Hereditary angio-oedema

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Hereditary angio-oedema is caused by a heterozygous deficiency of C1 inhibitor. This inhibitor regulates several inflammatory pathways, and patients with hereditary angio-oedema have intermittent cutaneous or mucosal swellings because of a failure to control local production of bradykinin. Swellings typically evolve in several hours and persist for a few days. In addition to orofacial angio-oedema, painless swellings affect peripheries, which causes disfigurement or interference with work and other activities of daily living. Angio-oedema affecting the gastrointestinal tract or abdominal viscera causes severe pain often with vomiting due to oedematous bowel obstruction. About 2% of swellings involve the larynx and can be fatal if untreated. About 50% of patients have laryngeal swellings that are potentially fatal despite prophylaxis. In this Seminar we review the clinical features, diagnosis, and management of hereditary angio-oedema, with specific emphasis on the new treatments available for acute swellings.

Introduction

The best known and more common form of hereditary angio-oedema is due to a genetic deficiency of C1 inhibitor; however, other forms of familial angio-oedema with normal concentrations of C1 inhibitor have been described in the past 10 years.[1] Here we focus on hereditary angio-oedema that is C1-inhibitor dependent. Patients with hereditary angio-oedema have episodic swellings that can affect any part of the body. The absence of associated urticaria and the slow timecourse of swellings distinguish hereditary angio-oedema from allergic or anaphylactic angio-oedema. Asymmetric cutaneous swellings affecting the hands, feet, face, or genitals, and swellings affecting the gastrointestinal tract, are most common (figure 1).[2,3] Intraoral swellings are rare but might progress to involve the larynx, and are of great concern to families affected by hereditary angio-oedema, about 30% of whom have had a family death from obstruction of the upper airway. In a prospective study,[2] 46% of attacks were peripheral in location, 33% gastrointestinal, and 6% oral. 15% of patients had swellings occurring simultaneously at more than one location.[2,4] Angio-oedema of the brain, joints, and abdominal viscera occur less often, and angio-oedema of the lower respiratory tract seems rare.[5]

Most episodes result in reversible disability lasting 1–5 days. About 40–87% of swellings related to hereditary angio-oedema are preceded (by up to 16 h) by prodromal erythema marginatum, substantial fatigue, or local discomfort (figure 1).[6,7] Swellings accumulate within several hours. Peripheral swellings are usually moderately painless. Intra-abdominal swellings typically start with low-level discomfort, abdominal distension, and nausea for several hours, before entering a phase of exponential progression to very severe pain with vomiting or diarrhoea and, in severe cases, fainting due to hypovolaemia. During the phase of maximum pain, routine radiographs might show distended bowel loops, which is suggestive of obstruction, and ultrasonography might show ascites.[8] Capsule endoscopy can allow substantial oedema of the mucosa to be visualised (figure 1; webvideo). Symptoms of hereditary angio-oedema are often mistaken for those of other acute abdominal disorders and many patients have a history of unnecessary surgery. Symptoms are at maximum intensity for up to 24 h before spontaneously resolving in a further day.[9,10] Figure 2 represents a typical time course of abdominal symptoms.

The symptoms of intra-oral swelling might be mild and slowly progressive for several hours before entering a phase of rapid progression to asphyxiation.[12] Patients who have had many non-obstructive laryngeal attacks, and physicians who are inexperienced in the management of hereditary angio-oedema, might not recognise the danger of intraoral swelling, which needs emergency treatment to arrest progression of the attack and sometimes a difficult intubation or emergency tracheotomy. Patients occasionally report abdominal or laryngeal attacks that are rapidly progressive and precipitous, and time from onset to death can be as short as 20 min.[12]

At times of physical and psychological stress, during treatment with angiotensin-converting-enzyme (ACE) inhibitors or after pharmacological or physiological exposure to oestrogens, risk of attacks is increased.[13–17] ACE inhibitors do not directly precipitate attacks, but act by increasing baseline concentrations of local bradykinin.[18] The mechanism of intervention for the other triggering factors is unknown. Known precipitating factors do not inevitably result in swelling, but instead reduce the threshold for start of an attack. Despite the reversibility of the angio-oedema, its unpredictable nature and in particular its association with stressful situations results in difficulties for the patient, their family, and their employers that are proportionate to the severity of the disorder. Yearly costs per patient in the USA that were

Search strategy and selection criteria

We searched PubMed from 1948, to June, 2011, the Cochrane database, clinical trials.gov, and Embase using the terms "hereditary angio-oedema", "hereditary angioedema", "C1 inhibitor", and "C1 esterase inhibitor" alone, and in combination with the terms "clinical trial", "meta-analysis", "practice guideline", and "randomised controlled trial". Full-text articles were retrieved for the most relevant articles. We did not have any exclusion criteria, although abstracts of papers that seemed irrelevant were not retrieved.

