location and then spread to another before resolving.

Hereditary angioedema affecting the abdomen or oropharynx can be associated with significant risk of illness and death. Abdominal attacks can cause severe abdominal pain, nausea, and vomiting. Bowel sounds are often diminished or si-
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lent, and guarding and rebound tenderness may be present on physical examination, leading in some cases to unnecessary abdominal surgery. A shift of fluids into the interstitium or peritoneal cavity during abdominal attacks can cause clinically significant hypotension. Laryngeal edema poses the greatest risk for patients with hereditary angioedema; although proper diagnosis and treatment should protect them, historical data have suggested that asphyxiation caused over 30% of deaths among patients with this disease in the past. Even today, patients occasionally die from asphyxiation, particularly in the absence of a proper diagnosis.

Hereditary angioedema results from a mutation in the C1-inhibitor gene. According to the C1-inhibitor gene mutation database (HAEdb, http://hae.enzim.hu), over 150 different mutations have been identified in patients with hereditary angioedema. There are two main types of hereditary angioedema: type I (accounting for 85% of cases) and type II (15% of cases). These are indistinguishable in clinical presentation but are caused by different mutations. C1-inhibitor mutations that cause type I hereditary angioedema occur throughout the gene and result in truncated or misfolded proteins that are not efficiently secreted, with decreases in both antigenic and functional levels of C1 inhibitor. Mutations that cause type II hereditary angioedema usually involve exon 8 at or near the active site, resulting in a mutant protein that is secreted but is dysfunctional; antigenic C1-inhibitor levels are normal but functional C1-inhibitor levels are low.
C1 inhibitor deficiency: consensus document

Summary

We present a consensus document on the diagnosis and management of C1 inhibitor deficiency, a syndrome characterized clinically by recurrent episodes of angio-oedema. In hereditary angio-oedema, a rare autosomal dominant condition, C1 inhibitor function is reduced due to impaired transcription or production of non-functional protein. The diagnosis is confirmed by the presence of a low serum C4 and absent or greatly reduced C1 inhibitor level or function. The condition can cause fatal laryngeal oedema and features indistinguishable from gastrointestinal tract obstruction. Attacks can be precipitated by trauma, infection and other stimulants. Treatment is graded according to response and the clinical site of swelling. Acute treatment for severe attack is by infusion of C1 inhibitor concentrate and for minor attack attenuated androgens and/or tranexamic acid. Prophylactic treatment is by attenuated androgens and/or tranexamic acid. There are a number of new products in trial, including genetically engineered C1 esterase inhibitor, kalikrein inhibitor and bradykinin B2 receptor antagonist. Individual sections provide special advice with respect to diagnosis, management (prophylaxis and emergency care), special situations (childhood, pregnancy, contraception, travel and dental care) and service specification.

Keywords: C1 inhibitor deficiency, hereditary angio-oedema, consensus, treatment, management

Introduction

This document was commissioned by the Primary Immunodeficiency Association (PIA). It represents a consensus from patients, experts and the literature on the diagnosis, therapy and management of C1 inhibitor (C1 INH) deficiency.

For the purpose of this document C1 INH deficiency will include both genetic [types I and II hereditary angio-oedema (HAE)] and acquired [acquired C1 inhibitor deficiency (formerly acquired angio-oedema, AAE)] forms of the disease. It should be noted that this is a rare disorder and much of the literature is based on case studies or small series. The syndrome of type III HAE is referred to where appropriate, but is not part of the spectrum of C1 INH deficiency and as such is not covered in depth in this document. The levels of evidence used are listed in Table 1.

Background

C1 esterase inhibitor deficiency [hereditary or acquired (HAE-AAE)] is characterized by the occurrence of subcutaneous and submucosal swellings in any part of the skin and the respiratory and gastrointestinal tracts. In the hereditary form, symptoms usually appear early in life and are normally accompanied by a family history. Although scattered reports of this disease can be traced back to the last century, hereditary angio-oedema reached its own identity in 1963 (for reviews see Cicardi et al. [1] and Fay and Abinun [2]).
C1 inhibitor deficiency: consensus document

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### Genetics and prevalence

The disease is inherited in an autosomal dominant manner. The spontaneous mutation rate is about 25% and more than 100 different C1 inhibitor gene mutations have been described [3]. The prevalence of the disease has been estimated at 1/50,000, with no reported bias in different ethnic groups. While it is unusual to find the disease without symptoms, there is an extreme variability in their frequency and severity [4]. There seems to be little, if any, correlation between symptoms and type of genetic defect with patients from the same family, and therefore sharing the same mutation, showing wide differences in phenotype [4].

