Current management of hereditary angio-oedema (C’1 esterase inhibitor deficiency)

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Hereditary angio-oedema is characterised by recurrent swellings in any part of the body and also by recurrent attacks of severe abdominal pain. The disease is inherited in an autosomal dominant manner but up to 25% of cases can occur as a spontaneous mutation. Attacks of swelling can be precipitated by trauma, certain drugs, and emotional stress. Treatment usually involves a combination of prophylaxis, using androgens or antifibrolytic drugs, and replacement with C’1 esterase inhibitor concentrate for acute attacks and before surgery or other traumatic procedures.

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ereditary angio-oedema (HAE) is characterised by recurrence of cutaneous and mucous membrane swellings in any part of the body. Symptoms usually appear early in life and are normally accompanied by a family history because the disease is inherited in an autosomal dominant manner. The spontaneous mutation rate is about 25% and more than 100 different C’1 inhibitor gene mutations have been described. The prevalence of the disease has been estimated at 1/50,000, with no reported bias in different ethnic groups.

In HAE type I (up to 85% of all patients), there is a deficiency in the amount of C’1 inhibitor protein present in the plasma as a result of only one gene functioning. However, plasma values are usually 5–30% of normal rather than the 50% value that might be expected. Interestingly, it has been shown that fibroblasts from some patients with type I HAE synthesise approximately 20% of normal amounts of C’1 inhibitor in vitro and also that the fractional catabolic rate of C’1 inhibitor is enhanced in asymptomatic patients with HAE from 0.025 to 0.035 of the plasma pool each hour, which might help to explain this discrepancy. There is also some evidence that certain amino acid substitutions found in type I HAE affect the intracellular transport of C’1 inhibitor and result in a strong reduction or the total impairment of protein secretion. In HAE type II, the circulating C’1 inhibitor concentration is normal but not all functional. Functional C’1 inhibitor synthesised by fibroblasts from patients with type II HAE is nearly 50% of normal, in contrast to the findings in patients with type I disease. High plasma concentrations of dysfunctional C’1 inhibitor are found because the mutant protein is secreted normally and its inability to form complexes with proteases increases its half life in the circulation. Dysfunctional proteins often result from substitutions at the reactive site residue Arg 444, but may also result from changes at several positions outside the reactive site loop. HAE type III has been described, where the C’1 inhibitor has a structural abnormality that binds to albumin, forming an inactive complex, and the plasma concentrations of C’1 inhibitor are normal or high.

C’1 inhibitor is the main regulator of the activation steps of the classical complement pathway. This protein is mainly produced in the liver, but also by activated monocytes and other cell types. C’1 inhibitor also regulates the activation of kallikrein, plasmin in the fibrinolytic pathway, the activation of factor IX in the coagulation cascade, and activated Hageman factor. In the presence of C’1 inhibitor deficiency the classical complement pathway can be inappropriately or prematurely activated. Immune complexes trigger the activation of the first component C’1 to C’1 esterase. C’1 esterase then acts with its natural substrates C’4 and C’2 to form the complex C’2,4 (C’3). This new complex leads to the activation of anaphylactoid-like substances and vasoactive peptides. C’1 inhibitor protein blocks both the spontaneous activation of C’1 and the formation of activated C’1, therefore not allowing the C’2,4 complex to be created. In the kinin releasing system, C’1 inhibitor deficiency allows for an increase in bradykinin. In the fibrinolytic system, C’1 inhibitor deficiency leads to an increase in fibrin split products. The coagulation pathway is affected by premature activation of factor IX. The end result is increased vascular permeability and massive uncontrolled oedema, but the precise chemical responsible for the oedema is still unknown.

CLINICAL CHARACTERISTICS
A diagnosis of HAE is suspected by a history of recurrent attacks of peripheral angio-oedema and of abdominal pain. Symptoms include recurrent circumscribed, non-pruritic, non-pitting oedema. It can affect virtually any part of the body, but is more common in the extremities. 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 previously reported in the literature.

Abdominal pain, nausea, and vomiting are the dominant symptoms in approximately 25% of all

Abbreviations: FFP, fresh frozen plasma; HAE, hereditary angio-oedema; HCV, hepatitis C virus; HGV, hepatitis G virus
patients, and are caused by constriction produced by intestinal wall and mesenteric oedema.  

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Classically, the oedema and swelling gradually develop over several hours, slowly increasing for 12–36 hours, and then subside after one to three days. Although it is rare to find the disease without symptoms there is an extreme variability in their frequency and severity. There seems to be little, if any, correlation between symptoms and type of genetic defect— even patients from the same family sharing the same mutation show wide differences in phenotype. Attacks of severe swelling can occur in some patients on a weekly basis and in others only happen once or twice a year.  

