

Original article

Oestrogen-dependent hereditary angio-oedema with normal C1 inhibitor: description of six new cases and review of pathogenic mechanisms and treatment

Background: Hereditary angio-oedema (HAE) is a rare condition in which there is a deficiency in the quantity or activity of C1 inhibitor (C1INH). Recently, an additional type of HAE with no alterations in the levels or the function of C1INH has been reported. It is defined as HAE with normal C1INH, and named type III HAE or oestrogen-dependent HAE. The aim of this study is to describe the clinical and laboratory findings of six new cases of type III HAE and to review the literature about this disease.

Methods: A short description of six women with recurrent angio-oedema is provided. The characteristics of the patients are compared with the previously reported case series in a literature-based review.

Results: The mean age of the patients at onset was 22 years (range 16–30). All of them had angio-oedema attacks during oestrogen-based contraceptive treatment and four reported episodes during pregnancy. Four patients reported a positive past family history. Two of them had experienced episodes of laryngeal oedema. None of the patients responded to corticoids or antihistamines during the attacks. Levels and functional activity of C1INH were within the normal range in all cases.

Conclusions: Clinical and laboratory findings mirror the observations of previous reports of oestrogen-dependent angio-oedema with normal C1INH. This is the first published series of type III HAE in Spain.

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Hereditary angio-oedema (HAE) is an infrequent genetic disease in which a mutation exists in the gene that codifies for the inhibitor of the C1 factor of the complement (C1INH), inducing a reduction in its synthesis (type I) or the formation of a dysfunctional protein (type II). Clinically, it is characterized by recurrent episodes of subcutaneous and sub-mucosal angio-oedema, which affect the skin, gastrointestinal tract and upper airways. These attacks do not respond to antihistamines, corticoids or adrenalin and usually subside spontaneously in 12–72 h (1). Recently, a new type of HAE, clinically indistinguishable from the previous ones, has been reported, in which alterations in the gene, or in the C1INH protein or function have been not found. It has been named HAE type III (2), oestrogen-dependent HAE (3) or HAE with normal C1INH activity (4). It was initially reported in women of the same family in relation to conditions of high oestrogen levels such as the use of oral contraceptives or pregnancy (2, 3). Recently, two missense mutations in the coagulation factor XII gene have been reported in affected women of different families (5). The aim of this study is to describe the clinical characteristics of six patients with recurrent angio-

oedema and normal C1INH, as well as to review the physiopathology, genetic alterations, and the treatment of this new type of HAE.

Case description

A detailed description of six women with recurrent angio-oedema is provided. The main clinical characteristics and laboratory findings of the patients are summarized in Table 1.

Case no. 1

A 33-year-old woman had experienced recurrent episodes of abdominal pain of unknown origin during her pregnancy. A previous pregnancy had ended on account of miscarriage. She reported that her mother developed recurrent angio-oedema attacks, although assessed C4 and C1INH levels and activity were always normal. At the age of 17, upon initiation of oral contraception, she was admitted to hospital because of ascites. She now consulted because of a recent episode of facial

Table 1. Clinical and laboratory characteristics of the six affected patients

	1	2*	3*	4	5†	6
Age at onset of angio-oedema attacks	17	30	27	24	20	16
Association with contraceptives	Yes	Yes	Yes	Yes	Yes	Yes
Association with pregnancy	Yes	Yes	No	Yes	—	Yes
Family members affected	Yes	Yes	No‡	Yes	No	Yes
Episodes of laryngeal oedema	No	Yes	No	No	No	Yes
Response to corticoids or antihistamines	No	No	No	No	No	No
Blood count and biochemistry§	Normal	Normal	Normal	Normal	Normal	Normal
Skin prick tests to foods¶	Negative	Negative	Negative	Negative	Negative	Negative
Immunoglobulins (A, M, G and E)	Normal	Normal	Normal	Normal	Normal	Normal
Autoimmunity profile**	Negative	Negative	Negative	Negative	Negative	Negative
Infection profile††	Negative	Negative	Negative	Negative	Negative	Negative
C4 levels	Normal	Normal	Normal	Normal	Normal	Normal
C1q levels	Normal	Normal	Normal	Normal	Normal	Normal
C1INH levels (mg/dl)‡‡	27.7	22.0	20.0	27.6	29.6	13.0
C1INH function (%)	93	85	96	65	83	92

*Tolerance of progestagen-based contraceptives.

