



Management of children with hereditary angioedema: a report of two cases

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Abstract

Dentists must take extreme care in treating patients with Hereditary Angioedema (HAE). Physical trauma, emotional stress, or anxiety during dental treatment could lead to an acute attack that may lead to a laryngeal obstruction. This article reviews clinical signs and symptoms, disease classification, pathophysiology, and treatment recommendations for HAE. Management of 2 patients with HAE is also presented. (Pediatr Dent 22:141-143, 2000)

Hereditary angioedema (HAE) was first described as a "syndrome" by Quincke in 1882,¹ and was later detected in 1888 by William Osler² to have a hereditary nature. Today HAE is a known autosomal dominant disorder of the classical complement pathway. Donaldson and Evans³ identified in 1963 that this edema was due to a biochemical abnormality of complement, specifically C-1 inhibitor protein. Patients afflicted with HAE can be classified within the three existing types. The identifying classification is dependent upon the amount, presence of, or functioning abnormality of the C-1 inhibitor protein.⁷ The majority of HAE patients are type I, recognized specifically as a marked decrease serum concentration of C-1 inhibitor protein. Normal values of C-1 inhibitor protein in type I patients range from 5-30% of the regulating normal values. Type II, which represents 15% of the patient pool, has normal or slightly elevated serum concentration of C-1 inhibitor protein, but is characterized as nonfunctioning protein, as described by Cullmen et al. in 1986. Type III HAE is characterized by the presence of a structural abnormality in C-1 inhibitor protein. The protein binds to the albumin molecule to produce a completely inactive complex in these patients.

Hereditary angioedema (HAE) is seen clinically as subepithelial edema of the face, larynx, oropharynx, abdomen, and extremities.⁴ The potential for an episode develops from physical trauma, emotional stress, and anxiety.¹ Dental manipulation, along with oro-maxilla-facial surgery, are the intensive procedures which give the patients an increased susceptibility to an acute attack. HAE is shown to develop over a period of time of several hours up to a lapse of 4 days. Clinically, HAE is nonpitting, nonpruritic, and nonpainful soft tissue swelling, often with the presence of significant ascites.⁵ Patients describe symptoms of nausea, vomiting, abdominal distention, and cramping.⁶ Radiographic abdominal surveys characteristically

show HAE to include "coin stacking," seen as regular thickening of the small bowels during acute attacks.⁶

The pathophysiological role of C-1 inhibitor protein is one in the classical complement pathway. It acts as a main regulator of the activation steps leading to the formation of complement. This particular protein has been shown to be produced in both the liver and activated monocytes. C-1 inhibitor protein also regulates inhibition of kallikrein, activated Hageman factor, the activation of factor IX in the coagulation cascade, and the plasmin in the fibrinolytic pathway. In the complement pathway, immune complexes trigger the activation of C-1 to C-1 esterase. The eventual formation of C-3 from C-2, C-4 and C-1 esterase leads to the complex of anaphylactoid-like substances and vasoactive peptides. The lack of, or inoperable C-1 inhibitor protein, results in a continued activity of the C-1r and C-1s proteins. This leads to the continued complement activation and depletion of both C-2 and C-4 peptides.⁸ The C-2 peptide has been shown to be accountable for the increased vascular permeability, along with edema through direct action on the postcapillary venules. The C-4 peptide has known anaphylatoxin activity, reacting with mast cells to release chemical mediators of immediate hypersensitivity. Serum levels of C-1 inhibitor, C-2, and C-4 are decreased,⁹ while C-3 peptide levels are sustained at normal levels. In the other cascades, the C-1 inhibitor deficiency leads to the increase in bradykinin in the kinin-releasing cascade, along with an increase in fibrin split products in the fibrinolytic system. The intrinsic clotting/coagulation system is affected by the premature activation of factor IX, leading to an increased vascular permeability. The aim to medical therapy would thus be targeted to the prevention of decreased levels of the C-1 inhibitor protein, as either a perioperative management or prophylaxis management.