In HAE type I (up to 85% of all patients), there is a deficiency in the amount of C1 INH protein present in the plasma. This is the result of only one gene functioning. However, plasma values are usually 5–30% of normal rather than the 50% value that might be expected [5]. Increased catabolism of C1 INH, even in asymptomatic patients, and possibly decreased production, are likely factors [3,5]. There is also some evidence that certain amino acid substitutions found in type I HAE affect the intracellular transport of C1 INH and result in a marked reduction or the total impairment of protein secretion [3].

In HAE type II, the circulating C1 INH concentration is normal or high but not fully functional. In vitro studies show that C1 INH production in type II HAE is normal in contrast to the findings in patients with type I disease [5]. High plasma concentrations of dysfunctional C1 INH are found because the mutant protein is secreted normally and it is unable to form complexes with proteases, which increases its half-life in the circulation. Dysfunctional proteins often result from substitutions at the reactive site residue Arg444, but may also result from changes at several positions outside the reactive site loop.

HAE type III has been described by Bork et al. [6]. In this paper, cases with typical clinical features of C1 INH deficiency were described with normal C1 INH level and function and a normal C4. These cases were all female and appeared to have a dominant mode of inheritance.

AAE is said to affect a tenth as many patients as HAE, although this may be an underestimate. AAE presents in older patients, has no family history and is associated with lymphoproliferative disease or, less commonly, autoimmunity [7,8].

### Immunology

C1 INH is the main regulator of the early activation steps of the classical complement pathway. This protein is produced mainly in the liver, but also by activated monocytes and other cell types [9]. C1 INH also regulates the activation of kallikrein, plasmin in the fibrinolytic pathway, the activation of factor XI in the coagulation cascade and activated factor XIIa. In the presence of C1 INH deficiency the classical complement pathway can be inappropriately or excessively activated. Immune complexes trigger the activation of the first component C1 to C1 esterase. C1 esterase then acts with its natural substrates C4 and C2 to form the complex C4b2a. Formation of this new complex (and associated C3 activation) leads to the production of anaphylactic, chemotactic and vasoactive peptides (C2b, C3a, C5a). C1 INH protein blocks both the spontaneous activation of C1 and the formation of activated C1, therefore not allowing the C2,4 complex to be created.

In the kinin releasing system, C1 INH regulates conversion of prekallikrein to kallikrein. C1 INH deficiency results in an increase in kallikrein, which in turn increases bradykinin production. Inhibitory effects of C1 INH on factor XIIa, factor XIa and plasmin have also been described. The end result is increased vascular permeability and massive local uncontrolled oedema. While there is some debate as to the exact component that contributes to the angio-oedema, there is accumulating evidence to support the involvement of bradykinin [4,10–12].

### Diagnosis

#### Clinical

A diagnosis of C1 INH inhibitor deficiency is suggested by a history of recurrent attacks of angio-oedema and of abdominal pain (see Table 2). Symptoms include recurrent circumscribed, non-pruritic, non-pitting oedema. Peripheral pain is not usually a feature, unless swelling occurs on pressure bearing areas or where subcutaneous tissue is limited. Oedema can affect virtually any part of the integument, but is more common in the extremities [13]. Episodes of swelling may also involve the upper respiratory tract, including the tongue, pharynx and larynx. This contributed to the 15–33% mortality from the disease reported previously in the literature [14]. Abdominal pain, nausea and vomiting are the dominant symptoms in approximately 25% of all patients, and are the result of constriction by intestinal wall and mesenteric oedema [15]. Urticaria is not a feature of C1 INH deficiency. However, prodromal erythema has been reported in up to 25% of patients which may be mistaken for urticaria [16,17].

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A diagnosis of C1 INH inhibitor deficiency is suggested by a history of recurrent attacks of angio-oedema and of abdominal pain (see Table 2). Symptoms include recurrent circumscripted, non-pruritic, non-pitting oedema. Peripheral pain is not usually a feature, unless swelling occurs on pressure bearing areas or where subcutaneous tissue is limited. Oedema can affect virtually any part of the integument, but is more common in the extremities [13]. Episodes of swelling may also involve the upper respiratory tract, including the tongue, pharynx and larynx. This contributed to the 15–33% mortality from the disease reported previously in the literature [14]. Abdominal pain, nausea and vomiting are the dominant symptoms in approximately 25% of all patients, and are the result of constriction by intestinal wall and mesenteric oedema [15]. Urticaria is not a feature of C1 INH deficiency. However, prodromal erythema has been reported in up to 25% of patients which may be mistaken for urticaria [16,17].

Classically, the oedema and swelling develop gradually over several hours, increasing slowly for 12–36 h, and then subside after 2–5 days. However, patients may experience
abdominal attacks with a very sudden and severe onset of pain and no visible oedema. Attacks of severe swelling can occur in some patients on a weekly basis and in others happen only once or twice a year.

Angio-oedema can be precipitated by minor trauma to the tissue, such as dental work (said to be a cause in up to 50% of all cases) [18,19], by certain drugs such as oestrogen [20] or angiotensin converting enzyme inhibitors, by emotional stress or by infection [21].