†Complement levels were also normal when assessed during an acute attack.

‡Affected daughter (case 2) but there is no presence of angio-oedema in ascendancy.

§Includes: red blood cells, haemoglobin, differential leucocytes count, platelets, renal and hepatic profile and thyroid stimulant hormone (TSH) levels.

¶Includes: milk, egg, peanut, soy, fish, wheat, nuts and shrimp.

**Includes: antinuclear and anti-thyroid antibodies.

††Includes: Hepatitis virus (B and C) and HIV serology.

‡‡Normal range 15–25 mg/dl. The subtle diminished levels of C1INH in case 6 do not explain the symptoms as the functional C1INH is normal. Genetic studies of mutations of genes codifying for C1INH in this patient were normal.

angio-oedema and severe abdominal pain for which she required attention in the emergency department and subsequent hospitalization. She was started on contraceptive oestrogens patches 2 month prior to the episode. On admittance, an abdominal ultrasonography showed ascites (exudate with normal biochemistry, negative culture and cytology) and intestinal swelling (intestinal wall 10.7 mm). An abdominal CT-scan confirmed the presence of perihepatic, pelvic and perisplenic fluid, and an extensive increase in thickness of a segment of the jejunal wall. The patient improved spontaneously after interrupting the contraceptives.

Case no. 2

A 37-year-old woman consulted because of recurrent episodes of laryngeal oedema since the age of 30. She reported initiation of oral contraceptives (oestrogens) 15 days before the first episode, which were held with subsequent clinical improvement. Later, she received hormonal contraception with linestrenol (progestagen) without complications. At the age of 35, during her third pregnancy, she developed eight episodes of angio-oedema involving the upper airway (arytenoids and uvula). Her two previous pregnancies underwent uneventfully. The last episode occurred during the birth of her third baby, subsiding spontaneously in a few days. After the last delivery she underwent tubal ligation and since then the patient is asymptomatic. She reported that her mother (Case no. 3) had recurrent angio-oedema in relation to treatment with oral contraceptives.

Case no. 3

A 58-year-old woman reported that at the age of 27 she suffered two episodes of facial angio-oedema associated with the initiation of oral contraceptives (oestrogens) on two different occasions, which subsided upon interruption of the treatment. She had undergone three normal pregnancies, one before and two after the episodes of angio-oedema. She later tolerated contraception with linestrenol (progestagen). She was not aware of a past family history of angio-oedema but has a daughter with oestrogen-induced angio-oedema (Case no. 2).

Case no. 4

A 26-year-old woman consulted because of an episode of facial angio-oedema (lips, eyelids, cheeks), without urticaria, which required hospital admittance and improved with intravenous tranexamic acid. The patient was on oral contraceptives (oestrogens) at the time of the above-mentioned attack. Oral contraceptives were withdrawn and a short course of tranexamic acid was prescribed upon discharge, with good response. During her first pregnancy, she had experienced a similar, although milder, episode of angio-oedema. She reported that her mother developed episodes of facial angio-oedema during her pregnancy, but had never taken oral contraceptives. Her sister, who had never been on oral contraceptives, had undergone two pregnancies during which she developed several episodes of angio-oedema of the face and hands. Another sister was asymptomatic although she

was on contraceptives. A sister of their grandmother and a maternal aunt reported angio-oedema attacks during their pregnancies.

Case no. 5

A 32-year-old woman reported episodes of facial angio-oedema and recurrent abdominal pain, without urticaria, which had begun 12 years ago. She had required attention at the emergency department on several occasions. These attacks were elicited by emotional stress and minor traumas and resolved spontaneously in 3 or 4 days. Multiple diagnostic tests were performed, including a laparoscopy, which were all normal. She reported having started oral contraceptives (oestrogens) 2 month prior to the onset of the episodes of angio-oedema. No other women in her family were affected. The patient was evaluated during an attack of angio-oedema and levels and function of C1INH and C4 concentration were normal. Contraceptives were withdrawn and as then she remains asymptomatic.