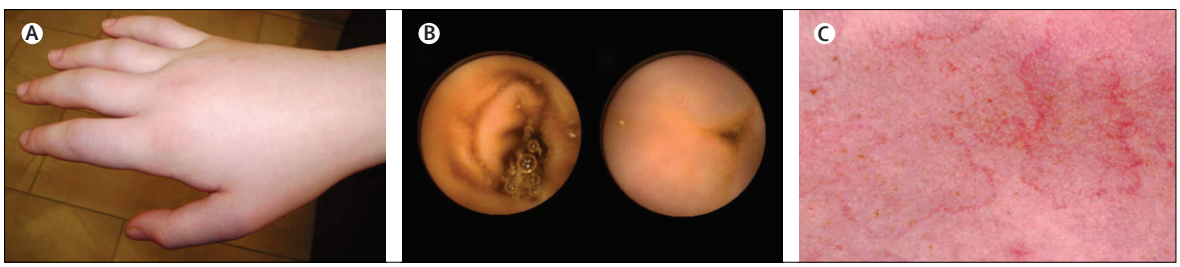

***Figure 1*: Clinical manifestations of hereditary angio-oedema**
(A) Angio-oedema of hand in patient with hereditary angio-oedema. (B) Capsule endoscopy during abdominal attack in patient with hereditary angio-oedema, showing ileal tract with normal mucosa and lumen (left), and oedematous ileum and substantially reduced luminal diameter, causing partial bowel obstruction (right). (C) Erythema marginatum on anterior chest wall of patient with hereditary angio-oedema 8 h before onset of abdominal symptoms.

calculated before the availability of definitive acute treatment were about US$42 000 overall, and $92 000 for severe disease.[19] Studies of angio-oedema do not necessarily account for the substantial and widespread costs of lost opportunity, or for the indirect costs to the family, the employer, or to society.

Epidemiology

Surveys of patients suggest that hereditary angio-oedema affects about 1 in 50–100 000 of any ethnic group, with many of those affected being unaware of their diagnosis.[6,20] Although the deficiency is lifelong, swellings rarely occur before the age of 2 years and are less frequent before adolescence. Mean age at onset of symptoms is about 8–12 years.[21] Incidence of swellings varies from more than one swelling per week to less than one per year.[2] In a random sample of 103 patients with hereditary angio-oedema, with and without long-term prophylactic treatment, the mean frequency of angio-oedema was once every 45·3 days.[4] Large differences in disease severity have even been noted within families, who naturally have the same mutation in C1 inhibitor. Polymorphisms away from the C1-inhibitor gene (particularly those affecting the contact system), environmental factors (such as emotional stress, exposure to infections, inflammatory stimuli), or low-level trauma, and variations in concentrations of sex hormones might all play a part in determining the frequency and severity of swellings.[2,13–17,22]

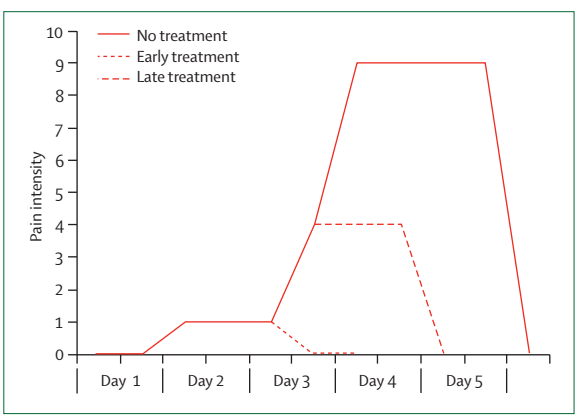

***Figure 2*: Pain intensity experienced during severe abdominal attack of hereditary angio-oedema[9–11]**
How early treatment can reduce pain and duration of attack. Continuous line shows time course of untreated attack. Dotted lines show time course of attacks treated with C1-inhibitor replacement early or late in course of attack.