Attacks are seen during childhood in most patients, although the diagnosis is usually made in the 2nd or 3rd decade of life. 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 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.  

Occasional patients will have their first symptoms even earlier, before the age of 1. 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.  

There is usually a family history of similar complaints.  

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, by certain drugs such as oestrogen and angiotensin converting enzyme inhibitors, by emotional stress (even in children), or by infection.  

Acute attacks of abdominal pain can mimic surgical emergencies and before diagnosis is established, patients with HAE frequently undergo unnecessary appendectomy or exploratory laparotomies. Equally, after diagnosis, there is always the worry that the abdominal emergency will not have surgery performed in good time. Barium studies, carried out during an acute attack, have been reported to show signs of massive submucosal oedema, spiculation, and fold thickening or effacement. 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 HAE the gastric mucosa was described as diffusely reddish and oedematous and the mucosal surface in involved areas bulged remarkably, mimicking a submucosal tumour. Histological examination of the bulging area merely showed moderate inflammatory cell infiltration of the lamina propria. These findings are relatively non-specific and response to treatment with C1 inhibitor concentrate may be the only way to differentiate a surgical condition from an acute attack of HAE.  

The diagnosis is classically confirmed by the low C4 concentration in the serum and in most cases by low amounts of C1 inhibitor protein, as assessed by immunohistochemistry. If C1 inhibitor values appears normal or raised and C4 is low, a test of C1 inhibitor function should be carried out. All such tests should be carried out on a fresh serum sample—one less than four hours old.  

**MANAGEMENT**  
Management of patients with HAE 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. Infected teeth should be looked for and treated, oral contraceptives and hormone replacement therapy should make minimal use of oestrogen, with progesterone only pills such as levonorgestrel being used, and alcohol should only be taken in very moderate amounts. Attacks are likely to become more frequent at times of lifestyle stress, so it may be sufficient to use prophylactic drugs during such periods only, thus minimising adverse effects. Nevertheless, there will be a group of patients who will require continuous, long term prophylaxis and careful thought should be given to the choice of drugs.  

**Long term prophylaxis**  
Long term prophylaxis should be considered in each individual, but it is necessary to devise a regimen for each affected individual guided by the severity of their disease. Frequent attacks of peripheral angio-oedema (extremities, trunk), although unpleasant and annoying, are not dangerous and do not require long term prophylaxis. However, prophylactic administration of antifibrinolytic agents (e-aminocaproic acid and tranexamic acid), androgens (methyltestosterone, fluoxymesterone, and oxymetholone), or synthetic, attenuated androgens (danazol or stanozolol) has proved useful in reducing the frequency or severity of attacks.  

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Antifibrinolytic agents seem to inhibit C1 and plasmin activation with consequent "sparing" of C1 inhibitor usage. They decrease the number and the severity of attacks, but are not as effective in this as the synthetic anabolic steroids. Their side effects include nausea, vertigo, diarrhoea, menorrhagia, postural hypotension, tachyphylaxis, fatigue, and muscle cramps with an increase in muscle enzymes concentrations, and concerns about thrombus formation and thrombotic episodes. However, recent reports have suggested that these side effects are less common than previously thought, particularly the thrombus formation. The finding of tumours of the retina and liver in experimental animals after long term use of tranexamic acid has limited its use in the USA, but not in Europe. Although a teratogenic effect of e-aminocaproic acid has been postulated in the period of embryonic growth and development, it is being used in the USA, and has been recommended during pregnancy. A starting dose of 0.5–1 g of tranexamic acid up to four times a day should be used depending on disease severity, reducing to 0.5 g once or twice a day as the attacks remit.

Anabolic steroids increase the hepatic production of C1 inhibitor protein. Their side effects, which are dose dependent, include weight gain, virilisation, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual irregularities, and liver function derangement. Decreased growth rate in children is the main contraindication for their use in this age group. Androgens can cause masculinisation of the female fetus and thus are not recommended during pregnancy. The most worrying effects of all the 17α-alkylated androgens, including danazol and stanozolol, are those on liver metabolism, in particular cholestatic jaundice, peliosis hepatitis, and hepatocellular carcinoma. The recently observed first cases of hepatocellular adenosomas developing in patients with HAE on long term prophylaxis with danazol have caused particular concern. A dose of 200 mg once or twice a day will usually suffice in adults, but because of the wide variations between individuals with this condition up to 400 mg twice a day may be required.
Long term prophylaxis of attacks in children