Case no. 6

A 37-year-old woman, who was 31-week pregnant, consulted because of episodes of angio-oedema. She reported recurrent episodes of angio-oedema without urticaria since the age of 15, affecting eyelids, lips, feet, hands and tongue. Since she was 20, the swelling involved the upper airway and she had required multiple visits to the emergency department although she had not needed orotracheal intubation. During these episodes, she frequently experienced abdominal pain, predominantly epigastric, which appeared either spontaneously or after mild traumas. She had been on oral contraceptives (oestrogens) since the age of 15, but there had been an increase in the severity and number of episodes at the age of 30 while changing the type of oral contraceptives, which were withdrawn thereafter. Attacks abated after oral contraceptives were discontinued. The patient had undergone two previous pregnancies with episodes of angio-oedema, without symptoms during labour. Angio-oedema attacks were also elicited by nonsteroidal anti-inflammatory drugs (NSAIDs). Her mother suffered recurrent angio-oedema with involvement of the upper airways requiring several orotracheal intubations, but no other family members were affected. She had two asymptomatic daughters, aged 4 and 14 years. Serum complement levels revealed a slight decrease of the C1INH with normal functional activity. Genetic studies of C1INH deficiency showed no mutations.

Discussion

C1 inhibitor deficiency may be acquired or hereditary (1). Acquired angio-oedema (AAE) is characterized by

either an increase in the catabolism of C1INH by the production of immune complexes (type I) or by the presence of anti-C1INH auto-antibodies (type II). Hallmarks of both types of acquired angio-oedema are a decrease in C1q factor and absence of a hereditary pattern. The production of the C1INH is normal or is even slightly increased. Type I has been related with B-cell malignancies and type II with the presence of auto-antibodies, which reduce the C1INH function (6, 7).

The hereditary form (HAE) is a rare disease; its global prevalence is around 1/50 000 and in Spain it is at least of 1.09/100 000 inhabitants (8). In this disorder, there may be a deficiency in the synthesis of C1INH (HAE type I) or protein levels may be normal with a significant reduction in its activity (HAE type II). The hereditary pattern is autosomal dominant. The genetic alteration is located in the gene that codifies for the C1INH and is different in the two types. However, in approximately a 20% of the cases, there are no affected relatives and correspond to *de novo* mutations (6). Hereditary angio-oedema is clinically characterized by recurrent, self-limited and unpredictable episodes of oedema that may affect the skin, gastrointestinal tract and upper airways. Approximately one-third of the patients suffer laryngeal angio-oedema at least once in their lifetime (9).

Recently an additional type of HAE with no alterations in the levels or the activity of C1INH or in the levels of C4 has been reported. It has been defined as HAE with normal C1 inhibitor (C1INH) activity, and named HAE type III or oestrogen-dependent HAE (2–4, 10). It typically affects women of the same family. This HAE is clinically indistinguishable from the HAE types I and II, presenting a similar frequency of laryngeal angio-

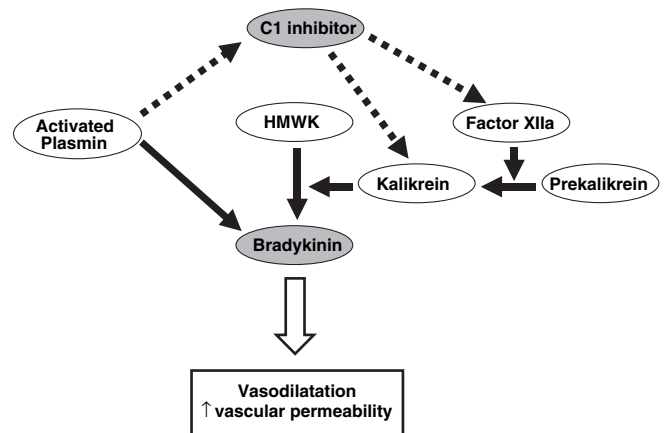


Figure 1. Schematic illustration of implicated ways of C1INH deficiency. A detailed relationship between C1INH and bradykinin is shown. There are several components of coagulation and kinins systems involved (see text). The stimulatory or inhibitory effect of the different mediators is denoted by solid and dashed lines respectively. HMWK, high molecular weight kininogen.

oedema (2). In the patients we describe, the frequency of laryngeal angio-oedema was of 33% (Table 1). As in HAE types I and II, the onset or the worsening of the attacks in HAE type III have been related with high oestrogen conditions (3, 10).