Pathogenesis and regulation of inflammatory pathways

C1 inhibitor belongs to the protein family of serine protease inhibitors and, as with other members of this family, functions with a suicide mechanism that has been compared to a mouse trap.[23] When the C1-inhibitor lands on its target protease, it is cleaved and the carboxyl-terminal end of the cleavage site—arginine 444—covalently binds the protease. The protease-binding part of the inhibitor is then rotated and inserted into its globular part to keep the protease in an inactive state.[24,25] Mutations altering the aminoacid sequence of the inhibitor almost invariably result in its deficiency. More than 200 different mutations have been described in families with hereditary angio-oedema. Less than 20% of these mutations are large insertions or deletions, the rest are missense, frameshift, splicing defects, or nonsense defects due to changes in one or several bases.[26] Mutations in the C1-inhibitor gene can either prevent synthesis of a protein product that is detectable in plasma resulting in hereditary angio-oedema type 1, or can allow the synthesis of a protein product with impaired function resulting in hereditary angio-oedema type 2. Mutations causing the type 2 disorder are located mostly on exon 8 and affect the nucleotides coding for the aminoacids that form the reactive site of the protein.[27]

C1 inhibitor acts as a regulator of several inflammatory pathways (figure 3). In the classic complement pathway, C1 inhibitor is the only inhibitor of the C1r and C1s complement components in the classical pathway, and inhibits mannan-binding lectin-associated serine protease 2 in the lectin pathway. Both pathways converge to activate complement components C4 and C2. Deficiency in C1-inhibitor results in chronic overactivation and consumption of these components, which are substantially reduced in the plasma of patients with hereditary angio-oedema. Overactivation of the classical and lectin pathways does not progress to the common pathway and C3 concentration is typically normal, probably because reactions occur in the fluid phase.[28] Abnormalities in the

