Hereditary angioedema: case report of a family

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Hereditary angioedema (HAE) is a rare disease resulting from deficiency of complement 1 esterase inhibitor (C1-INH). The clinical manifestations of this disease include recurrent attacks of self-limiting edema affecting face, extremities, gastrointestinal system and upper airways. In this report, we present eleven members of a family with HAE. Edema of the extremities was the most common symptom, occurring in ten patients. Three patients experienced severe laryngeal edema that required tracheotomy. Three patients developed facial and scrotal edema. Three patients experienced severe abdominal pain. The mean age at onset of symptoms was 11 years. C1-INH levels were undetectable in two patients and low in nine patients. CH50 was undetectable in all of the patients. C4 level for all patients was low. HAE in our first case, a 10-year-old boy, was diagnosed on the basis of low C1-INH, CH50 and C4, in addition to his familial history. Eleven members of this family, for whom laboratory studies could not be done, had similar symptoms and course. Two patients died as a result of laryngeal edema before establishment of dignosis. This case report indicates the importance of recognition and early treatment of HAE to prevent a potentially fatal outcome.

Key words: hereditary angioedema, complement 1 esterase inhibitor.

Hereditary angioedema (HAE) is a rare autosomal dominant disorder resulting from the absolute or the functional deficiency of complement 1 esterase inhibitor (C1-INH)[1,2]. The clinical manifestations of this disease are polymorphic and include recurrent non-pruritic and self-limiting soft tissue edema attacks that can involve face, extremities, and mucosal surfaces of the gastrointestinal tract and upper airways. The main cause of death in untreated patients is laryngeal edema[3,4].

Two types of HAE have been described. Type I HAE, the predominant form (85% of all patients), is characterized by decreased levels of C1-INH protein caused by a reduced synthetic rate of C1-INH. Type II (variant form) HAE is characterized by normal or raised levels of C1-INH that are functionally inactive[1,2]. Both types of HAE are characterized by low or absent levels of C2, C4, and CH50[1,3-5]. Less commonly, C1-INH deficiency occurs as an acquired form that may be associated with B-cell malignancies or with autoantibodies to C1-INH[6,7]. In this case report, we present the clinical features and course of a family with hereditary angioedema.

Case Reports

A 10-year-old boy (İ.A.) was admitted to our hospital with a history of intermittent edema attacks affecting mainly extremities, face and scrotum since he was six- months-old. There was no consanguinity. Laboratory studies were as follows: C1-INH 38 mg/dl, CH50 undetectable, C4 12 mg/dl, C3 114 mg/dl. His edema attacks were triggered after trauma. He reported that 21 members (11 males and 10 females) of his family suffered from episodic soft tissue edema. HAE was diagnosed on the basis of low C1-INH, CH50 and C4, in addition to his familial history. The pedigree of this family is given in Figure 1.

After the establishment of the diagnosis of HAE, we wanted to investigate other members of his family since they had shown similar symptoms. Blood samples could not be taken from 11

members: four had died and seven were either not available or did not give permission. Thus, including the case previously mentioned, C4, CH50 and CI-INH were studied in a total of 11 patients. The blood samples were immediately separated. C4 was measured by turbidimetric method (RA-XT, Technicon). The total hemolytic activity (CH50) and CI-INH were studied by standard radial immunodiffusion (The Binding Site Limited).

The age at onset of symptoms ranged from six months to 21 years (mean 11 years), and symptoms in most patients appeared in adolescence. The frequency of edema attack was usually four or five times a year.

None of the patients has been lost during the follow-up period of 10 years. Their history revealed that edema of the extremities was the most common symptom, occurring in 10 patients. Three of the patients experienced severe laryngeal edema