Preventive therapeutic management can be divided into three classifications: long-term prophylaxis; short-term/surgical prophylaxis; and acute medical intervention. Long-term treatment of HAE includes the use of antifibrinolytic agents (epsilon-aminocaproic acid [EACA], tranexamic acid) and androgens. The popular synthetic steroids in use are stanozolol and danazol. These drugs act to increase the hepatic production of C-1 inhibitor protein when given orally rather than parenterally.^{10,11} However, the use of such products does not

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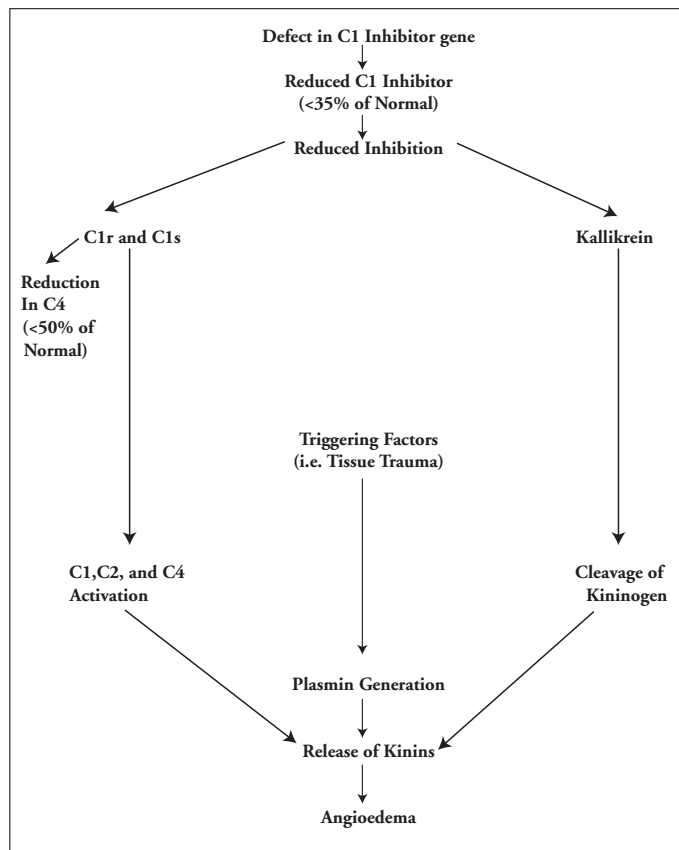


Fig 1. The complement system in hereditary angioedema.

come without side effects with long-term usage. HAE patients taking anabolic steroids may experience weight gain, premature closure of the epiphyses, hepatic dysfunction with elevation of enzymes, increased susceptibility to hepatocellular adenomas and carcinomas, amenorrhea, virilization, menstrual irregularities, and fatigue. Cardiac problems may also occur. This is particularly true in patients with uncontrolled hypertension or congestive heart failure. Stanozolol should be given at the lowest possible dose following routine patient/family history, physical, and routine labs values are evaluated. EACA and other antifibrinolytic agents effectively inhibit the C-1 and plasmin activation. The side effects with this therapy include thrombus formation, fatigue, muscle aches, and nausea.

Short-term or surgical management includes EACA, androgens, and the use of fresh frozen plasma to aid in the replacement of missing protein.¹² The ultimate goal of both the short-term and long-term therapy is to increase the C-1 esterase inhibitor levels. The treatment with fresh frozen plasma is divided into a two-step system. Two doses of plasma are given preoperatively—one the night prior to the one administered prior to surgery. This treatment is recommended for dental practitioners for oral maxillofacial surgery or in pregnant women. Fresh frozen plasma does have the increased risk of contamination along with the potential for spreading of disease.

In the management of acute HAE attacks, antihistamines, epinephrine, corticosteroids, and fresh frozen plasma should be considered. Tracheostomy may be necessary when total airway obstruction results. In 1996, Peltz et al.¹³ reported on the emergency care of a 40-year old woman with a markedly edemic

uvula and soft palate that had prolapsed posteriorly. Subcutaneous epinephrine, intramuscular diphenhydramine, and oral steroids were administered to control the amount of laryngeal edema. In this case, administration of epinephrine by metered-dose inhaler was not available. A one-ml syringe with a 27-gauge needle was used to direct an atomized jet of epinephrine (0.3 ml of 1:1000 soln) at her uvula. The result of this therapy was a reduction by 50% of uvular swelling and lack of dysphagia. In 1986, Warren et al.¹⁴ found that the mean peak plasma level of epinephrine, following oral inhalation from a meter-dose inhaler (15 puffs of 2.4 mg of epi.), was 16% of the mean peak level after subcutaneous administration of 0.3 mg of epinephrine. The current recommendations for the treatment of acute anaphylaxis when there is airway obstruction is parenteral administration of epinephrine 0.1-0.5 mg subcutaneously or intramuscularly with simultaneous administration of meter-dose inhaled epinephrine.