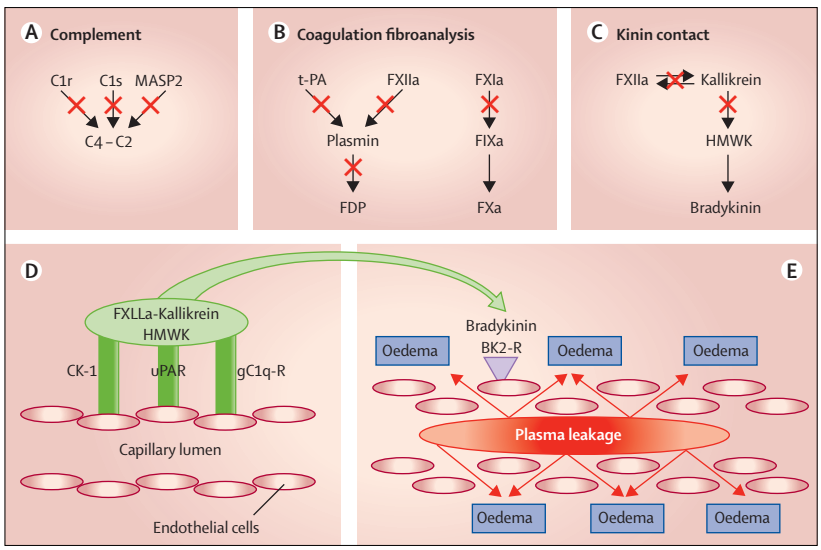

***Figure 3*: Serine proteases controlled by C1 inhibitor in pro-inflammatory cascade systems**
Red crosses indicate inhibition by C1-INH. (A) C1 inhibitor blocks activated C1r, C1s, and *MASP2* in complement system, which prevents excessive proteolysis of C4 and C2 components. (B) In coagulation system, C1 inhibitor blocks activated FXIIa and FXIa preventing thrombin formation through activation of FIXa and FXa. In fibrinolytic system C1 inhibitor might have a role in preventing formation of plasmin by inhibition of t-PA and FXIIa, and also prevents formation of FDP by inhibition of plasmin. (C) In contact-kinin system, through inhibition of FXIIa and active plasma kallikrein, C1 inhibitor controls positive amplification loop of activation of these two enzymes, thus preventing release of bradykinin by internal cleavage of HMWK. (D) Deficiency of C1 inhibitor allows excessive formation of plasma kallikrein and FXIIa, which are bound in complex with HMWK to specific receptors CK-1, gC1qR, and uPAR on endothelial cells. (E) Uninhibited active plasma kallikrein releases bradykinin that acts as paracrine hormone, stimulating specific G-protein coupled BK2-Rs that increase capillary permeability allowing oedema formation. *MASP2*=mannan-binding lectin serine protease 2. t-PA=tissue plasminogen activator. FXIIa=coagulation factor XII. FXIa=coagulation factor XI. FIXa=coagulation factor IX. FXa=coagulation factor Xa. FDP=fibrinogen degradation products. C1-INH=C1 inhibitor. HMWK=high-molecular-weight kininogen. BK2-R=bradykinin type-2 receptor. CK-1=cytokeratin 1. uPAR=urokinase plasminogen activator receptor. gC1qR =globular head of C1q receptor.

complement pathway are important in diagnosis, but are probably not responsible for swellings.

A second pathway is the contact pathway in which C1 inhibitor regulates coagulation factor XII (Hageman factor) and kallikrein, which controls production of bradykinin and leads to angio-oedema in patients who are C1-inhibitor deficient.[29] Bradykinin is a potent local vasodilator that has a paracrine mode of action that activates adjacent G-protein-coupled receptors of the bradykinin type-2 receptor that are constitutively expressed on many cells. Another type of specific receptor, bradykinin type-1, which is expressed after inflammatory stimuli, has also been described. Although the physiological role of the type-1 receptor is unclear, it might also have a role in the pathogenesis of symptoms of hereditary angio-oedema.[30] Bradykinin is the main mediator of angio-oedema in hereditary angio-oedema. In patients with the disorder, baseline concentrations of systemic bradykinin are increased. Concentrations further increase in episodes of angio-oedema and are much higher when blood is obtained from a swollen limb than when it is simultaneously obtained from the unaffected limb.[31–33] One family with a C1-inhibitor gene mutation affecting complement regulation, but with preserved kallikrein inhibitory activity, did not have angio-oedema; however, they did present with systemic lupus erythematosus (SLE) because of the acquired deficiency in C2 and C4.[34]

Clotting and fibrinolytic pathways are a third type of pathway regulated by C1 inhibitor. The actions of C1 inhibitor on clotting factors XI and thrombin, and its inhibition of plasmin and tissue-type plasminogen activator, do not result in phenotypic abnormalities, but do influence angio-oedema pathogenesis.[35] Other actions of C1-inhibitor include its binding to several extracellular matrix components, to complement component C3b in a way that is analagous to factor H, with E- and P-selectins on endothelial cells, and directly to endotoxin.[36] This binding seems to be independent of the protease activity of C1 inhibitor. Although the relevance of these interactions to patients with hereditary angio-oedema is unclear, they might be relevant to future therapeutic uses for C1 inhibitor. The various anti-inflammatory effects of C1 inhibitor have shown promise in non-human testing in other indications, such as stroke, multiple trauma, and graft rejection.[37,38]

Diagnosis

Patients with hereditary angio-oedema typically have a mean delay of more than 10 years between onset of symptoms and diagnosis.[20] This delay is important because conventional treatments, such as corticosteroids and antihistamines, are unlikely to be effective, and because most deaths occur in those who are undiagnosed.[2,39] Deficiency of the C4 complement component, and normal concentration of C3, is typical of hereditary angio-oedema, even in asymptomatic patients, and has been recommended as a screening test.[40] However, C4 concentration is occasionally normal even in untreated patients,[41] and definitive diagnosis requires measurements of C1 inhibitor. 85% of patients have low concentrations of C1-inhibitor protein (hereditary angio-oedema type 1), and 15% have normal or high concentrations of a non-functional C1-inhibitor protein (type 2). Functional measurements of C1 inhibitor are needed for patients with the type-2 disorder.[42]