Acute attacks of abdominal pain can mimic surgical emergencies and, before a diagnosis of HAE is established, patients frequently undergo unnecessary appendicectomy or exploratory laparotomy. Equally, after diagnosis, there is always the concern that true abdominal emergencies will not have surgery performed in good time [4]. Barium studies, carried out during an acute attack, show massive submucosal oedema, spiculation and fold thickening or effacement [22]. The gastrointestinal involvement appears to be segmental and transient with reversion to normal by several days after an attack. In a report of an endoscopy carried out during an acute attack of C1 INH deficiency the gastric mucosa was described as diffusely reddish and oedematous and the mucosal surface in involved areas bulged remarkably, mimicking a submucosal tumour [23]. Histological examination of the bulging area merely showed moderate inflammatory cell infiltration of the lamina propria [23]. These findings are relatively non-specific and response to treatment with C1 INH concentrate may be the only way to differentiate a surgical condition from an acute attack of C1 INH deficiency [4].

### Laboratory

Laboratory tests should be performed in an accredited laboratory registered with a suitable quality assurance scheme (e.g. UK National External Quality Assessment Scheme). Serum C4 level is a good screening test for C1 INH deficiency as serum C4 is invariably low in untreated HAE (C4 < 30% of mean normal level) [24]. It has been shown that for untreated C1 INH deficiency low C4 has 100% sensitivity, 100% negative predictive value and is thus an effective screening test [24]. All patients who are suspected of having C1 INH deficiency should have a C4 level measured. If C4 is normal it is not usually necessary to proceed to C1 INH analysis [24]. If the C4 level is low then C1 INH level and function should be assessed.

The diagnosis of type I HAE (85% of cases) is by demonstrating low amounts of C1 inhibitor protein, as assessed by immunochemistry. If C1 inhibitor value appears normal or raised (and C4 is low), a test of C1 inhibitor function should be carried out [18,25]. An absence of function suggests a type II defect. All such tests should be carried out on a fresh (or freshly frozen) serum sample, i.e. one less than 4 h old.

If C1 INH function or/and level are low and C4 is low then a repeat sample should be obtained to confirm the findings. The low prevalence of the condition means that false positives are common [24]. All testing should be undertaken off treatment, including the administration of C1 INH concentrate or fresh frozen plasma, to allow reversion to untreated levels. Ideally this should be for more than a week but longer if borderline levels are obtained.

Interpretation in very young children is difficult, owing to a paucity of data regarding reference ranges in children. C4 is not a reliable indicator in the very young as, again, the reference range is extended downward with respect to the adult reference range [26]. Data suggest that C1 INH is reduced by 30–50% in normal neonates (cord blood analysis), both antigenically and functionally [27]. In children under 1 year of age a low C1 INH (less than 30% mean adult level) confirms the diagnosis of HAE. However, the diagnosis cannot be excluded in a child under 1 year of age, even if the C1 INH level and function are normal. In this case, investigations should be repeated when the child is over 1 year.

There is evidence that pitfalls in the diagnosis are common, with 11 of 42 cases reviewed recently found to have a questionable diagnosis [28]. Established or transferring cases should be reviewed for validity of the diagnosis. In the presence of a low C1 INH level or function but a normal C4 the diagnosis of HAE must be questioned. We would advise that, in these circumstances, C1 INH be rechecked by a different method (evidence level 4). Currently, genetic tests are not indicated routinely; however, under certain circumstances a genetic test may be of use, if available. In cases where the diagnosis is established, C4 and levels of C1 INH and function may be useful to monitor treatment effect.

### Management

**Primary prevention**

Management of patients with C1 INH inhibitor deficiency should cover their long-term, short-term and acute needs. It is important in the general management of these patients to search for potentially treatable triggers of attacks and deal with them.

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geal trauma [101] (level of evidence 3). In all situations the clinician should consider the postpartum period one of higher risk of acute attacks.

**Contraception**

Oestrogens should be avoided where possible. The use of combined oral contraceptives exacerbate symptoms in HAE patients [102,103] (evidence level 3). A recent study reported that over 60% of HAE types I and III patients have more frequent attacks on oestrogens [20] (evidence level 2). In general, progesterone-only pills such as levonorgestrel are preferred. Progesterone may have a mildly protective effect. No published data exists regarding the use and safety of intrauterine devices.

**Dental care**

Trauma can precipitate acute oedema in patients with C1 INH deficiency. For this reason dental work carries a risk of triggering an attack. Fatal laryngeal attacks have been reported following tooth extraction [88]. However, attacks are unpredictable. Extensive dental work may be carried out without complication and conversely minor work may sometimes precipitate an attack [104].

All patients should be warned of the increased risk of an attack in the 36 h following dental procedures and should have rapid access to C1 INH replacement in the event of an attack [105], irrespective of whether they have received prophylaxis. Recommendation for prophylaxis should take account of the proposed dental procedure and of previous reactions experienced by the patient.

