Hereditary angioedema. Long-term follow-up of 88 patients. Experience of the Argentine Allergy and Immunology Institute

J. E. Fabiana, A. Avigliano and **J. C. Dupont**

SUMMARY

Since the detection of the first patient with hereditary angioedema (HA) in 1978, 88 new patients belonging to 16 families have been referred to our clinic. Eighty patients had Type I disease, 5 Type II, and 3 Type III (secondary). We describe the clinical onset, frequent complications, diagnostic tests of the complement system, and abnormalities of the coagulation pathway linked to complement activation. Particular attention was paid to family members who could present succedaneum symptoms. The results of danazole and other therapies and protective and preventive treatment for surgery also are discussed.

Key words: Hereditary angioedema. Preventive treatment surgery.

INTRODUCTION

The initial description of hereditary angioedema by Quincke (1) in 1882 included features such as episodic edema of subcutaneous tissue and/or mucosa that affect the face, extremities, genitalia, dorsal region, and abdomen. In the abdomen, HA can simulate acute surgical conditions. Renal colic, vomiting and/or diarrhea are often observed in some patients. The main expression of HA is acute laryngeal edema and death by asphyxia. In children under the age of 10, intestinal colic and edema of the extremities are the most frequent manifestations.

Patients with HA have episodes of local swelling, usually affecting the face, extremities, upper airway, and gastrointestinal tract. It frequently causes recurrent abdominal pain (with or without ascitis). Early diagnosis is important because the disease has potentially life-threatening complications.

HA complications observed in our group were: death of a 10 year-old child from laryngeal asphyxia, membrane-proliferative glomerulonephritis in an 8 year-old, and death of a patient with Type III HA from tonsillary edema.

Intestinal colic frequently appears alone or associated with other manifestations of edema.

The trigger events are not clear; they may be traumatic, psychological, or related with drug administration or menstruation. These acute episodes tend to last 48 to 72 hours and often remit spontaneously. Patients are commonly treated with steroids or antihistaminic drugs. As a result of the disappearance of symptoms, the correct diagnosis of HA may be delayed (diagnostic error). Symptoms vary between individuals and families and within the same family (2) (clinical polymorphism). We have observed asymptomatic disease in several patients 60 years-old or older.

ETIOLOGY, PATHOGENESIS, AND INHERITANCE

The disease is hereditary, as first observed by Osler (3) in 1889. Inheritance is autosomal dominant with incomplete penetration. This characteristic obliges us to examine the family tree thoroughly. In our experience with hereditary angioedema, mutations are spontaneous in 37% and three is no family history of the disease (4) (table I).

The disease may occur in grandparents and be inherited by grandchildren. "Spontaneous" HA was transmitted hereditarily in 6 families in our series.

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Table I

Inheritance pattern in 16 family groups of 88 patients with hereditary angioedema: 55 men, 33 women (19 under the age of 10 years). The average age at time of diagnosis was 23 years

	No. of families
Two or more generations	10
Spontaneous with second HA generation	2
Spontaneous with no HA generation	1
Spontaneous with no offspring	3

Figure 1.—Relative percentages of symptoms during episodes.

Recently, the C1 inhibitor gene was cloned and mapped to chromosome 11, making it possible to demonstrate that this gene is abnormal in patients with hereditary angioedema and that different mutation can be responsible. Most of the genetic abnormalities are point mutations or small deletions and insertions. Major gene rearrangements, with partial deletions or duplications, account for 15% to 20% of mutations and are usually related to clusters of repetitive DNA sequences, known as Alu repeats. These repeats, which represent processed forms of 7SL RNA genes, are present in the C1 inhibitor gene as well as in many others and facilitate DNA recombination. The mutations responsible for hereditary angioedema usually impair DNA transcription, but the disease has also been reported in association with untranslated RNA and with defects impairing the secretion of mutant protein (5).

PATHOGENESIS

C1 inhibitor is central to the regulation of the complement, coagulation, and contact (kinin-forming) systems. As a member of the family of the serine protease inhibitors (serpin), C1 inhibitor acts as a "suicide protein" by forming complexes with the target proteases. It inhibits C1r and C1s in the complement system, HF (Hageman Factor) and kallikrein in the contact system, factor XI in the coagulation system, and plasmin in the fibrinolytic system. Patients with C1-inhibitor deficiency have low plasma levels of C4 and C2, the substrate of the C1r-C1s complex.