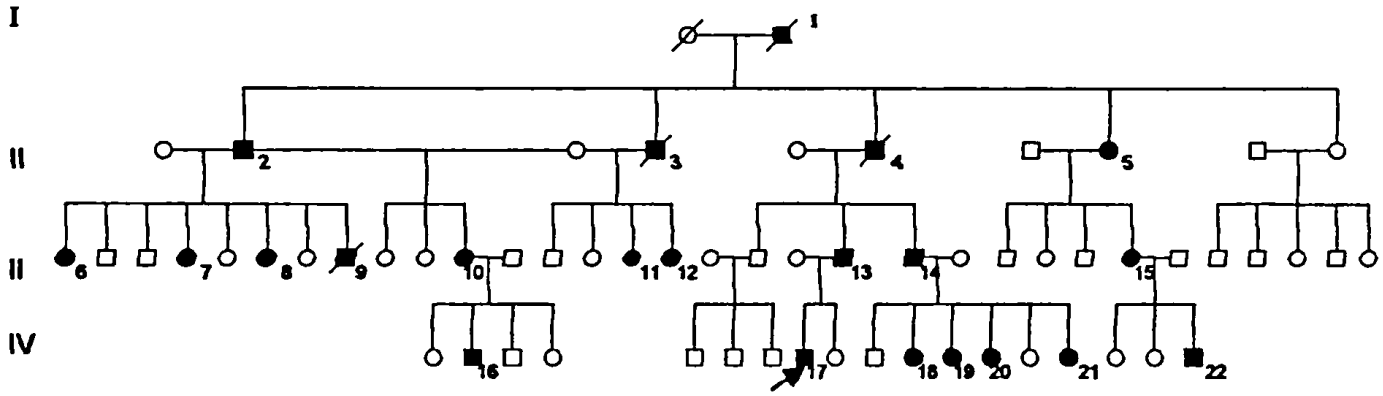

Fig. 1. Pedigree of the family. Circles denote females; squares, males. Open cricles and squares denote unaffected persons; closed circles and squares denote affected persons. Deceased persons are indicated by an oblique line.

The characteristics and laboratory findings of all the patients are given in Table I. C1-INH levels were undetectable in two patients, 12.1 mg/dl (36% of normal) in one patient, 38 mg/dl (11.5% of normal) in four patients, 39 mg/dl in one patient, 53.8 (15.9% of normal) in one patient and 76.6 mg/dl (23.3% of normal) in two patients. CH50 was undetectable in all patients. C4 level for all patients was low.

that required tracheotomy, three developed facial edema, and three experienced severe abdominal pain associated with vomiting and diarrhea related to gastrointestinal involvement. Two patients developed scrotal edema. Extremity, facial, and gastrointestinal system (GIS) edema were seen in 10, four, and three patients, respectively.

They reported that the symptoms lasted one to four days and then subsided spontaneously if

Table I. Characteristics and Laboratory Findings of the Patients

No	sex	Localization of edema	Age at onset of symptoms (year)	Number of attacks per year	C1-INH (mg/dl)	C4 (mg/dl)
6	female	extremity, face GIS	UN	UN	76.6	14
7	female	extremity, face, GIS	UN	UN	12.1	13
8	female	GIS	UN	UN	38	11
10	female	extremity, face, lrynx	10	3-4	38	10
13	male	extremity, larynx	10	8-10	38	9
14	male	extremity, larynx	10	3-4	UD	8
16	male	extremity	10	3-4	53.8	4
17	male	extremity, face, scrotum	1/2	3-4	38	12
19	female	extremity	11	5-6	39	4
20	female	extremity	10	5-6	UD	10
22	male	extremity, scrotum	21	8-10	76.6	14

UN: unknown.
ND: not done.
UD: undetectable.
GIS: gastrointestinal system.
The normal value C1-INH is 332±25 mg/dl.

there was no laryngeal edema. Symptoms were precipitated mainly by trauma, anxiety, cold weather, and tooth extraction, but sometimes developed without any triggering factors.

Five of the patients, whose ages ranged from 13 to 45 years, had received danazol therapy (400 mg daily) irregularly for a period ranging from one to three years prior to admission to our hospital but the drug had been discontinued because of its side effects, such as weight gain, hirsutism, and acne. There was not enough information about monitorization and treatment of the patients. These patients reported a reduction in both severity and frequency of edema attacks after this treatment, but one patient developed laryngeal edema.

We treated acute edema attacks with epinephrine, steroid, and antihistaminic drugs. Fresh frozen plasma (FFP) was used successfully to treat facial edema associated with buccal edema and life-threatening edema attacks in two patients. They reported that although there was no history of allergy, they had been diagnosed as allergic disease and had been treated accordingly.

Eleven members of this family had similar symptoms and course. Two patients died as a result of asphyxia secondary to laryngeal edema before the establishment of diagnosis.

Discussion

C1-INH is the main regulator protein of the activation steps of the complement pathway and it regulates inhibition of C1r, C1s, active Hageman factor, kallikrein, plasmin, and actived factor IX. A deficiency of C1-INH can result in a lack of regulation of the complement system and in the release of some mediators, leading to the increased vascular permeability responsible for clinical symptoms[3,4,8,10].

Diagnosis of type 1 HAE is usually established by positive family history and reduced serum C4, C1-INH, and CH50 levels, even when the patients are symptom-free[1-5]. The C1-INH level of patients with HAE is less than 20 to 30 percent of normal. The defect is transmitted as an autosomal trait, but can occur spontaneously as well, with no family history. These cases probably represent a newly acquired mutation[5]. About 15 to 25 percent of patients (type II HAE) have normal or elevated C1-INH levels. These patients have been shown to have non-functional protein[1,3,5]. There are a few patients with acquired angioedema (AAE). AAE usually starts after the fourth decade of life without family history. AAE type is characterized by the presence of antibodies to C1-INH and by the increased catabolism of C1-INH associated with benign or malignant B-cell lymphoproliferative disorders[6,7].