Some drugs such as angiotensin converting enzyme inhibitors may trigger attacks of angio-oedema in patients with HAE. These drugs increase the levels of bradykinin, a powerful mediator that induces vasodilatation and increases vascular permeability. In these cases, there seems to be a deficiency in the metabolism of bradykinin because of an enzymatic defect (11). Furthermore, worsening of symptoms in two unrelated female patients associated to angiotensin II receptor antagonists has been reported in type III HAE (12).

To date, NSAIDs have not been reported to trigger attacks of angio-oedema in HAE patients. Nevertheless, patient no. 6 reported episodes of angio-oedema after the consumption of these drugs. Angio-oedema induced by NSAIDs is occasionally caused by an IgE-mediated reaction. Nevertheless, the most frequent mechanism is intolerance, in which a disturbance in arachidonic acid metabolism induces an excessive production of leukotrienes. In NSAID intolerance, reactions occur with different NSAIDs of unrelated chemical groups (13). This was probably the case in patient no. 6.

C1 inhibitor is a serin-protease that regulates the classic route of the complement, engaging fractions C1r and C1s of factor C1 of the complement. It also acts inhibiting kallikrein within the system of kinins, and inhibiting the

activation of coagulation factors XI and XII. C1 inhibitor is consumed by plasmin, a mediator whose metabolism generates bradykinin. Bradykinin induces vasodilatation and increases vascular permeability, directly mediating angio-oedema attacks in HAE patients (14). On the other hand, the consumption of the C1INH by plasmin favours the uncontrolled activation of the system of kinins which entails the additional synthesis of bradykinin. Thus, the activation of plasmin constitutes a fundamental event for the development of these attacks (6, 15) (Fig. 1). Patients with slight-to-moderate deficiencies of C1INH do not experience angio-oedema attacks. In fact, to have 35–40% of the normal level of C1INH, or an activity > 30% is sufficient to avoid symptoms (6). In one of our patients (Case no. 6) levels of C1INH were discreetly low (13 mg/dl), but corresponded to 87% of the inferior limit of normality (15 mg/dl), its activity remaining normal.

Increased oestrogen levels, on account of exogenous oestrogens or during pregnancies, have been reported to induce angio-oedema in previous studies (2, 3, 10). During pregnancy, oestrogens play a fundamental role in aspects, such as the growth of the breasts and the uterus, the regulation of the sodium potassium pump and the increase of the uterus-placenta flow. Several mechanisms have been reported by which oestrogens can increase the levels of bradykinin and induce episodes of angio-oedema (Fig. 2) (3, 16–18). Binkley and Davis (3) have suggested that oestrogen-mediated angio-oedema may be explained by a mutation in the androgen-responsive element located in the promoter region of the gene that codifies for C1INH. Elevated oestrogen concentrations may increase the levels of the sexual hormone binding protein and reduce the amount of free androgens available to ligate the mutated element, reducing the synthesis of C1INH. All our patients suffered angio-oedema attacks related with the use of contraceptives containing oestrogens and in four of them, pregnancy also induced angio-oedema attacks.

It is interesting to highlight that in the largest published series of type III HAE (2), 15 of the 36 patients presented episodes of angio-oedema not related with oestrogen consumption or pregnancy, which suggests that not all the phenotypes of the disease are oestrogen-dependent. A similar phenomenon has also been observed in patients with HAE types I or II (19).