Danazol, C1 INH concentrate and FFP have all been recommended for prophylaxis [88,104,106]. We believe that correction with C1 INH is to be preferred for more invasive dental procedures (e.g. extractions). It is more physiological than treatment with attenuated androgens and is more likely to reliably achieve normal levels of C1 INH. Furthermore, use of C1 INH overcomes any potential doubt regarding adherence with anabolic steroids (evidence level 4).

**Travel**

The following advice is taken from the Primary Immunodeficiency Association (PIA) advice for HAE patients when travelling in the United Kingdom and abroad. Further advice can be obtained via the PIA website [http://www.pia.org.uk]. The advice falls into two broad categories: general administrative advice and that related to emergency treatment.

**General advice**

Wear a Medic Alert bracelet. Obtain form E111 from your local post office if travelling in Europe. Arrange travel insurance that will cover HAE. Discuss the situation well in advance with your consultant for advice on medication and emergency treatment. A doctor's letter will be required in order to take C1 INH through airport controls. Medications should be declared at the baggage checks and carried as hand luggage in a coolbag.

**Emergency advice**

Carry a consultant's letter giving instructions about emergency treatment and a 24-h emergency advice telephone number (translated if travelling abroad). All HAE patients should have an emergency dose of C1 INH to keep with them when travelling away from their home base, as well as standard treatment.

**Children**

Attacks are seen during childhood in most patients [18,107]. Although the diagnosis is usually made in the second or third decade of life [18,108,109], it is well documented that between 50% and 75% of patients had their first attack by the age of 12 years. Data from the largest patient group studied (over 340 patients from 120 different kindreds) and followed over a period of more than 20 years [1,4,7,54,110] confirms that almost 40% had onset of their symptoms before the age of 5 years, and 75% before the age 15. Data from smaller studies on children only provide more striking evidence that most experienced their first symptoms in early childhood, before the age of 6 years [58,111]. Occasional patients will have their first symptoms even earlier, before the age of 1 year [27,110,112,113]. Attacks in children are usually not as frequent and/or severe as in adults, except the recurrent colicky abdominal pain seen in 40–80% of children [55,58,107].

It is important to note that attacks of laryngeal oedema can occur at any age and may be life-threatening [79]. For this reason, particularly where there is a family history, children should be tested at an early age. There are few data confirming the reference range for C1 INH in the very young. We would advocate testing both C4 and C1 INH to confirm the diagnosis in these circumstances.

**Long-term prophylaxis of attacks in children**

This is a relatively unexplored issue [58,111], and most references state that the use of antifibrinolytics and androgens are not recommended because of the serious side effects of these drugs [25,76].

Severe or life-threatening attacks of C1 INH deficiency are less common during childhood but they do occur. Although earlier reviews suggest prophylaxis is rarely required in children [15,55], this view is changing with increasing experience with tranexamic acid. Long-term prophylaxis is
Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond

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Hereditary angioedema (HAE), a rare but life-threatening condition, manifests as acute attacks of facial, laryngeal, genital, or peripheral swelling or abdominal pain secondary to intra-abdominal edema. Resulting from mutations affecting C1 esterase inhibitor (C1-INH), inhibitor of the first complement system component, attacks are not histamine-mediated and do not respond to antihistamines or corticosteroids. Low awareness and resemblance to other disorders often delay diagnosis; despite availability of C1-INH replacement in some countries, no approved, safe acute attack therapy exists in the United States. The biennial C1 Esterase Inhibitor Deficiency Workshops resulted from a European initiative for better knowledge and treatment of HAE and related diseases. This supplement contains work presented at the third workshop and expanded content toward a definitive picture of angioedema in the absence of allergy. Most notably, it includes cumulative genetic investigations; multinational laboratory diagnosis recommendations; current pathogenesis hypotheses; suggested prophylaxis and acute attack treatment, including home treatment; future treatment options; and analysis of patient subpopulations, including pediatric patients and patients whose angioedema worsened during pregnancy or hormone administration. Causes and management of acquired angioedema and a new type of angioedema with normal C1-INH are also discussed. Collaborative patient and physician efforts, crucial in rare diseases, are emphasized. This supplement seeks to raise awareness and aid diagnosis of HAE, optimize treatment for all patients, and provide a platform for further research in this rare, partially understood disorder.