The clinical manifestations of HAE are polymorphic and include recurrent attacks of edema affecting the extremities, face, GIS, genitalia, and airways[3,4]. Edema of the extremities was the most common symptom in our cases. The edema is typically described as non-pruritic and painless. Laryngeal edema is the most feared complication. It can present rapidly and responds poorly to epinephrine, frequently requiring a tracheotomy to open the airway. Laryngeal edema influences the mortality rate, which may vary from 15 to 33 percent. The mortality rate in our cases was nine percent. Severe abdominal pain due to bowel wall edema is also common[4]. However, 18 percent of our patients had a history of severe abdominal pain. Sometimes the edema of the bowel wall may resemble an acute abdominal condition and many of these patients undergo an unnecessary laparotomy[4].

The first manifestations of HAE can appear at any age, but particularly at adolescence[3,4]. Mean age at onset of symptoms of our cases was 11 years. Although attacks may occur without any reason, trauma, stress, and cold are potential triggering factors. HAE usually lasts 24 to 72 hours and disappears spontaneously if there is no laryngeal involvement[3,4]. The patients should be warned about the triggering factors and avoid them when possible. The edema attacks of our cases were usually precipitated by trauma, anxiety, dental procedures or cold.

Treatment of the acute episode in patients with HAE remains the most difficult aspect in management. Epinephrine, corticosteroids, an antihistaminic, purified C1 inhibitor protein, or epsilon aminocaproic acid (EACA) may be partially effective in the management of acute attack. FFP has been used successfully. However, it should be noted that FFP could worsen the attack by supplying complement proteins; some authors recommend it not be used in the acute attack[3-5,8]. Long-term prophylaxis with the attenuated androgens (stanazol and danazol) has been used effectively daily or on alternate days in adults and children. The maintenance dose is

established by clinical response rather than by normalization of serum levels of C1-INH or C4. Long-term therapy depends on the severity and frequency of attacks[3,4,9]. We observed that the severity and number of attacks decreased in patients treated with danazol. The androgens have some side effects, such as hepatic damage and virilization, but these usually disappear after the drug is stopped[3,4]. Recently, interferon-λ has been shown to stimulate C-INH protein production[10].

Hereditary angioedema (HAE) is in fact poorly recognized by physicians, as in our cases. Most commonly, HAE is considered an allergic disease. Some physicians may not take into consideration the seriousness of this disease. Also, some physicians, frightened by the possibility of an allergic reaction, are hesitant to give the necessary antibiotic, analgesic or other drugs to such patients. Tho date only two drugs, estrogens and angiotensin-converting-enzyme inhibitors, have been proven detrimental in C1-INH deficient patients by facilitating attacks[4].

In this paper, we presented a family with type I HAE, eleven members of which were followed-up in our outpatient and emergency clinics. The main problem for patients with HAE is misdiagnosis due to the fact that the disease is relatively unknown. This case report also indicated the importance of recognition and early treatment of HAE to prevent a potentially fatal outcome.

REFERENCES

1. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema. Am J Sci 1963; 35: 37-44.
2. Rosen FS, Alper CA, Pensky J, Klemper MR, Donaldson VH. Genetically determined heterogeneity of the C_1 esterase inhibitor in patients with hereditary angioneurotic edema. J Clin Invest 1971; 50: 2143-2149.
3. Baldwin J, Pence HL, Karibo JM, Massey EN. C1 esterase inhibitor deficiency: three presentations. Ann Allergy 1991; 67: 107-113.
4. Agostoni A, Cicardi M, Cugno M, Storti E. Clinical problems in the C1-inhibitor deficient patient. Behring Inst Mitt 1993; 93: 306-312.
5. Arreaza EE, Singh K, Grant JA. Hereditary angioedema: clinical and biochemical heterogeneity. Ann Allergy 1988; 61: 69-74.
6. Caldwel JR, Ruddy S, Schur PH, Austen KF. Acquired C1-inhibitor deficiency in lymphosarcoma. J Immunol Immunopathol 1972; 1: 39-52.
7. Jackson J, Sim RB, Whelan A, Feigheri C. A IgG autoantibody which inactivates C1 inhibitor. Nature 1986; 323: 722-724.
8. Karlis V, Glickman RS, Stern R, Kinney L. Hereditary angioedema. Case report and review of management. Oral Surg Oral Med Oral Pathol 1997; 83: 462-464.
9. Barakat A, Castaldo AJ. Hereditary angioedema: danazol therapy in a 5-year-old child. Am J Dis Child 1993; 147: 931-932.
10. Zahedi K, Prada AE, Davis AE. 3rd Structure and regulation of the C1-inhibitor gene. Behring Inst Mitt 1993; 93: 115-119.