Acute attacks of angioedema simulate the appearance of cleaved, high-molecular-weight kininogen, the substrate of kallikrein and bradykinin release.

Defective synthesis of C1INH accounts for 90% of Type I cases. When assayed antigenically, C1INH level is less than 30% of normal. Landerman (6) and
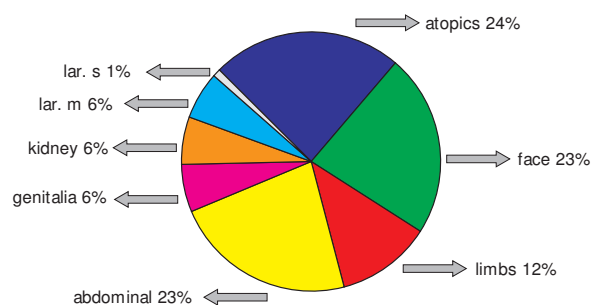
Donaldson (7) found abnormalities in the kallikrein cascade and in the complement system. Lepow, et al (8) purified C1INH.

CLINICAL FEATURES

The characteristics of the disease make early diagnosis difficult. Cases are frequently (and erroneously) associated to allergy. Swelling is thought to be caused by the release of vasoactive peptides that have proved difficult to identify. Histamine has no role in this type of edema, which probably is due to the generation of substances with kinin activity. Whether the substance is a complement-derived, kinin-like peptide or bradykinin itself is unclear. Other vasoactive substances may also be involved (9). In 1965, Rosen, et al (10) described a small group of patients with C1INH function and normal or increased antigen levels. In our series, 5.68% (5 patients) of our cases were of this type (type II).

A third group of patients was described by Caldwell, et al (11) in 1975. These patients have clinical manifestations of angioedema secondary to systemic disease such as colon cancer, lymphoproliferative diseases, autoimmune diseases, anti-idiotype antibodies, and others. These clinical forms of
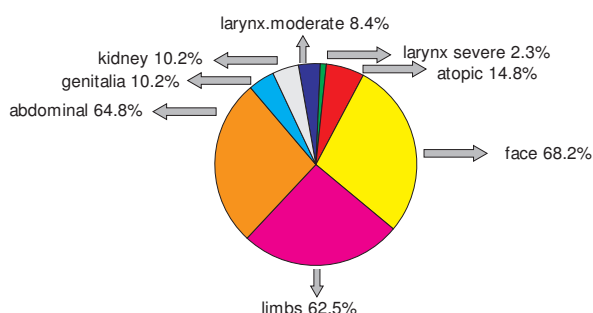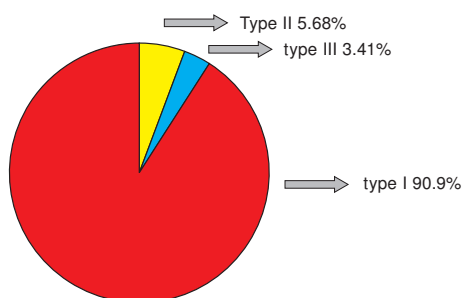

Figure 2.—Symptom location in children under 10 years.

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Figure 3.—Distribution of HA types.

——— Inhibited by C1 INH.

Figure 4.—Adapted from Kaplan (13).

angioedema tend to appear in the adult age and are infrequent in childhood. In our series, 3 patients (3.41%) belonged to this group, Type III (Figs. 1 to 3).

IMMUNOLOGICAL DIAGNOSIS

At the Argentine Allergy and Immunology Institute we have diagnosed 88 patients with HA since 1978. In this population, we detected 19 previously asymptomatic patients under the age of 10 years when symptoms began, the youngest of them 4 months-old (later corroborated at the age of 18 months).

In the complement system, C1INH deficiency is characterized by low antigenic levels of C4 component due to increased consumption of this protein (Fig. 4). Serum levels of C2 esterase also are low.