This is a relatively unexplored issue,14 15 and most references state that the use of antifibrinolytics and androgens is not recommended because of the serious side effects of these drugs.20 21 Because severe or life threatening attacks of HAE are less common during childhood, it is rarely necessary to start long term prophylaxis in children.22 23 Long term prophylaxis is justified only in severely affected children, defined by frequent attacks of laryngeal oedema (one or more attacks each month) and/or frequent, recurrent attacks of colicky abdominal pain causing distress and disability. In this situation, antifibrinolytics are preferred to androgens.24 25 The individual minimal effective dose, irrespective of serum concentrations of C4 and/or C1 esterase inhibitor, for both antifibrinolytics and/or androgens used for long term prophylaxis has to be established and careful clinical and laboratory follow up of hepatic and renal functions and blood coagulation is mandatory.26 27 However, benefit of long term administration of high dose e-aminocaproic acid (12–24 g/day) in children was associated with side effects in all, but with the dose adjusted for each child’s need (6 g/day and 12 g/day for <11 year olds and >11 year olds, respectively), the control of symptoms was still satisfactory without unpleasant side effects.28 Tranexamic acid at a dose of 50 mg/kg/day or 1.5 g/day29 30 has been used long term with similar benefit and no side effects. The use of danazol in children31 32 is a cause for concern, even when used with caution.33 34 The finding of an increased incidence of arterial hypertension in patients with HAE treated with danazol long term35 further highlights the theoretical possibility of an increased risk of arteriosclerosis because the long term use of androgens has been reported to decrease the concentration of high density lipoproteins.36 37 38 However, it has been proposed that the long term use of antifibrinolytics, by plasmin inhibition, could also predispose to arteriosclerosis.39 40 This is of particular interest if long term prophylaxis is to be started during childhood because several decades of treatment may be needed.

C1 inhibitor concentrate has been used successfully for long term replacement in selected adult patients,41 and more recently it has been shown to be superior to a placebo in a double blind controlled study.42 Based on the clinical benefit seen in these patients, a role for C1 inhibitor concentrate in long term prophylaxis for children has been suggested,43 supporting the few earlier proposals.44 45 The psychological benefit to both the children and their parents by the possibility of home availability of the concentrate, or even of treatment at the earliest sign of an attack involving the upper airway is an important advantage of replacement treatment with C1 inhibitor concentrate,46 47 48 although the disadvantages and major obstacles to this approach to the management are expense49 and the possibility of viral transmission, even with the use of heat treated preparations of C1 inhibitor concentrate.46

Treatment of acute attacks

This depends on their severity. Episodes of peripheral swelling only usually do not require treatment, but stanzolol (up to 6 mg/day) can be given during an attack.70 Involvement of the upper airway usually begins slowly; voice alteration and dysphagia will precede total airway obstruction. If there is any suspicion of airway involvement C1 inhibitor concentrate should be given promptly at a dose of 1000 to 1500 IU (vide infra). This both shortens the duration of attacks by about a third and also halves the time to the beginning of the relief of symptoms.71 For acute attacks of abdominal oedema, pain relief should be given at an appropriate level and C1 inhibitor concentrate should be infused at the same dose as above (vide infra). The patient should be closely observed because the median time, on average, to the beginning of the relief of symptoms after concentrate infusion is about six hours, with resolution after 24 hours.72 If symptoms persist at a high intensity after this, an alternative diagnosis should be considered.

Treatment of choice for acute attacks manifesting as airway obstruction and life threatening asphyxia and/or severe colicky abdominal pain is replacement with C1 inhibitor concentrate.47 73 74 80 C1 inhibitor concentrate is available throughout Europe, it has been used in Australia81 and Canada,69 but although it has been available since the early 1980s,76 and shown to be effective in a controlled trial,82 the USA authorities have still not approved its use (FS Rosen, personal communication, October 1998). In an uncontrolled trial during long term follow up of 14 children with HAE, acute attacks in six children were treated with a single dose of 500 IU of C1 inhibitor concentrate (Immuno AG, Vienna, Austria) on 30 separate administrations. Progression of facial and laryngeal oedema was aborted 30–60 minutes after the infusion and gradually disappeared over the next 24–36 hours. The dose had to be repeated after 60 minutes on only two separate occasions because laryngeal oedema continued to progress. Concentrations of C1 inhibitor and C4, when measured 12 and 24 hours after the infusion in two patients, showed an expected increase. None of the children required endotracheal intubation or tracheotomy, and no side effects were observed.

If concentrate is not available then fresh frozen plasma (FFP) may be given, although this may worsen symptoms during the acute phase because it contains a high concentration of complement components.

Short term prophylaxis

Short term prophylaxis for surgical procedures is the third arm of treatment in these patients. If surgery or dental work is to be carried out on a planned basis, an infusion of C1 inhibitor concentrate should be given (or if this is not available, FFP) six to 12 hours before the procedure.77 78 It is impossible to predict the requirements of an individual patient in such a situation—in general, one infusion of 1500 IU of concentrate should be sufficient for dental work and most planned surgery for an adult patient, but a top up may be required, particularly if there is postoperative infection.