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Key words: AAE, acquired angioedema, angioedema, C1 esterase inhibitor, C1-INH, HAE, HANE, HANO, hereditary angioedema, hereditary angioneurotic edema, angioneurotic edema, chemically induced angioedema, human SERPING1 protein

INTRODUCTION

This supplement, like the 2003 C1 Esterase Inhibitor Deficiency Workshop and the many patient and physician...
Since then, the 2 subsequent workshops and other patient-advisors and welcomed guests for the presentation of awareness and research funding but also as ethical HAE, not only in a traditional capacity of raising physician initiatives is their inclusion of patients with exchanges between academia, industry, and patients. Workshop and other HAE initiatives, fostering free been welcomed to the C1 Esterase Inhibitor Deficiency to improve the lives of their patients dramatically through HAE is an attractive field because it offers doctors a chance and data to attain statistical significance. Nonetheless, cians and researchers to pool their anecdotal experiences effects of antifibrinolytics and steroids currently in use, requires a lifelong, individualized calculation of benefits and risks. These drawbacks are well known to the small community of physicians who deal frequently with these diseases and are a feature of life for those patients who suffer frequent or severe attacks.

Nonallergic angioedema as a model for the treatment of rare diseases

(Kayla Williams, BS, MA, MFA, and Henriette Farkas, MD, PhD,* Cambridge, Mass, and Budapest, Hungary)

In recognition of these challenges, several national and international physician and patient initiatives have begun in the past 2 decades. In many ways, the field of nonallergic angioedema, and especially HAE, is becoming an exemplar for the understanding and management of rare diseases. The estimated frequency of HAE is 1:50,000.\(^7\) As in many uncommon conditions, HAE’s infrequent incidence fosters collaboration, forcing cians and researchers to pool their anecdotal experiences and data to attain statistical significance. Nonetheless, HAE is an attractive field because it offers doctors a chance to improve the lives of their patients dramatically through study but also via educated case management. As such, it has brought together a group of motivated and compasionate physicians. The pharmaceutical industry has also been welcomed to the C1 Esterase Inhibitor Deficiency Workshop and other HAE initiatives, fostering free exchanges between academia, industry, and patients.

Indeed, perhaps the most distinctive feature of HAE physician initiatives is their inclusion of patients with HAE, not only in a traditional capacity of raising awareness and research funding but also as ethical advisors and welcomed guests for the presentation of scientific abstracts and talks. The first C1 Esterase Inhibitor Deficiency Workshop, held in Hungary in 1999, was the earliest meeting to follow this model. Since then, the 2 subsequent workshops and other patient-association gatherings in the United States and Canada have followed its inclusive precedent. Such a high level of patient involvement reflects not only the close relationship between knowledgeable physicians and their patients but also regional shortcomings in diagnosis and treatment. Because of the incapacitating and life-threatening aspects of the disease, patients and their families from areas where HAE is largely unknown have been forced to become educated enough to explain the disorder to strangers and, often, emergency department personnel to obtain the proper treatment. Even patients whose cases are managed by a competent local practitioner may have attacks while traveling or when their doctor is unavailable and thus may need to articulate their condition to someone entirely unfamiliar with the disease. By incontrovertible necessity, patients with HAE are one of the best-educated patient populations, and this is especially true in areas where satisfactory therapy for acute attacks is unavailable.

For patients and physicians alike, the Internet facilitates increasingly more communication, both personal and scientific. For patients with HAE, it can help to reduce the isolation of having a rare disease. Many patients first contact their national patient association online and use e-mail to stay in touch with fellow patients. The Internet is also being used by physicians and scientists to support a private patient registry and a public, constantly updated human C1-INH gene \((C1NH)\) mutation database. Through this online contact and regular meetings open to all, information about nonallergic angioedema is shared rapidly among a small, concerned group. Nonetheless, the need to educate more physicians and the general public remains. The rarity of nonallergic angioedema increases the likelihood that clinicians, especially general practioners or emergency department personnel, may never have seen a case. Patient organizations and other groups have thus worked to create emergency passports for patients with known HAE to carry and educational materials to distribute to emergency departments.

Scientific opportunities and current areas of controversy

(Kayla Williams, BS, MA, MFA, Cambridge, Mass)

Nonallergic angioedema is a puzzle with relatively well-defined borders: many specific \(C1NH\) mutations resulting in HAE have been identified, and the symptomatic results are known. However, several central pieces are missing. Despite recognition of functional C1-INH deficiency as the cause of most forms of nonallergic angioedema, the specific mechanism of attack generation has not been definitively described. Likewise, symptoms similar to those of nonallergic angioedema have now been reported in patients with normal amounts of functional C1-INH.\(^8\)

Multiple pathways have been proposed for the chemical cause of angioedema attacks. The murine HAE model developed by Han et al\(^9\) shares similarities with the human form of the disease but diverges from typical HAE in the triggering of angioedema. Despite homozygous C1-INH...
Angioneurotic edema

