Hereditary Angioedema With Normal C1 Inhibition

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Until recently, it was assumed that hereditary angioedema was a disease resulting exclusively from a genetic deficiency of the C1 inhibitor. In 2000, families with hereditary angioedema, normal C1 inhibitor activity, and protein in plasma were described. Since then, numerous patients and families with this condition have been reported. Most of the patients were women. In many of the affected women, oral contraceptives, hormone replacement therapy containing estrogens, and pregnancies triggered the clinical symptoms. In some families, mutations in the coagulation factor XII (Hageman factor) gene were detected in the affected persons.

Introduction

Until recently, hereditary angioedema (HAE) was considered a disease resulting exclusively from a genetic deficiency of the C1 inhibitor (C1-INH). In 1985, this author observed a large family in which five women suffered from recurrent angioedema of the skin associated with relapsing episodes of abdominal pain attacks and episodes of upper airway obstruction. Surprisingly, all of the women had normal C1-INH function. One of the family members had asphyxiated secondary to sudden laryngeal edema. Since then, this author has paid special attention to similar patients. In 2000, 10 families with this disease were described [1]. In these families, a total of 36 women, but not a single man, were affected. All patients had normal C1-INH concentration and activity with respect to C1 esterase inhibition, ruling out both types of HAE (HAE type I and HAE type II). We proposed to call this hitherto unknown disease *hereditary angioedema with normal C1 inhibitor occurring mainly in women* or *hereditary angioedema type III*. However, we were aware that this denomination (HAE type III) might be a generic diagnosis and turn out to include various clinicogenetic entities. Subsequently, two additional families were described, with seven affected women in one family and four in the other [2,3]. Recently, clinical data on an additional 29 women with HAE type III were presented [4]. Because all 76 patients from the studies cited above were women, it was assumed that the clinical phenotype might be limited to the female sex. However, in 2006 we described a family with dominantly inherited angioedema and normal C1-INH, in which not only five female but also three male family members were clinically affected [5]. Later on, a number of patients with HAE type III were reported [6,7,8•,9,10].

In 2001, this author initiated a microsatellite scan of the total genome (performed by Dr. C. Hennies, Max-Delbrück Center, Berlin, Germany) in four of the HAE type III families, which revealed major linkage signals for chromosomes 6 and 16 but not for chromosome 5 (unpublished data). By following a functional hypothesis that the genetic defect might be located in the coagulation factor XII (FXII) gene, we selectively investigated the FXII gene on chromosome 5 [11•]. In May 2006, we identified the causative genetic mutations in six index patients of 20 families and in 22 patients of the corresponding six families: two different missense mutations have been verified, which were responsible for the disease according to the cosegregation pattern (see below) [11•]. The location of these mutations is the same locus, 5q33-qter of the Hageman factor or coagulation FXII gene (Online Mendelian Inheritance in Man, #610619). One mutation leads to a threonine-to-lysine substitution (Thr309Lys) and the other to a threonine-to-arginine substitution (Thr309Arg). The mutations were located on the exon 9. In our investigation, we also found that the index patients of 14 other families with HAE and normal C1-INH did not show these mutations (see below) [11•].

Because the two mutations in the FXII gene could be found only in some families with HAE III and not in others, we now use the following classification of HAE:

- HAE-C1-INH: hereditary angioedema due to a genetic C1-INH deficiency (with a subtype I and a subtype II; numerous mutations)
- HAE-FXII: hereditary angioedema due to the two known mutations in the coagulation FXII gene
- HAE-unknown: hereditary angioedema with an unknown genetic cause (normal C1-INH activity in plasma; no causative mutation in the gene