C1-inhibitor function is usually measured in reference laboratories with two methods: a chromogenic assay that detects the capacity of C1 inhibitor in patients' serum to inhibit the ability of C1s to affect a colour change in a chromogenic substrate; and an ELISA that measures the ability of C1 inhibitor in patients' serum to bind to exogenous biotinylated C1s. Both assays function well in optimum conditions, but refrigeration or delay in samples being processed results in functional measurements that are artifactually low, particularly for the chromogenic assay.[43] ELISA works differently from the more commonly used chromogenic assay, and results are not directly comparable. Local determination of normal ranges might result in a higher cutoff with the ELISA than is recommended by the manufacturer.[41,43] Routine blood tests, such as blood count, creatinine, electrolytes, and C-reactive protein, are unaffected by deficiencies in C1 inhibitor.

Differential diagnosis

Clinical and laboratory findings should be considered when hereditary angio-oedema is diagnosed (panel), with one study suggesting that up to 25% of patients had a doubtful diagnosis.[44] C4 concentrations might be reduced in SLE, hypocomplementaemic urticarial vasculitis, cryoglobulinaemia, or cytokine-release syndromes. In these situations, C1 inhibitor will be consumed, but rarely to the extent of measurable deficiency. Thus normal concentrations of C4 in an untreated patient, or C4 deficiency with atypical clinical features that are suggestive of inflammatory disorders, should alert the clinician to the possibility of sample deterioration causing artifactually reduced function of C1 inhibitor.

SLE-like syndromes occasionally complicate hereditary angio-oedema, and secondary C1-inhibitor deficiency (acquired angio-oedema) might complicate lymphoproliferative or autoimmune disorders, including SLE.[45,46] By contrast with hereditary angio-oedema, symptoms of acquired C1-inhibitor deficiency start at an older age and there is no family history. Features of lymphoproliferative disease, or, most typically, an asymptomatic monoclonal gammopathy of unknown significance are sometimes present.[47] C1q concentrations are normal in hereditary angio-oedema but are often reduced in acquired C1-inhibitor deficiency; measurements might be helpful when secondary deficiency is suspected.[47] Although genetic diagnosis is not normally needed, it might be helpful to resolve diagnostic doubt or for children aged less than 1 year in whom plasma and serum testing can be unreliable.[48]

Angio-oedema with no urticaria that does not respond to antihistamines is typical of bradykinin-mediated angio-oedema. Other presumed bradykinin-mediated angio-oedemas, such as hereditary angio-oedema type 3 (associated with mutations in coagulation factor XII), hereditary angio-oedema induced by angiotensin-converting-enzyme inhibitor, and some idiopathic angio-oedemas might mimic hereditary angio-oedema. However, unlike in hereditary angio-oedema, swellings in bradykinin-mediated angio-oedemas mostly affect the face, mouth, and larynx, and there is no abnormality in the complement pathway or in C1 inhibitor.[49,50] The accurate differentiation of bradykin-mediated angio-oedema from histamine-mediated angio-oedema and from hereditary angio-oedema will be important for future treatment options. Figure 4 is a suggested algorithm for diagnosis of hereditary angio-oedema. By contrast with diagnostic testing, which despite the pitfalls is usually straightforward, no routinely available tests are available to diagnose acute attacks in patients with known hereditary angio-oedema and atypical symptoms,[52] and such tests are urgently needed. Treatment of attacks is costly but most effective if given early in the attack when symptoms and signs are non-specific.

Management and prophylaxis

Almost every patient with C1-inhibitor deficiency will have episodes of angio-oedema during their lifetime with substantial morbidity and mortality.[2] The first episode can be (but is rarely) fatal;[12] therefore, every patient needs a plan for treatment of acute attacks, irrespective of the severity or frequency of symptoms. For those with frequent or disabling attacks occurring more than once a month, long-term prophylaxis should also be considered.[53,54] 17-α-alkylated attenuated androgens, such as danazol, stanozolol, oxandrolone, and tibolone, and (unattenuated) methyl-testosterone, reduce the frequency and severity of attacks in most patients.[55,56] International consensus now recommends reduced doses—ie, a maximum of 200 mg danazol or 2 mg stanozolol daily.[57] High doses increase the risk of side-effects. Historically, side-effects are common and relate either to the residual androgenic properties of the drug, or to the 17-α-side-chain.[57,58] Regular liver function, cholesterol, and blood-pressure monitoring, and biannual liver ultrasonography to exclude hepatic adenoma, are specifically recommended for patients who need these drugs long-term.[57,60] Fibrinolytics, such as tranexamic acid or aminocaproic acid, are also used as prophylactics either continuously or at the early stages of mild attacks.[61,62] Fibrinolytics are of partial benefit at best, and not effective in severe or established attacks.[63,64] They are used for children in preference to androgens, which might affect growth.

