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Hereditary Angioneurotic Edema, an Anesthetic Dilemma

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Hereditary angioneurotic edema is a rare inherited disease that presents unusual problems in anesthetic management. The condition is manifest as an episodic swelling of the skin, subcutaneous tissue and mucous membranes that may be induced by trauma.[1]

REPORT OF A CASE

A 29-year-old woman was scheduled for a ureteral suspension operation necessitated by stress incontinence. Past history revealed that since the age of 6 years she had had episodic bouts of swelling of the hands and feet, spontaneously receding in 24 to 48 hours and not associated with any other sign or symptom. There is no known precipitating factor. She had a history of larnygeal edema four years prior to the present admission. At that time she had been given an unknown "intramuscular medication." The laryngeal edema had receded in 24 hours. The patient had first been seen in our hospital nine months prior to this admission for difficulty in breathing. Examination at that time had revealed supraglottic edema of the endolarynx. Her C1 esterase inhibitor level was 2.4 mg/ml (normal, 9 mg/ml). The laryngeal edema had receded spontaneously in 24 hours, and she had been discharged three days later.

Vital signs were: blood pressure 110/70 mm Hg, pulse rate 84/min, and respiratory rate 16/min. Results of physical examination were essentially normal except for findings of pelvic relaxation.

Results of laboratory studies, chest x-ray, EKG, electrolytes, liver function tests, creatine phosphokinase, lactate dehydrogenase, blood urea nitrogen, and creatinine were all within normal limits. The patient was premedicated with diphenhydramine, 75 mg, im. A unit of fresh frozen plasma was thawed before the start of the procedure. Spinal anesthesia was achieved with 10 mg tetracaine plus 0.2 mg epinephrine with an equal volume of 10 per cent dextrose in water. Sensory anesthesia was obtained to segment T6. The surgical procedure proceeded without any untoward incident. The postoperative course was uneventful, and the patient was discharged five days postoperatively.

DISCUSSION

Hereditary angioneurotic edema was first described by Sir William Osler.[2] The swelling is due to an acute non-inflammatory edema, and is usually circumscribed, non-pitting, nonpuritic, and relatively painless.[3]

Death may ensue when the pharynx or larynx is involved. Mortality rates range from 25 to 30 per cent when there is edema of the larynx and pharynx.[4] Fatal laryngeal edema has occurred following tonsillectomy and tooth extraction.[5]

This disease is inherited as an autosomal dominant trait. Our patient has a strong family history of "sudden deaths." Her father, at 56 years of age, died of laryngeal edema; a maternal aunt at 48; a maternal uncle at 28; a second maternal uncle at 48. All died sudden deaths believed to be the result of acute asphyxiation. The patient's daughter, 8 years old, had started having episodic swelling of the hands, feet, and face at the age of 1 year. The swelling is usually precipitated by trauma. The daughter has had laryngeal edema necessitating hospitalization and treatment with fresh frozen plasma three times. The diagnosis of hereditary angioneurotic edema is made on the basis of the family history, clinical picture, and low levels of C4 and C1 esterase inhibitor.[6]

The first component of the complement system is in an inactive state in the serum. It is activated under certain conditions, setting off the complement cascade (fig. 1).[2] The enzyme, C1 esterase inhibitor, regulates the first step in the complement cascade. A deficiency of this enzyme, as in hereditary angioneurotic edema, leads to an uncontrolled activation and accumulation of vasoactive substances C2, C3, and C5. These substances produce edema by increasing vascular permeability.[3]

An attack may be precipitated by trauma. Sheffer, Austen and Rosen[1] have proposed a mechanism of edema due to trauma. Hageman factor is activated by trauma, which interacts with other cofactors and initiates fibrinolysis, thus converting plasminogen to plasmin. Plasmin activates C1, thus producing the complement cascade, and with accumulation of vasoactive substances, edema ensues.[7]

The problem with this particular patient was prevention of laryngeal edema with the trauma of surgery. The ideal therapy would be replacement of the enzyme deficiency, but this is very expensive, and the intravenous half-life of the enzyme is only four days.[8] Steroids, phenothiazines, and antihistamines have generally not been effective in the management of the edema.[9]

The mechanism of the development of the edema suggests that inhibition of the formation of plasmin or plasmin-like substances will produce prophy-