In one of our patients (Case no. 6), episodes of angio-oedema had occurred during all her pregnancies, while another patient (Case no. 2) had been asymptomatic during two previous pregnancies but reported angio-oedema during the third. The reason for this clinical variability is not known. On the other hand, one of the patients (Case no. 3) developed attacks of angio-oedema after the consumption of oral contraceptives but not during pregnancy. This case is quite peculiar because oestrogens attain maximal levels during pregnancy, up to 50 times greater than that in the nonpregnant women. This would suggest that in certain cases a protective effect

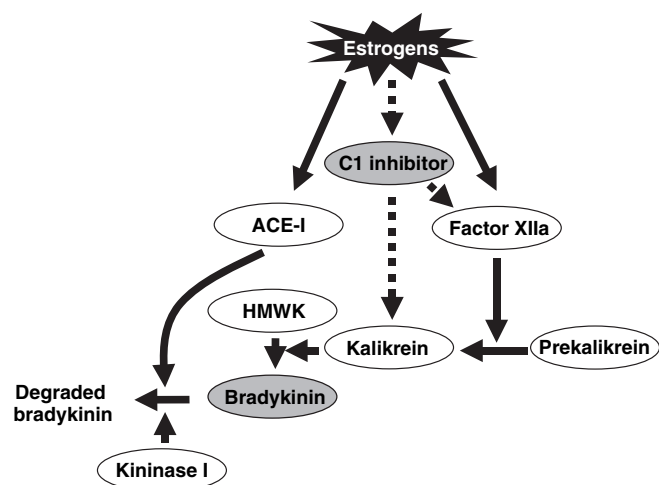


Figure 2. Influence of oestrogens on the development of angio-oedema attacks in patients with HAE. Oestrogens increase the production of bradykinin through the inhibition of C1INH and the activation of factor XII. Furthermore, they decrease its degradation due to the inhibitory effect of angiotensin converting enzyme-I (ACE-I). The stimulatory or inhibitory effect of the different mediators is denoted by solid and dashed lines respectively. HMWK, high molecular weight kininogen.

to the endogenous but not to the exogenous oestrogens exists, although this is speculative. Unlike what happens in type III HAE, the frequency of attacks in types I and II does not vary or sometimes even diminishes during pregnancy (19). One of our patients (Case no. 2), suffered an episode during labour, as well as during the pregnancy. The other three patients with angio-oedema during pregnancy (Cases no. 1, 4 and 6), did not report attacks during childbirth labour or the expulsive phase, suggesting a clinical pattern similar to other types HAE. The reason of this 'protection' during childbirth is not known.

The hereditary pattern of type III HAE has been a matter of discussions. Initially Bork et al. (2), suggested a dominant X-linked inheritance pattern, as all the affected patients were women. However, in another classic publication, Binkley and Davis (3), reported an Italian family with oestrogen-induced angio-oedema in which the inheritance pattern was consistent with a dominant autosomal trait, in which some men seemed to be asymptomatic carriers of the abnormality. Later, Martin et al. (20) reported a similar pattern of inheritance in a French family, in which the gender-linked inheritance was categorically ruled out. Gupta et al. (21) have reported kindred of three brothers with HAE limited to the skin that responded to antihistamine treatment; C1INH levels and function were normal. The possible recessive inheritance pattern of this family and the clinical features may indicate that it could correspond to a different condition. Recently, Bork et al. (22) have also reported a family in whom three male patients developed the disease suggesting indeed an autosomal inheritance. However, the reported male cases are anecdotic. On the other hand, it is important to mention that patients reported in Cases no. 3 and 5 did not have known affected family members, a fundamental criterion for the diagnosis (2). However, Case no. 3 has an affected daughter (Case no. 2), which suggests a *de novo* mutation, as it seems to be the case in patient no. 5. In fact, *de novo* mutations have already been reported in up to 20% of cases of HAE type I and HAE type II (23). Thus, it would be logical to think that the same may happen in HAE with normal C1INH. We have to keep in mind that the accomplishment of genetic studies has only been possible for a few decades and that HAE type III is a recently reported entity. In another interesting study, Bork et al. (10) found that 96% of patients with angio-oedema triggered by oestrogens had some hereditary form of angio-oedema (HAE due to C1INH deficiency or HAE with normal C1INH), and therefore they raise the question whether they are the same disease or different diseases with a similar clinical picture in which the pathogenic alteration is not directly linked to the C1INH esterase.