In the laboratory diagnosis, antigenic concentrations of C4 in serum are the first indicator of HA. Antigenic C4 values are 30% of normal value (normal 20-60 mg/dl) at any time. In Type I HA, antigenic C1INH values are about 30% of normal, frequently less than 10 mg/dl. Normal C1INH values are 17-31 mg/dl (by radial immune diffusion, RID). Functional C1INH is required to characterize this illness as Type II. Using the Kent and Fife method for measuring functional C1INH, values are lower than 80% (normal range: 80-120%).

CH50 values are low at any time without treatment, about 100 ± 20 HU CH50 (2). In secondary angioedema (Type III), C1q is always low, thus differentiating Type III from the other types of HA.

In Type I, C1q was decreased in 10% of our adult patients at the beginning of the study, indicating intensive complement activity (12).

In our population of HA patients, 56% had circulating immune complexes (CIC) as evaluated by two different methods (C1q in solid phase and complement consumption). We attribute this increase in immune complexes to consumption of
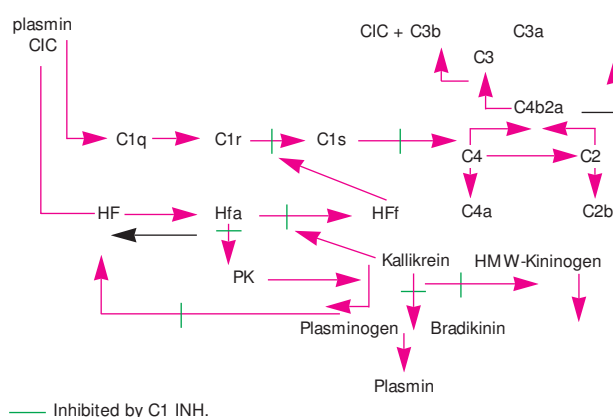
C4 and C2 by the activated complement system, thus impeding the generation of C3 convertase and production of C3b fragment, the main component of plasmatic CIC clearance. On the other hand, C3 turnover involves the most active fraction of the complement system, so the C3 fraction remains within normal values, even during episodes. C4 is always low, even between episodes.

HF activation determines an active fraction, HFf, which activates C1r and consumes C1s, C4, and C2. C1 is decreased in 90% of our cases in Type I and II HA (Fig. 4).

COAGULATION AND COMPLEMENT IN HA

C1INH regulates not only the complement system, but also the contact and fibrinolytic systems of coagulation, so these systems share links.

• C1INH is important for the inactivation of Hfa (activated) and HFh (fragment of the contact system. It inhibits approximately 90% of the protein and its fragment (14).

• C1INH is clearly an important inhibitor in the control of the plasma kinin-forming system. In 1962, Landerman demonstrated that the plasma of patients with HA was deficiency in kallikrein-inhibiting capacity compared with normal plasma (15).

• C1INH also regulated plasmin, the fibrinolytic protein, and in 1952 the group of Lepow demonstrated that this protein could reciprocally inactivate serum complement (16).

It is interesting to note that strenuous exercise, anxiety, and trauma; the only demonstrated causes of HA episodes, also enhance fibrinolysis.

Two different hypotheses have been proposed to explain the pathogenesis of HA episodes. The first

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hypothesis involves a C2 fragment: the authors suggest that activated C1 cleaves C4 and C2, and a fragment of C2 kinin formed during cleavage could produce edema, thus causing HA episodes.

The second hypothesis attributes episodes to bradykinin produced in this system. Recently, the group of Davis (17) published an interesting article in which they suggest that bradykinin triggers HA. They studied a family without HA who presented a dysfunctional C1INH; in this mutant, Ala 443 (P2) has been replaced by Val. The protein has less inhibitory activity toward isolated C1r, C1s, and intact C1, but can completely inhibit Hfa and Kallikrein.

Consequently, the normal inhibition of the contact system and abnormal inhibition of the complement system in members of a family without HA episodes suggest that episodes are triggered by bradykinin generated in the contact system.

At present, most researchers believe that this is the most likely hypothesis. In earlier studies (18) we found fibrin deposits in the skin biopsies of asymptomatic patients with HA between episodes. Recently, Cugno, et al (19) demonstrated the active participation of thrombin in HA episodes. This observation could be related with our findings, because thrombin, the enzyme responsible for fibrin formation, occurs during edema episodes.