Abstract
Angioneurotic edema is a rare (1/100,000 births/inhabitants in France for the hereditary form) but potentially severe disease (risk of fatal laryngeal edema). It is a relapsing subcutaneous or submucosal edema caused by a deficiency in C1Inh (inhibitor of the C1 fraction of complement). From one individual to another, the episodes can be very different, but in a given individual, they often recur at the same site. The localization of the edemas varies widely: the limbs, the ENT (ear, nose, throat) region (life-threatening), digestive tract (the episode resembles a surgical emergency) etc ... These edemas appear after trauma or stress, even minor; they do not respond to corticosteroids or antihistamines. Angioneurotic edema can be hereditary (autosomal dominant inheritance) or acquired (associated with a lymphoproliferative syndrome; presence of anti-C1Inh autoantibodies). All clinically suspicious cases should be subjected to the in-depth exploration of C1Inh (dosages of C3 and C4, weighted and functional dosage of C1Inh, immunoblot, search for anti-C1Inh antibodies). Hereditary forms are treated with Danazol and Tranexamic acid; concentrated C1Inh (blood-derived product) is used exclusively for very severe episodes. The treatment of acquired forms is not codified.

Keywords
angioneurotic edemas / angioedemas / C1Inh / danazol / C1Inh concentrate
deliveries must be done if possible and peridural anesthesia is possible. Tranexamic acid can be proposed during pregnancies after the first term. Danazol must be avoided. C1Inh concentrate must be present in the delivery room; it must be administrated in case of caesarean or in case of attack during delivery. There no more gynaecological events (abortion, cancer....) than in general population. Fertility is the same.

Etiology

Classification

1) Hereditary ANE
Is transmitted by autosomal dominant inheritance; thus all affected individuals are heterozygotes. It appears particularly in adolescents and young adults (20-40 years old) and can have two forms:
type I, which concerns 85% of the cases, is caused by the defective synthesis of C1Inh (low levels of C1Inh);
type II, affects 15% of the cases and is the consequence of a functional abnormality of C1Inh (normal concentration of C1Inh but a low level of functional activity).

2) Acquired ANE
Develops especially in individuals over 50 years and can be induced in three situations:
type I results from the excessive intake of C1Inh secondary, which results into the hyperactivation of the classical complement pathway mediated for example by immune circulating complexes (in lymphoproliferative syndrome, autoimmune disease...);
type II is the consequence of the neutralization of C1Inh by antibodies;

3) Oestrogen dependant angioedema
Angioedema appeared with oestrogen treatment (contraceptive pill, substitutive hormonal treatment) or during pregnancies. We can find a low C1Inh functional level.

4) Angioedema appeared with ACE inhibitors (with an incidence of 1-3/1,000 users per year) and with angiotensin antagonist receptors.

Pathophysiology

C1Inh (the only known inhibitor of C1), controls the classical complement pathway, the contact phase of coagulation and the fibrinolytic cascade. It inhibits factor XII by 90%, and kallikrein and plasmin by 42%. In the case of a C1Inh deficit, any endothelial trauma will overactivate the contact phase of coagulation and the classical complement pathway, and will lead to the release of large quantities of bradykinin and kinin-like substances which will trigger edema.

Method of biological diagnosis

The weighted dosage of C1Inh must be measured in serum (collected in a dry tube). Three techniques are available: radial immunodiffusion, electroimmunodiffusion and nephelometry. C1Inh function is analyzed by measuring the inhibitory activity of plasma C1Inh (collected on citrate or EDTA) against C1s with the kinetic test devised by the Immunology Laboratory of Grenoble. Other determinations can be performed with other substrates; commercially are sold available kits (e.g.,The binding site, Quidel, etc.). The C1Inh protein is analyzed by vertical electrophoresis throught a sodium dodecyl sulfide-polyacrylamide gel (SDS-PAGE), followed by C1Inh immunoblotting. In this way, the native (that is to say functional) forms of C1Inh can be distinguished by their higher molecular mass, 105 kDa, from those that have been truncated (non-functional), 95 kDa, or those complexed with C1s. The search for anti-C1Inh antibodies is done by enzyme-linked immunosorbent assay (ELISA). The result is positive or negative; the antibody level is not measured, as it has no clinical value. Indeed, it has been shown that the level is not correlated with the severity of the disease.

Prenatal diagnosis/genetic counseling

For hereditary ANE, genetic studies are in progress. There are many mutations, with the discovery of almost one different mutation per family (more than 300 mutations).
For a child born to an affected parent, it is not necessary to undertake prenatal genetic testing. Nor is it necessary to measure C1Inh in cord blood because the concentration does not reach its maximum before the 6th month of life.
To determine if a child is affected, C1Inh should be dosed after the 6th month.

Unresolved questions

Genetic studies are advancing and will probably help improve our understanding of the wide variety of clinical pictures.
Therapeutic management is not optimal; available treatments have major side effects. New therapies are needed; bradykinin-receptor antagonists and kallicrein inhibitors may be of benefit in treating ANE.
Acquired ANE are poorly known; no therapeutic protocol has been well defined.