The C1-inhibitor replacement, cinryze, has been licensed for prophylaxis in the USA on the basis of a double-blind crossover study of patients who had frequent attacks (more than two per month).[65,66] Patients were assigned to 12 weeks of 1000 units of C1-inhibitor twice weekly, or placebo for 12 weeks, before crossing over to the other group. C1-inhibitor prophylaxis was strongly associated with fewer swellings that were reduced in severity, shorter duration of attacks, a lower total number of days of swelling, and fewer on-demand C1-inhibitor

Panel: Criteria for diagnosis of hereditary angio-oedema

Diagnosis is obtained with one clinical and one laboratory criterion. When clinical criterion is family history, the individual is an asymptomatic carrier of hereditary angio-oedema.

Clinical criteria

- Recurrent subcutaneous angio-oedema that is non-pitting, non-pruritic, non-erythematous, and self limiting, and usually lasts for more than 12 h with no major urticaria
- Unexplained, recurrent abdominal pain (often accompanied by vomiting and diarrhoea), which spontaneously resolves in 24–72 h
- Recurrent oral, pharyngeal, or laryngeal oedema
- Documented family history of hereditary angio-oedema

Laboratory criteria

- Antigenic concentrations of C1 inhibitor <50% of normal values obtained on two separate occasions after first year of age
- Functional levels of C1 inhibitor <50% (chromogenic assay) or <84% (ELISA assay; local normal ranges might vary) of normal values obtained on two separate occasions after first year of age[39,41]
- Mutation in C1-inhibitor gene that modifies protein synthesis or function

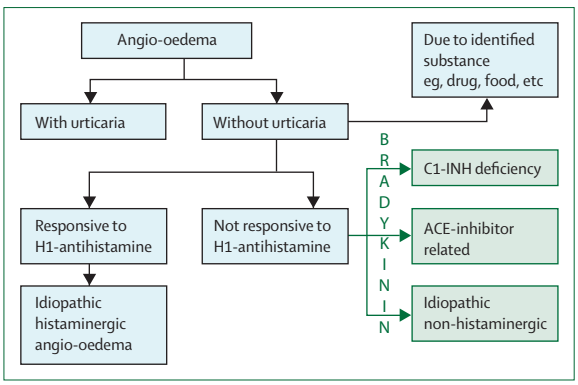

Figure 4: **Algorithm for diagnosis of angio-oedema due to C1-inhibitor deficiency**
Angio-oedema occurs in absence of relevant urticaria flare and without cause-effect correlation with exposure to specific food or drug. In cases of doubt, to rule out histamine-mediated angio-oedema, patients should have continuous treatment with anti-H1-histamine receptor at a daily dose that is 2–3 times more than that recommended for allergic rhinitis. If angio-oedema recurs with this treatment regimen, and onset of angio-oedema did not occur while patient was treated with ACE-inhibitor, bradykinin-mediated angio-oedema is probable and biochemical tests for C1 inhibitor deficiency should be repeated, with genotyping if available. Adapted from reference 51.

treatments. However, this prophylaxis did not completely abolish attacks for everyone, and two of 22 patients had more frequent swellings when in the active treatment group than when on placebo.[65,66] Thus, as with other forms of prophylaxis, C1 inhibitor seems to raise the threshold for swellings but might not completely abolish them; however, variations in the frequency or dose according to individual needs could improve control. Because androgens are contraindicated during pregnancy, although unlicensed, C1-inhibitor prophylaxis is particularly useful when prophylaxis is needed.