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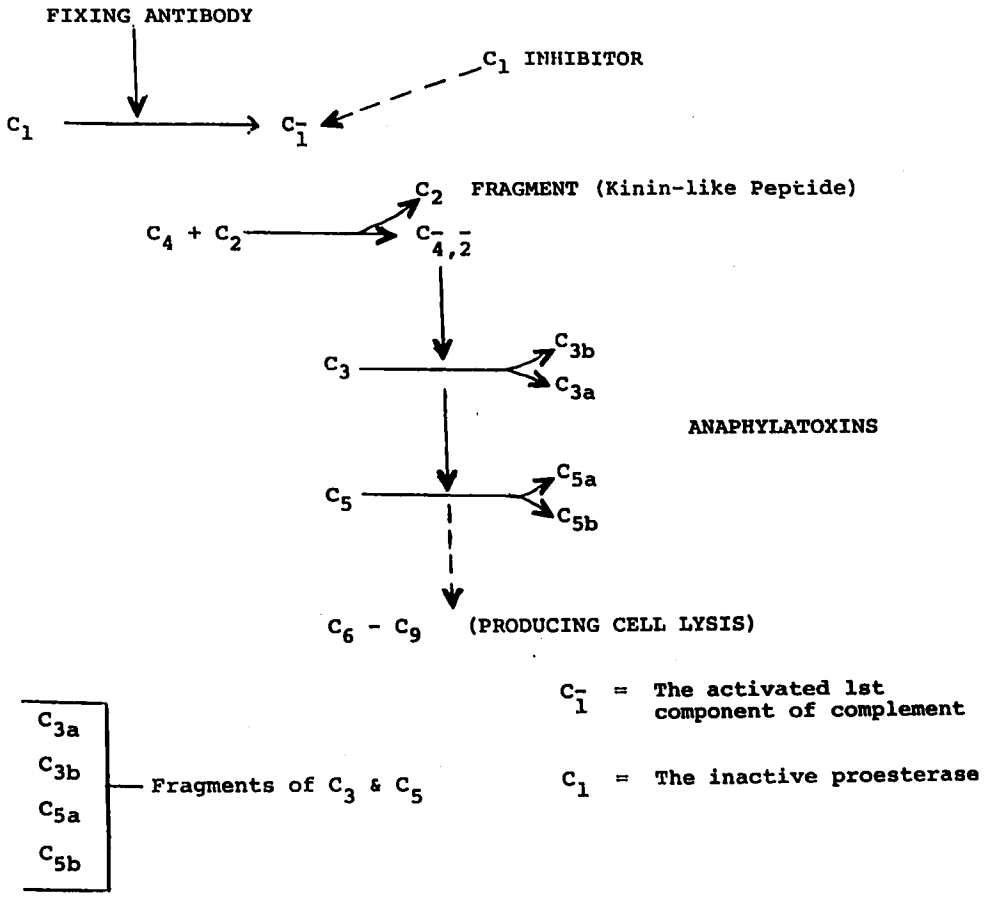

FIG. 1. The complement cascade. The first component of the complement cascade, C_1, is normally present in the serum in an inactive state. Under certain conditions it becomes activated (C_1^-). The C_1 inhibitor closely regulates the progression of the complement cascade (C_2 to C_9). A deficiency of this enzyme may lead to an accumulation of complement fragments C_2, C_3, and C_5, which have vasoactive properties. (From Gwynn,[2] with permission of the author and publisher.)

laxis. Epsilon-aminocaproic acid and tranexamic acid are plasminogen inhibitors. These drugs have been successfully used in the prophylactic management of the disease.[1,2,5,9,10]

Johns *et al.*[9] reported the case of a patient with hereditary angioneurotic edema who underwent excision of a parotid tumor. Their management included administration of epsilon-aminocaproic acid (EACA). They gave EACA, 2 g, iv, preoperatively, then 2 g intraoperatively. This was followed by 1 g EACA every hour for 72 hours, then 2 g orally every four hours to the fifth postoperative day, without any untoward complication. Gwynn[2] suggested a dosage schedule for prophylactic management of pediatric patients with hereditary angioneurotic edema. These investigators used large amounts of EACA, despite the side effects, which are fatigue, muscle and abdominal pain, muscle weakness, thrombotic phenomena, and elevation of serum creatine phosphokinase and amylase. Some patients receiving EACA may still experience attacks, so it does not guarantee the prevention of edema.[11]

Tranexamic acid, a more potent inhibitor of plasminogen activation than EACA, has been used. The effective dose has been reported to be 1 g daily.[1] Cinnerazine, an antihistamine, 20–30 mg daily, has also been used with good results. Methyltestosterone for males and oxymetholone, an androgen with low virilizing potential, have also been found effective in the management of the disease.[5,11,12] The mechanism of action is unknown.

For management of acute episodes of the disease, fresh frozen plasma and large doses of epinephrine have been used effectively.[3,14,15] Pickering *et al.*[13] showed that infusion of 400 ml of fresh frozen plasma during an acute episode produced clinical improvement within 20–40 minutes. Gwynn[2] pointed out that this method of treatment has the theoretical danger that the plasma also supplies the plasma proteases and complement fragments for the plasma enzymes, and so may aggravate the situation. There was, however, no untoward reaction in Pickering's patients treated with fresh frozen plasma. Roth *et al.*[15] reported treatment with 1 ml epinephrine, 1:1000 every hour for acute attacks threatening the upper airway. He suggested that using high dosages of epinephrine directly decreases post-capillary and venule permeability.