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Hereditary Angioedema: A Life-Threatening Disorder

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Publication: Revista Societății Române de Alergologie și Imunologie Clinică, vol. nr. p. 12-17, 2005

Abstract
Although hereditary angioedema (HAE) accounts for only a small fraction of all cases of angioedema, it is the most common genetically linked clinical disorder caused by deficiency of a protein associated with complement activation, low C1-inhibitor (C1-INH) function. There is a currently widespread recognition in the allergy and clinical immunology community as a clinical entity. It is known to cause attacks that may be complicated by incapacitating cutaneous swelling, life-threatening upper airway obstruction, and severe gastrointestinal colic. Recent physiochemical and genetic studies have contributed significantly to our understanding of the structure of the inhibitor protein. Measurement of serum C4 titer is an efficacious screening test, although some authors find that occasionally normal values does not rule out HAE. C1-INH studies should be performed if there is a high index of clinical suspicion. The importance of making the correct diagnosis cannot be overemphasized. It can avert fatal consequences, such as airway obstruction, and unnecessary abdominal surgery. C1-INH replacement therapy represent an efficacious treatment of acute attacks. The application of preventive measures avoid need for dramatic emergency interventions. Potential new therapies with kallikrein inhibitor, bradykinin receptor antagonist and recombinant C1-INH has been developed and clinical trials are ongoing.

Introduction
Hereditary angioedema (HAE) is characterized by episodic local subcutaneous edema and mucosal swelling of the upper respiratory and gastrointestinal tracts, caused by a genetic insufficiency of C1 esterase inhibitor (C1-INH). It should be noted that this is a rare disorder and much of the literature is based on case studies or small series. First medical documents about HAE belongs to Heinrich Quincke (1882) (1) and Sir William Osler (1888). Osler was the first to fully describe its clinical features (2). In 1962, before any of the complement defects were known, Landerman et al. (3) suggested that the symptoms might be due to dysregulation of the kinin system. HAE reached its own identity in 1963, when Donaldson and Evans demonstrated a deficiency of C1 esterase inhibitor (C1-INH) in the plasma of patients with this disease (4). The progress made in our knowledge of this rare disease over the last decades is astonishing. There is a currently widespread recognition of C1-INH pathology in the allergy and clinical immunology community as a clinical entity. The incidence of HAE is estimated by most authors at 1:10,000-1:50,000, and the gene encoding C1-INH mapping is localized in chromosome 11q12-q13.1 (5). Since the disease is very rare, it is not uncommon for patients to remain undiagnosed for many years. Because of serious complications of attacks and the advance in the management of HAE, the condition must be clearly recognized by both primary care physicians and specialists.

Clinical manifestation
Patients can present with any combination of recurring cutaneous angioedema, abdominal pain, or acute airway obstruction lasting from 4 hours to 4 days (6). The age of HAE onset varies considerably. Most commonly, symptoms begin at school age; half of patients had symptoms within the first decade of life, and another third by the second decade (3). There also seems to be an increased frequency of attacks during puberty or adolescence. No single sex predominates and no
Hereditary Angioedema: A Life-Threatening Disorder

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Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant)

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Background: In hereditary angioedema, bradykinin is assumed to be the most important mediator of edema formation.

Objective: To assess whether the selective bradykinin receptor-2 antagonist Icatibant is effective in acute edema attacks of hereditary angioedema.

Methods: In this uncontrolled pilot study, 15 patients with 20 attacks were treated with Icatibant. The attacks were analyzed by using a standardized and validated visual analog scale measurement and compared with historical data of untreated attacks. Plasma bradykinin concentration was measured before and 4 hours after intravenous Icatibant treatment.

Results: Symptom intensity decreased within 4 hours after administration of Icatibant; the median time to onset of symptom relief was 1.50, 1.42, and 1.13 hours in the intravenous and 0.58 and 0.45 hours in the subcutaneous groups, respectively. The median difference in the 10-cm visual analog scale 4 hours after start of treatment was 4.11 cm (95% CI, 1.72-6.07). Compared with untreated attacks, Icatibant treatment reduced the mean (SD) time to onset of symptom relief by 97% from 42 ± 14 to 1.16 ± 0.95 hours (all groups combined). Median bradykinin concentration was 7-fold above the norm during acute attacks at 48.5 pmol/L and decreased to 18.0 pmol/L 4 hours after Icatibant infusion or injection.

Conclusion: Icatibant was effective in treating acute attacks of hereditary angioedema.

Clinical implications: This is the first report demonstrating the clinical usefulness of antagonizing bradykinin binding to bradykinin receptor-2 in hereditary angioedema.

