Hereditary Angioedema

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Introduction

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a disease to keep under close observation because sudden deaths from airway obstruction may occur. In the past 10 years there have been 2 deaths from laryngeal edema in diagnosed Danish patients with HAE because of ineffective treatment of acute attacks. Only brief descriptions of the condition, and the proper management of it, can be found in dermatologic and medical textbooks, and the disease is unfamiliar to many medical professionals.

HAE is a rare disorder affecting between 1 in 10,000 and 1 in 50,000 persons. In Denmark, we know of about 75 patients, but a considerable number of undiagnosed patients has to be assumed. Symptoms are related to a quantitative (type I) or qualitative (type II) deficiency of C1 esterase inhibitor (C1-INH) caused by mutations in the C1-INH gene. HAE develops in individuals who are heterozygous for C1-INH deficiency and the disease is inherited as an autosomal dominant trait. C1-INH is an important regulatory protein in the complement cascade. Attacks of angioedema are initiated by a complex activation and interaction of the complement system, the contact system and the fibrinolytic system, which results in the generation of vasoactive substances including bradykinin.

Clinical features

Clinically, HAE is characterized by recurrent self-limiting episodes of localized edema leading to skin swellings (extremities, face, genitals), abdominal pain attacks (colicky pain, often associated with vomiting, diarrhea, and circulatory symptoms) or, more rarely, potentially life-threatening upper airway obstruction (3). Before specific treatment was available, the mortality rate for this disease reached 50% in some families and the disability up to 100–150 days per year (2, 5). Urticaria is not a symptom of HAE, however, attacks can be preceded or accompanied by a reticular erythematous rash, the so-called chicken wire erythema, which may be mistaken for urticaria. Attacks typically last 2–3 days and are often followed by a symptom-free interval of several weeks or months. Usually, the clinical symptoms of HAE start in childhood or adolescence.

Frequency and severity of symptoms may be increased by estrogens and ACE inhibitors. Clinical symptoms may start or exacerbate after starting with estrogen-containing oral contraceptives or hormonal replacement therapy. ACE inhibitors are contraindicated in HAE. Trauma or pressure may trigger skin swellings while psychological stress may trigger skin swellings and abdominal pain attacks. Facial swelling and/or laryngeal edema can be provoked by dental procedures such as dental extraction or by tonsillectomy or intubation.

Diagnosis

An examination of the patient's history will often show that several family members have been periodically affected by symptoms indicative of HAE. Many have ancestors who died suddenly from asphyxia. However, up to 25% of HAE cases occur due to *de novo* C1 inhibitor mutation. The diagnosis of patients with suspected HAE should be confirmed by laboratory tests that measure absolute and functional levels of C1-INH, and C4. Levels of C1-INH function can range from 5–30% of normal persons rather than the 50% value that might be expected. If C1-INH function and/or level is low and C4 is low, then a repeat sample should be obtained to confirm the findings. Differential diagnosis includes mainly other types of recurrent angioedema such as acquired angioedema due to C1-INH deficiency with and without an underlying malignancy, urticaria-associated angioedema, idiopathic angioedema, angioedema due to ACE inhibitors and other drugs, and the recently described HAE with normal C1-INH occurring predominantly in women.

Treatment

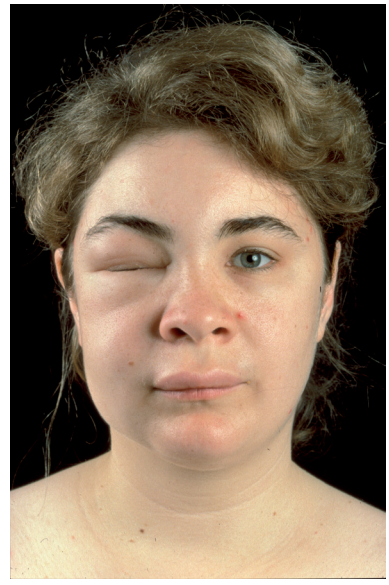
Management of patients with HAE requires more than only medication treatment. Patients have to be informed about their disease, especially about emergency situations, how the onset of emergency situations can be recognized, and what patients must do at such occasions. It is important that patients are supplied with multilingual info-cards with treatment guidelines and with C1-INH concentrate for emergencies. A treatment center or a physician with experience guiding and treating patients with HAE should be consulted.

The management of HAE requires attention to three areas: treatment of acute episodes, long-term prophylaxis, and short-term prophylaxis.

In the treatment of acute attacks, purified C1 inhibitor concentrate has been shown to be effective since 1973. Acute attacks of the disease with oral, pharyngeal or laryngeal involvement should promptly be treated with intravenous C1-INH concentrate 500–1000 units in adults. This treatment is also recommended for severe and painful abdominal attacks. A randomized, placebo-controlled trial of therapy with C1-INH for acute attacks of HAE found that approximately 69% of attacks treated with the concentrate responded completely within 30 min of the infusion and 95% responded after 2 hours (9, 10). No licensed C1-INH replacement product is available in Denmark or the other Nordic countries, but Berinert® P (ZLB Behring, Marburg, Germany) can be used on a named basis after permission from the Danish Medical Agency. This product was licensed in Germany in 1979 and has been in use in Denmark since the early 1980's after special permission. Ever since 1986 the product has been pasteurized. No case of viral transmission has ever been documented with Berinert® P (6) but special precautions should be taken because it is a blood product. In Denmark we now transfuse about 350,000 units of C1-INH product per annum. C1-INH therapy has increased dramatically over the past five years as patients and physicians are becoming more aware of the availability of the C1-INH treatment. Selected Danish patients with frequent attacks have been taught self-administration of C1-INH concentrate, and patients also now have the option to travel abroad with C1-INH concentrate. As far as we know, no Danish patients are yet taking regular C1-INH replacement therapy as long-term prophylaxis.