In our patient, the primary physician decided against prophylaxis because of the mild form of the disease. Fresh frozen plasma was available to treat edema if it occurred. Care was directed toward prevention of unnecessary trauma, partic-

ularly in the upper airway by use of conduction anesthesia.

References

1. Sheffer AL, Austen KF, Rosen FS: Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med 287: 452–454, 1972
2. Gwynn CM: Therapy in hereditary angioneurotic edema. Arch Dis Child 49:636–640, 1974
3. Beck P, Willis D, Davis GT, et al: A family study of hereditary angioneurotic edema. Q J Med 42:317–339, 1973
4. Klemperer MR, Rosen FS, Donaldson VH: A polypeptide derived from the second component of human complement ($C^1$2) which increases vascular permeability (abstr). J Clin Invest 48:44a–45a, 1969
5. Landerman NS: Hereditary angioneurotic edema. 1. Case report and review of literature. J Allergy 33:316–329, 1962
6. Ohela K, Rasanen JA, Wager O: Hereditary angioneurotic edema. Genealogical and immunological studies. Ann Clin Res 5:174–180, 1973
7. Pillemer L, Ratnoff OD, Blum L, et al: The inactivation of complement and its components by plasmin. J Exp Med 97:573–589, 1953
8. Donaldson VH: Therapy of "the neurotic edema." N Engl J Med 286:835–836, 1972
9. Johns ME, Vanselow MA, Boles R: Hereditary angioneurotic edema. Treatment with epsilon aminocaproic acid during surgery. Arch Otolaryngol 99:388–389, 1974
10. Pence HL, Evans R, Gurnsey LH, et al: Prophylactic use of epsilon aminocaproic acid for oral surgery in a patient with hereditary angioneurotic edema. J Allergy Clin Immunol 53:298–302, 1974
11. Davis PJ, Davis FB, Charache P: Long term therapy of hereditary angioedema (HAE). Preventive management with fluoxymesterone and oxymetholone in severely affected males and females. Johns Hopkins Med J 135: 391–398, 1974
12. Denneky JJ: Hereditary angioneurotic edema. Report of a large kindred with defect in $C^1$1 esterase inhibitor and review of literature. Ann Intern Med 73:55–59, 1970
13. Pickering RJ, Kelly JR, Good RA, et al: Replacement therapy in hereditary angioedema. Lancet 1:326–330, 1969
14. Cohen G, Peterson A: Treatment of hereditary angioedema with frozen plasma. Ann Allergy 30:690–692, 1972
15. Roth M, Schreier L, Cutler R: Adrenalin treatment for hereditary angioneurotic edema. Ann Allergy 35:175–179, 1975

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Removal of Radial-artery Thrombi Following Percutaneous Cannulation for Monitoring

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Thrombotic occlusion of the radial artery frequently occurs following percutaneous cannulation of this vessel for monitoring purposes.[1] Ordinarily the thrombi are asymptomatic, since there is usually adequate collateral blood flow to the hand via the ulnar artery. Occasionally, however, when ulnar arterial flow is compromised or the palmar arterial arches are incomplete, occlusion of the radial artery can cause ischemia or even frank gangrene of the hand and wrist.[2] Cannula-induced thrombi may also occlude cutaneous branches of the radial artery, resulting in necrosis of the skin over the cannula tip.[3] In an effort to remove such thrombi, a technique that is a modification of that described by Snyder and Amplatz[4] for removing clot from the femoral artery following arteriography has been developed.

Methods

The subjects of this study were 70 consecutive patients scheduled for major elective operative procedures. During the preoperative interview, both the risks and the benefits of radial arterial cannulation, and the nature of this study, were explained in detail to each patient, and informed consent was obtained. Allen's test[5] invariably showed brisk radial and ulnar arterial circulation to the hand, and Doppler examination revealed a patent radial artery prior to cannulation. Teflon 18-gauge catheters† were placed percutaneously in the radial arterial lumen just prior to induction of general anesthesia. They were flushed with a continuous infusion of heparinized 0.9 per cent saline solution (2 units/ml) via an Intraflow system‡ at a rate of 3 ml/hr.

Arteriography was performed on the morning after operation by injecting 5 ml of contrast solution§ while an x-ray of the wrist and hand was taken. The films were interpreted independently by two radiologists, and the amount of thrombus visible in the

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§ 25 per cent sodium diatrizoate, USP. Winthrop Laboratories, New York, N.Y.