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Angioedema is clinically characterized by self-limiting episodes of marked edema involving the skin, gastrointestinal tract, and other organs. Various forms of acquired and hereditary angioedema (HAE) share this clinical presentation. HAE was first described by Quincke1 and Osler.2 “Classic” HAE is associated with a quantitative (type I) or qualitative (type II) deficiency of C1 esterase inhibitor (C1-INH) resulting from mutations of the C1-INH gene. To date, more than 180 mutations have been reported.3,4 Recently, a third type of HAE has been described that is not associated with a C1-INH deficiency and occurs mainly in women.5,7 In some of these families, mutations in the coagulation factor XII gene have been found in the affected women.8

Clinically, HAE caused by C1-INH deficiency is characterized by recurrent bouts of edema. Skin swelling is located mostly on the extremities, the face, or the genitals.9 Abdominal attacks are often associated with severe pain, vomiting, diarrhea, and symptoms of hypovolemia.10 Laryngeal edema is potentially life-threatening, and many cases of asphyxiation have been reported.11-13

The pathogenesis of the acute edema attacks of HAE is not completely known. The low plasma concentration of functionally active C1-INH permits the activation of the kallikrein-kinin system, the early steps of the classical complement pathway, and even the fibrinolytic system, causing the release of vasoactive peptides. Recent data suggest that bradykinin is the most important mediator of HAE attacks: (1) bradykinin was found increased in plasma during acute attacks of HAE,14,15 (2) bradykinin levels were higher in blood drawn from an angioedema site compared with the levels in systemic circulation,16 and (3) a mouse deficient in both the C1-INH and the bradykinin receptor-2 (BR-2) gene revealed diminished vascular permeability, suggesting that the bradykinin/BR-2 pathway mediates angioedema formation.17
(SD ± 12.3 hours; range, 0.5-45.2 hours) on average. All patients reported that all treated swellings were considerably shorter than usual. Nine abdominal attacks in 7 patients were treated with Icatibant. According to the patients’ reports, Icatibant was markedly and rapidly effective in all attacks.

In 2 treated attacks in 1 patient, a recurrence of the abdominal pain attack occurred 14 and 17 hours after treatment with Icatibant, respectively (patient 11 in Table I). A male patient experienced a mild recurrence of a combined attack (skin swelling at several sites and abdominal pain attack) 20 hours after administration of Icatibant (patient 13). In a further male patient who was treated with Icatibant because of a skin swelling and a simultaneous abdominal attack, 20 hours after treatment, a new cutaneous swelling occurred (patient 15). A female patient experienced a swelling of the left foot. Twenty-seven hours after treatment with Icatibant, she experienced a relapse at the same site (patient 10). The 5 attacks were successfully treated with the rescue medication, 1000 U (3 attacks) or 500 U (2 attacks) Berinert P. Still, all patients initially responded to Icatibant and showed symptom relief.

After s.c. injection, local reactions were noted in all patients, including itching, urticarial wheal, erythema, and mild burning pain. Pain lasted for some minutes, itching urticarial wheal for some hours, and residual erythema cleared within 24 hours. All symptoms resolved spontaneously and did not demand medical intervention. In none of the patients was the response severe enough that the patient would consider refusing therapy. One patient experienced moderate headache more than 4 hours after the infusion of Icatibant. There were no other adverse events assessed as related to the study drug. Local skin irritation at the i.v. infusion site was not reported. None of the patients had an increase of blood pressure.

Plasma bradykinin was consistently (in all attacks) increased as much as 30-fold above normal levels (median increase 7-fold). At 4 hours after Icatibant infusion, median bradykinin was decreased from initial 48.5 to 18.0 pmol/L (Fig 2; n = 12). Similarly, 4 hours after subcutaneous administration of Icatibant, bradykinin was decreased from 75.0 to 30.5 pmol/L, but this decrease did not reach significance (n = 8).

**DISCUSSION**

Current treatment of patients with HAE includes long-term prophylaxis and treatment of acute edema attacks. Long-term prophylaxis with attenuated androgens (mainly danazol and stanozolol) is effective in many patients. However, a number of side effects were reported, including virilization in females, weight gain, and even liver cell adenoma and carcinoma. Although attenuated androgens reduce the total number and the severity of attacks considerably in most patients, use in children, teenagers, and women in child-bearing age is problematic. Long-term administration of tranexamic acid is less effective but shows fewer adverse events. Acute attacks can be efficiently treated with C1-INH concentrate. The C1-INH concentrate is derived from human plasma and has to be injected intravenously. High plasma bradykinin levels are found in patients with acute attacks of HAE, and bradykinin is likely to mediate the clinical symptoms via its receptor BR-2.

In the current uncontrolled proof-of-concept study, we assessed a new mode of treatment in HAE, a BR-2 antagonist Icatibant. The BR-2 antagonist Icatibant has a high specificity for the B2-receptor and inhibits a variety of B2-mediated effects. Its half life in plasma is 2 to 4 hours. It is degraded by peptidases, and the degradation products are excreted via the kidneys. Until now, the effectiveness has been assessed in seasonal allergic rhinitis and asthma. Furthermore,