Prophylaxis can be used during periods of high-risk for a swelling. Traditional indications for short-term prophylaxis include surgical procedures, particularly dental work. Local trauma increases the risk of swellings, which typically occur 4–48 h after surgery.[13,67] Swellings usually occur in the area of trauma; therefore, dental work is of particular concern because of the risk of intra-oral swelling extending to involve the larynx. Consensus guidelines recommend use of C1-inhibitor concentrate before the procedure or, if this is unavailable, the dose of attenuated androgen should be doubled for 5 days before and 2 days after the procedure, which can reduce the risk of swelling; however, efficacy data are scarce.[57,58] Fresh frozen plasma contains C1 inhibitor, and case reports suggest that 2–3 units of this plasma might be an alternative when C1 inhibitor is not available.[68] In practice, decisions about prophylaxis will be made pragmatically dependent on the site and invasiveness of the procedure and on the frequency and severity of symptoms that the patient usually experiences. Whatever the decision, there is an increased risk of swelling and there should be a plan for emergency treatment. Because of the slow onset of surgically induced swellings, hereditary angio-oedema is not a contraindication for community or day-case treatment, nor should emergency procedures be delayed if prophylaxis is not immediately available. Other indications for short-term prophylaxis, usually with attenuated androgens, would be during high-risk periods due to emotional stress, such as interviews, exams, or celebrations, or when swellings would be particularly inconvenient, such as holidays. Treatment of prodromal symptoms with C1-inhibitor concentrate is also effective and might need lower doses than those needed for a fully developed attack. In practice, this treatment is feasible only for those who are trained in self-administration.[11]

Treatment

Options for treatment of established swellings have increased in the past few years and include replacement of C1-inhibitor with plasma-derived products (ie, cinryze or berinert P), bradykinin receptor and kallikrein antagonists, and a recombinant C1 inhibitor. All treatments are effective for swellings at any site. After treatment, most patients take 15–120 min before onset of relief, and major swellings might take up to 24 h to completely resolve.[10,65,66,69–78] Swellings respond more quickly when treated early in the course of the attack.[10] However, treatment is costly, and a balance should be made between early treatment of an attack that might never become severe, and late treatment resulting in a substantially increased period of disability.

Plasma-derived C1 inhibitor has been used for more than 25 years and has been effective in double-blind placebo-controlled trials.[65,72,76,77] A dose-finding trial—which was limited by small size and use of only 3 tested doses of C1 inhibitor—indicated that doses of 20 units per kg are substantially more effective than placebo, whereas the traditional dose of 10 units per kg is not.[72] Increased doses have not been tested for plasma-derived C1 inhibitor, but doses of up to 50–100 units per kg have been investigated with ruconest. These studies suggest that most patients respond to doses of 50 units per kg or more.[75,78,79] However, ruconest cannot be directly compared with plasma-derived C1 inhibitors for which dose-finding studies are needed. In fact, observational studies suggest that low doses of C1 inhibitor—1000 or even 500 units—might be effective in some cases. Small swellings or very early symptoms might be effectively treated with low doses, which is usually achievable only in the context of self-administration or other rapid-access programmes. A first dose, with a second one if symptoms persist, has been tested;[66] however, the population that used single or repeated dose has been analysed only cumulatively and therefore the specific advantage or disadvantage of this approach cannot be determined. Ruconest is harvested from the milk of genetically modified rabbits, and although its protein structure is identical to that of plasma-derived C1 inhibitor, it has different glycosylation. This difference does not seem to affect the biological activity of ruconest, but does result in a much reduced half-life of mean 3 h compared with 24 h or more for plasma-derived C1 inhibitors.[75,80]

Drug-related adverse reactions and development of clinically important antibodies have not been seen in trials, even after repeated administration. However, in a phase 1 studiy,[74] a healthy volunteer with severe rabbit allergy and high concentrations of rabbit-specific IgE had an anaphylactic reaction after intravenous ruconest.