If no C1-INH concentrate is available at the hospital, fresh frozen plasma can be used instead in emergency situations. However, a paradoxical exacerbation of symptoms occasionally occurs. It is important to know that acute attacks of HAE do not respond to corticosteroids and antihistamines (which are effective in urticaria and eventually in other forms of angioedema). Epinephrine may have a sparse and very transient effect on swelling, but it does not alter the course of the attack.

For long-term prophylactic treatment of HAE attenuated androgens have



Facial edema in hereditary angioedema.

been widely used during the last 30 years. Attenuated androgens have the ability to increase the C1-INH level and more than 90% of treated subjects do obtain significant remission (5). Numerous patients are treated with danazol, a synthetic 17-alpha-alkylated androgen. However, this drug has been taken off the market in Denmark and neighbouring countries in 2003, and since that time it has been very difficult to gain access to danazol, that is often only available for a very short time. It is important to be aware of potential side effects of anabolic androgens. The most important dose-related side effects are hepatotoxicity, virilization, hypertension, hypercholesterolemia, depression and hemorrhagic cystitis (4, 1). Because of the potential side effects of danazol, the dosage should be titrated down to find the lowest dose which confers adequate prophylaxis. Regular follow-ups of patients with laboratory checks and ultrasound examination of the liver are neces-

sary if patients are treated with this drug. The major contraindications to therapy with attenuated androgens are pregnancy and lactation, prostate cancer, and childhood. Oxandrolone is another synthetic anabolic steroid that has been used in a variety of pediatric conditions including HAE in children.

Antifibrinolytic agents inhibit plasminogen activation with consequent sparing of C1-INH usage. The antifibrinolytic drug tranexamic acid can be modestly effective in preventing angioedema attacks in HAE. The response in children is better than in adults and tolerability is rather good.

Before certain dental treatments and surgical procedures, short-term prophylaxis with C1-INH concentrate is used depending on the type of operation.

New treatments for HAE attacks are on the horizon. A Dutch biotechnology company has made a recombinant C1-INH concentrate from the milk of transgenic rabbits. DX-88 is a kallikrein inhibitor that is undergoing phase III clinical trial. Icatibant is a bradykinin receptor antagonist that has shown positive results in clinical studies. The drug is expected to be launched later this year, as the drug has gained fast-track designation. All the three drugs have received orphan drug status in Europe. With the new drugs in hand, it will become easier to tailor treatment to the individual patient depending on attack frequency, severity and access to medical care at a given time. Also personal preferal of the patients and the side effect profile is important. The ultimate goal is to replace or augment defective C1 inhibitor gene sequences, but this has not yet been realized.

General considerations

With support from the European commission's Fifth Framework Programme an international network of 10 European centers specialising in the treatment, follow-up and research in HAE was established. Researchers, laboratory experts and clinicians, including the authors of this article, involved in the field of HAE have been working together to expand knowledge on HAE. A working online HAE register (http://www.haeregister.org) has been established and more than 1,100 entries of patients have been collected. Also a working online HAE mutation register (http://hae.biomembrane.hu) has been established. The register contains more than 180 different mutations. The group investigates an eventual association between geno- and phenotype. It also investigates the efficacy and side effects of existing treatments and among other collect data on the influence of sexual hormones on the disease course.

An observation from one of the group members is that the eradication of *Helicobacter pylori* from the gastrointestinal tract can improve HAE (7). The elimination of this potential trigger factor can reduce frequency of edematous episodes and improve the patients' quality of life. It seems as though screening for *H. pylori* infection and eradication of the pathogen is justified in all patients with HAE.

Physicians are working together with patients' associations to enhance the patient–physician relationship and improve the quality of life in patients with HAE. Established in 2001, the Danish HAE Patient Support Group (http://www.hae.dk) runs a website and issues newsletters. It also organizes annual meetings where patients can meet health care personnel and exchange views with each other. The patient organization has a fruitful relationship with foreign patients' associations and is part of the global umbrella organization (http://www.haei.org).

In summary, many patients with HAE have received delayed or no diagnoses, while other patients have been correctly diagnosed, but then treated incorrectly with high doses of corticosteroids and antihistamines in an emergency situation, which are not effective. Deaths from airway obstruction still occur, and in the past 10 years there have been 2 unnecessary deaths from laryngeal edemas in diagnosed Danish HAE patients (personal communication). It is important to recognize, that all HAE patients are at risk of having a severe episode of angioedema, potentially involving their airways. All patients should be offered the opportunity for home possession of C1-INH concentrate (8). Because of the high potential for morbidity and mortality associated with HAE, the

treating clinicians should maintain a certain degree of experience and knowledge of the disease, or refer the patient to a treatment center, where this expertise is found. Being a hereditary disorder, HAE is a lifelong affliction for patients and their family members.

Further reading

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