As C1INH level and activity and C4 values are normal in type III HAE patients, it seems unlikely that a mutation in the C1INH gene would be the cause of the

disease, as it is in HAEI and HAEII, in which up to 150 different mutations of this gene have been reported (9, 19, 20). Recently, the first evidence of genetic alteration in the patients with HAE and normal C1INH has been reported by Dewald and Bork (5). The authors describe two different missense mutations in the gene (F12) that codifies for coagulation factor XII (Hageman factor). According to the authors, these mutations generate structural and functional changes in factor XII leading to a hyperactivation of this protein. The two mutations are located in position 1032 of exon 9 of the gene F12 (*c.* 1032C → A and *c.* 1032C → G). These alterations were found in six affected patients belonging to five different families. On the other hand, these were absent in the analysis of 145 healthy subjects. Moreover, Cichon et al. (24), as well as reporting the same mutation (*c.* 1032C → A) in two new families showed that this mutation increases factor XII activity, demonstrating the pathogenic relevance of the mutation in type III HAE.

The management of HAE should always cover two fundamental aspects: the handling of acute attacks, and the long-term prophylactic treatment. It is well known that neither corticosteroids, antihistamines nor adrenalin are useful for the treatment in the acute phase. On the other hand, androgens require approximately 2 days to initiate their activity and anti-fibrinolytics have only a subtle effect. The only treatment that is considered rapidly effective is the administration of intravenous C1INH concentrate (6, 19) but it does not seem to be effective in type III HAE. Unfortunately the availability of this treatment is very limited, especially considering that some patients develop episodes of laryngeal angio-oedema with a mortality up to 25% (3). In contrast with the resistance to anti-fibrinolytics previously reported, one of the patients (Case no. 4) received treatment with intravenous tranexamic acid during an episode of angio-oedema with improvement of symptoms.

As the increase of bradykinin seems to be a common characteristic to all types of HAE, recently developed drugs for HAE such as icatibant, a bradykinin receptor antagonist (25, 26) or DX-88 (ecallantide), a plasma kallikrein inhibitor (27), could be an effective treatment for the management of acute episodes in type III HAE.

The prophylactic handling of HAE has classically relied on two types of drugs: attenuated androgens and anti-fibrinolytics. Attenuated androgens are the most effective treatment and usually are well tolerated. Adverse side-effects such as, hepatotoxicity and virilization are unusual. Androgens increase C1INH levels and diminish the frequency of angio-oedema attacks. The clinical benefit of androgens is reached with smaller doses than those necessary to obtain significant changes in the C1INH level, so dose adjustment must be based on symptoms and not on laboratory data. Recently, it has been reported, that attenuated androgens have been effective in HAE with normal C1INH (4, 28).

Anti-fibrinolytics are the second type of prophylactic treatment. It is not certainly known how these drugs act in HAE, but it is thought that they avoid the activation of factor XII because of their anti-plasmin activity, which induces the conversion of prekallikrein to kallikrein (19, 29). Cicardi et al. (30) reported effectiveness of tranexamic acid in a cohort of 15 patients (10 women) with idiopathic angio-oedema. According to the clinical characteristics, several of these women may have had a non-diagnosed type III HAE. Bork et al. (2) reported failure of tranexamic acid treatment in two HAE type III patients.

In oestrogen-dependent HAE or type III HAE, the mainstay of treatment is the avoidance of oral contra-

ceptives. Pregnant patients represent an important problem. Androgens are contraindicated because they interfere with the sexual maturation of the foetus. Anti-fibrinolytics are also contraindicated because of their prothrombotic effect.

In conclusion, according to the characteristics of their clinical picture, familiar history and the association with oestrogen level increase, we believe that the above-reported patients are cases of oestrogen-dependent HAE with normal C1INH. Although it has been possible to define important aspects of this entity, many questions remain unanswered, especially regarding the underlying genetic heterogeneity, the physiopathological mechanisms and the specific treatment.

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