Icatibant acetate, a subcutaneous synthetic peptide blocker of the bradykinin-2 receptor, has been assessed in two double-blind trials;[63] one in the EU and Israel against tranexamic acid, the other in America (ie, North and South America [USA, Brazil, Argentina]) against placebo. In a comparison with tranexamic acid, subcutaneous icatibant acetate provided faster onset of relief and time to full resolution for swellings at all sites. Whereas in a comparison with placebo, icatibant acetate was effective for the treatment of peripheral swellings, but not for abdominal pain. These findings probably indicate an underpowered trial with subjective outcome measures (visual analogue scores), and failure to censor patients who received nonspecific treatments, such as narcotic painkillers or intravenous rehydration, which would be expected to improve pain scores. Both trials showed a higher use of adjunctive and rescue treatments in the placebo or tranexamic acid group than in the icatibant group. Icatibant has been tested in animals and human beings for various indications and seems to have few systemic side-effects; the incidence of systemic adverse effects in the trials was similar between the icatibant group and the placebo or tranexamic acid group. Local erythema and pain at the injection site is almost universal with icatibant. About 10% of those treated with icatibant have recurrent swellings after 16–24 h, which are usually at the same site.[64,70] Although recurrent swellings are usually slow in onset, swellings occasionally develop rapidly. A second injection of icatibant or C1-inhibitor treatment is effective.[64,72]

Ecallantide, a small recombinant protein kallikrein antagonist that is synthesised in *Pichia pastoris*, has been licensed in the USA for the treatment of acute hereditary angio-oedema. In three double-blind placebo-controlled studies,[81–83] ecallantide was better than placebo in improving symptoms measured by one of two composite measurements—treatment outcome score and mean symptom-complex score—which were designed to indicate overall severity of disease symptoms. The subcutaneous formulation of ecallantide improves convenience. However, administration outside a health-care facility is not recommended: of 187 patients given to subcutaneous ecallantide (the marketed form) 4% had hypersensitivity events, including anaphylaxis in 2%.[84] 8% of participants developed antibodies to either *P pastoris* or ecallantide itself, of which 2% seemed to be neutralising. However, neither the occurrence of reactions nor effectiveness correlated with the presence, class, or neutralising ability of antibodies. Nine patients who had reactions underwent desensitisation, and four were then rechallenged with no adverse effects.[85]

Self-administration programmes have been helpful in enabling early access to treatment, and are recommended by consensus guidelines.[57,58,86–89] However, such programmes have been limited to the small proportion of patients willing to have intravenous administration of C1 inhibitor. Icatibant was licensed in Europe in 2008, for administration by health-care professionals, and was licensed for self-administration in 2011.[90] Icatibant's subcutaneous route of administration might enable an increased number of patients to control their own acute attacks; therefore, the need for emergency health-care facilities will potentially be reduced, as will the disadvantage incurred by the unpredictable episodic disablement that attacks bring.

Future directions

Progress in the management of acute attacks has been rapid, and several effective drugs are now available. These drugs will enable early treatment of attacks, which will prevent the development of disabling symptoms and improvements in quality of life. Self-administration programmes will reduce patients' reliance on acute hospital services. More information about optimum dose, pharmacokinetics, and feasibility of subcutaneous treatment with C1 inhibitor, and about how use of icatibant and ecallantide can be best timed, will enable improved use of resources.

Safe, convenient, and effective prophylactic drugs are needed, and although none are in trials, gene therapy is a possibility. Alternatively, oral acute drugs could reduce the need for prophylaxis. Because early treatment would be best in view of non-specific symptoms, sensitive and specific methods for diagnosis to confirm an early attack are needed. Quality of life and pharmacoeconomic data are needed to support possible increases in future demand for treatment.

Contributors

We both drafted and revised the Seminar. HL provided figures 1A, 1C, and 2, and MC provided figures 1B, 3, and 4. HL did the literature search with assistance from MC who contributed published works that had not been identified in searches of PubMed.

Conflicts of interest

HL has received payment for advisory board membership from Shire, CSL Behring, Dyax and Pharming; consultancy fees from Shire, CSL and Pharming; payment for expert testimony from Pharming; payment for lectures from Shire, CLS Behring; payment for development of educational presentations from CSL Behring and Shire, and travel and accommodation support from CSL Behring, Shire, and Viropharma. MC has received payment for board membership from Shire, CSL Behring, Dyax, ViroPharma, and Pharming; consultancy fees from Shire, Dyax, and Pharming; payment for expert testimony from Pharming and Dyax; payment for lectures from Shire, Pharming, CLS Behring, and ViroPharma; payment for manuscript preparation from Shire and ViroPharma; and payment for development of educational presentations and travel and accommodation support from Shire. MC holds a patent from Dyax for methods for preservation of organs and tissues.

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