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Administration of antifibrinolytics or attenuated androgens, starting five days before the procedure and the following two days thereafter,79 is an alternative. Tranexamic acid has been used at a daily dose of 4 g (1 g four times daily) for adults74 79 or 2 g (500 mg four times daily) for children,80 given 48 hours before and after surgery. However, it seems that most authors prefer attenuated androgens even in children17 at a dose of 100–600 mg/day for danazol or 2–6 mg/day for stanozol, given 48 hours before and after surgery.78 79 80

Last but not least, thorough explanation of the nature of the disease to both children and their parents is essential for successful management of HAE.

TREATMENT DURING PREGNANCY

Treatment of the disease during pregnancy has special problems. Of published reports, some anecdotes report worsening of the disease,72 but few attribute stillbirths to the disease.83 In a series of 25 pregnancies in affected patients, only two had an increase in frequency of attacks, and none of these was related to the delivery itself.84 Ideally, all prophylactic drugs should be stopped during pregnancy and, if possible, before conception. If prophylaxis is required, tranexamic acid...
at standard doses should be used. Severe attacks during pregnancy should be treated with concentrate as in the non-pregnant patient. Vaginal delivery does not require special precautions; there may be local swelling of the vulva and infusion sites but this will usually settle without intervention. If an operative delivery is required, concentrate and infusion sites but this will usually settle without local swelling of the vulva and infusion sites but this will usually settle without intervention. If an operative delivery is required, concentrate should be given if endotracheal intubation is to be carried out but, if possible, regional analgesia should be used.\textsuperscript{25}

**C1 inhibitor concentrate: safety concerns**

The viral safety of C1 inhibitor concentrate, as with any blood product, is always a matter of concern. There are reports of transmission of hepatitis C virus (HCV) by non-virus inactivated C1 inhibitor concentrates used before 1985.\textsuperscript{31,32,33} Several studies confirmed the safety of a heat treatment step in the production of a C1 inhibitor concentrate;\textsuperscript{34} \textsuperscript{35,36} and no transmission of the human immunodeficiency virus, HIV, or hepatitis C virus (HGV) was observed in these studies. Nonetheless, because it has recently been shown that HGV could be transmitted in both unmodified and virus inactivated concentrates,\textsuperscript{37} surveillance of patients treated with concentrate is essential.\textsuperscript{38}

C1 inhibitor concentrate should only be given for severe attacks of swelling where there is a risk of airway involvement and for severe attacks of abdominal pain. Liver function and viral status of these patients should be monitored regularly and careful records kept of all infusions given. Patients should be fully informed of the potential risks and involved in treatment decisions.

Recombinant preparations of C1 inhibitor concentrate are being developed with phase I/II trials to be undertaken (PL Yap, personal communication, 2001) and if successful would overcome many of these difficulties.

It is perhaps surprising that FFP, known to be effective in the treatment of acute attacks\textsuperscript{14} \textsuperscript{15} \textsuperscript{16} and in short term prophylaxis,\textsuperscript{17} \textsuperscript{18} \textsuperscript{19} \textsuperscript{20} but carrying significant risks of viral transmission, anaphylactoid reactions, alloimmunisation, and excessive intravascular volume\textsuperscript{21} is preferred as replacement treatment in the USA.\textsuperscript{22} \textsuperscript{23} \textsuperscript{24} \textsuperscript{25}

**Take home messages**

- Hereditary angio-oedema (HAE) is caused by mutation of the C1 inhibitor gene, and is inherited in an autosomal dominant manner.
- Defective C1 inhibitor protein causes inappropriate activation of the classical complement pathway and also has effects on the coagulation cascade, all of which result in massive, uncontrolled oedema.
- Patients suffer from peripheral angio-oedema, abdominal pain, and nausea, and swelling of the upper respiratory tract contributes to the mortality associated with the disease.
- Treatment usually involves a combination of prophylaxis and replacement, depending on the individual patient’s needs at any particular time.
- Longterm prophylactic drugs include antifibrinolytics and androgens, although antifibrinolytics are preferred to androgens in children.
- Treatment of acute attacks is usually by replacement with C1 inhibitor concentrate, which is also used for short term prophylaxis for surgical procedures, although antifibrinolytics or attenuated androgens are sometimes used.
- However, the viral safety of C1 inhibitor concentrate is of concern and it should only be given for short term prophylaxis or severe attacks of swelling.

**REFERENCES**

23 Abinun M. Diagnosis and treatment of hereditary angioedema, a genetically determined deficiency of C1 inhibitor. MSc Thesis, Medical School, University of Belgrade, 1988.