In a group of symptomatic patients, we studied parameters of the coagulation and complement systems before and after treatment with danazole. We observed an increase in the plasma concentrations of C1INH, C4, protein C (PC), plasminogen (plg), and HF coagulant activity (HFc) after drug treatment. These observations confirmed published findings and motivated us to begin a more detailed study of the links between these two systems.

TREATMENT BETWEEN EPISODES

The clinical use by Gelfand (20) of danazole, an attenuated androgen, increased hepatic synthesis of C1INH by the normal gene.

We prescribed doses of 400 mg/day for 14 days ant then measured biochemical markers. Serum C1INH did not reach normal levels, but the patient remains free of clinical symptoms. However, a marked increase to below-normal values was observed of serum C4 fraction levels, possibly due to a double mechanism, a decrease in activation and an increase in liver synthesis.

At our institute, minimal effective doses are evaluated as follows:

1) If the patient had CIC, CIC should disappear from serum after 14 treatment days.

2) C4 fraction levels increase by 80% with respect to baseline value.

The resting period must not exceed 5 days. Danazole was found to be ineffective at doses lower than 200 mg/day in the early treatment period (21).

This drug is indicated in adult men or women with frequent, life-threatening symptoms. Common adverse effects are weight gain, hirsutism in women, and impaired libido in men. We observed microhematuria in two male patients and abnormal hepatogram in two women.

Epsilon aminocaproic acid (EACA) is another recommended drug. We prescribe doses of 1 g/day to prevent episodes in adults, and half that dose in children as needed. The mechanism of action is unknown. Adolescents, children with relatively frequent episodes, or young women with mild edema episodes and no laryngeal or mouth edema are treated. Tachyphylaxis in frequent after a one-year treatment with 1 g/day.

TREATMENT OF EPISODES

We reserve the administration of C1INH concentrates for rescue treatment. We prescribe 1000 U to each family to keep at home for emergency use because the product is very expensive and difficult to obtain in Argentina.

The transfusion of fresh plasma in acute episodes of laryngeal edema was beneficial in four of our patients. However, its use is controversial because plasma may add C1 esterase-activating factors and transmit HIV virus.

For acute bowel episodes we prescribe EACA, which is relatively effective in relieving symptoms.

Of 3 patients with secondary HA (type III), one was associated with systemic lupus erythematosus and two had no other primary disease diagnosed.

One of these two patients died of tongue edema initiated by an episode. In this case, the androgen previously used at doses of 800 mg/day did not improve symptoms or immune system determinations. Fresh plasma transfusions were not effective during acute episodes.

Although some minor procedures may trigger episodes, many of our patients who had dental extractions before diagnosis did not have serious problems. However, we recommend caution in the case of dental treatment, insertion of nasogastric tubes, tonsil surgery, or other interventions on the mucosa because HF activation *in situ* may originate bradykinin release. In these cases we recommend danazole 400 mg/day for 14 days before and 7 days

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after the intervention, or C1INH concentrates when the androgen is not indicated, especially in children.

CONCLUSIONS

1. C4, the first marker of the disease, should be evaluated in every patient with recurrent edema or bowel colic of no known cause at any age.

2. After C4, we assay antigenic C1INH, C1q, and functional C1INH if antigenic C1INH is normal or high.

3. Atopy is associated with HA in 24% of adults and 14% of patients under 10 years of age.

4. HA can skip generations.

5. Spontaneous appearance of HA is caused by different genetic disorders. This situation is frequent.

6. Family members must be studied when HA is detected. It is important to detect asymptomatic children.

RESUMEN

Desde la detección del primer paciente con angioedema hereditario (AH) en 1978, se han remitido a nuestra clínica 88 pacientes nuevos pertenecientes a 16 familias. Ochenta pacientes tuvieron enfermedad de tipo I, cinco de tipo II y tres de tipo III (secundario). Describimos el comienzo clínico, las complicaciones más frecuentes, estudios diagnósticos del sistema de complemento y alteraciones de la vía de coagulación relacionadas con la activación de complemento. Se prestó atención especial a familiares que podrían presentar síntomas sucedáneos. También examinamos los resultados de danazol y otros tratamientos como tratamiento protector y preventivo para intervenciones quirúrgicas.

Palabras clave: Angiodema hereditario. Tratamiento protector y preventivo.

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