Case report: DF

DF is a 4-year, 9-month old male who presented to the dental clinic of Children Medical Center of Dallas with a chief complaint of sensitivity of teeth in the lower left quadrant in response to foods and temperature for the first time on 12/12/1996. DF was known to have hereditary angioedema but was otherwise a healthy child. DF took no medications, had no known drug allergies, and had been hospitalized 9 months previously for the treatment of pneumonia. HAE had been diagnosed when nonpainful, nonpitting, nonitching soft tissue edema had been precipitated by tissue manipulation or trauma.

The intraoral examination consisted of use of only a mirror to avoid any soft tissue trauma. Examination revealed that DF had full primary dentition with healthy soft tissue and multiple carious lesions. Since the lower second primary molar seemed to be the source of discomfort, a sedative temporary filling was placed in the occlusal carious lesion of that tooth. No local anesthesia or rubber dam was used and no radiographs were taken at this visit to minimize manipulation of the oral tissues.

Treatment options were discussed with the patient's mother and the patient's allergist. It was decided that the necessary dental care would best be delivered in a controlled setting where the angioedema could be treated should it occur. Also, since pretreatment with steroids and fresh frozen plasma was required, the use of both of these agents could be minimized by delivering the treatment in one visit. Therefore, DF was scheduled for a full mouth dental rehabilitation in the operating room under general anesthesia.

DF's physician was consulted and the following recommendations were made: 1) systemic corticosteroid therapy for six days prior to the scheduled treatment date; 2) I.V. fresh frozen plasma two hours prior to the procedure; and 3) admission to the hospital for observation postoperatively. DF underwent an uneventful general anesthetic with nasotracheal intubation. A clinical and radiographic examination were performed. The restorative measure of treatment consisted of seven stainless steel crowns, one pulpotomy, and one occlusal amalgam restoration. A prophylaxis and topical fluoride treatment were also performed. No complications were evident at the end of the procedure. The patient was extubated and transferred to the

post anesthesia care unit. On the day of the procedure, no complications other than mild nausea were reported. However, asymptomatic mild swelling of lips was evident the following morning. Since this was not thought to be true angioedema symptoms, the patient was discharged home and the mother was instructed to report back to the hospital if the conditioned worsened. In a follow-up phone consultation two days after the procedure, the mother reported that all the swelling had resolved.

Case report : AR

AR is a 6-year, 10-month old girl who reported to the dental clinic of Children's Medical Center with a chief complaint of hypoplastic first permanent molars and over retained primary lateral incisors. Review of the medical history revealed that AR had hereditary angioedema and asthma. She was taking Ventolin and Prealone as needed. The family history revealed that mother and grandmother both were afflicted with the disease (the age of onset being 9 years and 18 months, respectively). In addition, the patient's aunt had expired 5 years previously as a result of an angioedema crisis. AR had her first angioedema crisis at 4 years of age. This crisis consisted of a non-life threatening edema of the face and treated with epinephrine subcutaneously and Prednisone for 5 days. The latter drug seemed responsible for an erythema on the face. Complement analysis results confirmed the diagnosis of hereditary angioedema.

The oral examination at this visit consisted of a non-traumatic clinical exam only. Soft tissues appeared to be within the normal limits. A concurrent finding was that all first permanent molars and the erupting permanent central incisors appeared to be hypoplastic. Extra oral examination was within normal limits. Treatment options were discussed with the patient's mother. Due to the patient's medical condition, the decision was made to treat AR under general anesthesia so that all treatment could be performed at one visit.

AR's allergist was consulted and the following recommendations were made:

- 1) A trial course of epsilon-aminocaproic acid (Amicar), which is shown to nonselectively increase C4 and CH50 levels, was given to normalize the complement system. This was chosen over steroid treatment, due to the previous history of adverse reaction to prednisone.
- 2) A full mouth dental rehabilitation was scheduled to coincide with the end of the one-week trial of Amicar. The prophylactic use of fresh frozen plasma was refused by the mother and admission to the hospital for observation post-operatively was not deemed necessary in this case since the patient's mother was adept at recognizing and treating angioedema.

In the operating room, AR received a full clinical and radiographic examination, a topical fluoride treatment, and the needed amalgam restorations of the first permanent molars. In addition, three overretained primary lateral incisors were extracted. There were no noted complications during or after the procedure.

The oral examination post-operatively revealed that all restorations were intact and soft tissue seemed to be within normal limits.

Conclusions

1. Hereditary angioedema can result in potentially life threatening subepithelial swelling.
2. Manipulation of oral tissues should be avoided until medical consultation has been obtained.
3. If treating a patient with hereditary angioedema, be prepared to treat an acute episode.
4. Treatment of a child with HAE requires a cooperative effort between the pediatric dentist and the pediatric allergist/immunologist.

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