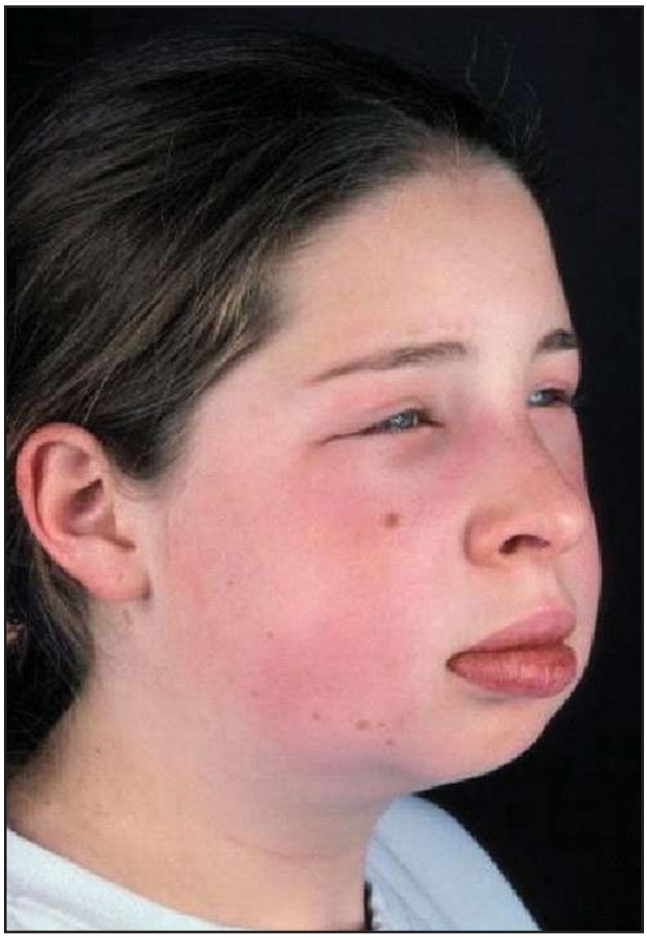

Figure 1. Facial swelling in a patient with hereditary angioedema due to the Thr309Lys mutation in the FXII gene.

coding for C1-INH; none of the known FXII gene mutations Thr309Lys or Thr309Arg)

HAE-FXII and HAE-unknown constitute the group of "HAE with normal C1-INH" or "HAE type III."

Clinical Presentation

Clinical symptoms

The clinical symptoms of HAE with normal C1-INH include the following: recurrent skin swellings (Fig. 1), abdominal pain attacks, tongue swellings, and laryngeal edema. Until now, only a relatively small number of patients and families have been described. In 2000, we reported that 36 patients exhibited relapsing skin swellings and/or attacks of abdominal pain and/or recurrent laryngeal edema [1]. Urticaria did not occur at any time in any of these patients. The skin swellings lasted 2 to 5 days; they affected mainly the extremities and the face, and the trunk less frequently. The abdominal attacks likewise lasted 2 to 5 days and were manifested as severe, cramp-like pains. In a more recent study, a total of 138 patients with HAE with normal C1-INH who belonged to 43 unrelated families were examined [12•]. A majority of patients had skin swellings (92.8%), tongue swellings (53.6%), and abdominal pain attacks (50%). Laryngeal edema (25.4%) and uvular edema (21.7%) also were frequent, whereas edema episodes of other organs were rare (3.6%). Facial swellings and tongue involvement occurred considerably more frequently compared with HAE-C1-INH. The number of patients with recurrent edema of only one organ was higher than in patients with HAE-C1-INH. Erythema marginatum was not observed. Hence, HAE with normal C1-INH levels shows a characteristic pattern of clinical symptoms. There are many differences in the clinical symptoms and course of disease between this type of HAE and the classic type of HAE, HAE-C1-INH (Table 1).

The clinical manifestation of HAE type III is highly variable, and penetrance of the disease may be low; thus, we have observed obligate female carriers, even in their seventh decade, without any clinical symptoms [1,4]. Therefore, a considerable number of asymptomatic carriers may exist in the population.

Death by asphyxiation due to upper airway obstruction

In our patient series described in 2007, one female asphyxiated at the age of 16 during her first laryngeal edema attack [12•]. A second female asphyxiated at the age of 36 after 10 episodes of upper airway obstruction, a third at the age of 38 during her eighth airway attack, and a fourth at the age of 48 after a tongue swelling.

Onset of clinical symptoms

In our series of 138 patients, the mean age at onset of the disease was 26.8 years (SD ± 14.9 years; range 1–68 years) [12•]. Onset of clinical symptoms occurred in the first decade of life in 11 (8%) patients, in the second decade in 60 (43.5%) patients, in the third decade in 22 (15.9%) patients, and later in 45 (32.6%) patients. Hence, the number of patients with disease onset in adulthood was significantly higher in HAE with normal C1-INH compared with HAE-C1-INH.

Potentially Provoking Factors

Role of estrogens

In many women, clinical symptoms either begin or are exacerbated following the intake of oral contraceptives or hormone replacement therapy, or during pregnancy [1–4]. This observation has led to the assumption that the clinical manifestation of this new type of HAE is estrogen-dependent. Binkley and Davis [2,13] observed patients with typical symptoms of recurrent angioedema that were restricted to conditions of high estrogen levels, and thereby created the conception of an "estrogen-dependent" or "estrogen-associated" HAE. However, in an analysis of 228 angioedema patients receiving oral contraceptives or hormone replacement therapy, it was demonstrated that in only 24 of 39 women (62%) with HAE type III were the clinical symptoms induced or exacerbated after starting oral contraceptives or hormone replacement therapy; correspondingly, 15 of 39 women (38%) tolerated exogenous estrogens without any influence on their disease [4]. Almost identical numbers were observed with respect to women diagnosed

Table 1. Features of hereditary angioedema with normal C1-INH that serve to differentiate it from hereditary angioedema due to C1-INH deficiency

Patients have normal C1-INH protein and activity
Mostly women are clinically affected
The number of children already affected before the age of 10 years is low; clinical symptoms start in adulthood in more patients
There are more disease-free intervals during the course of the disease
Symptoms are less frequent
Facial swellings, mainly lip swellings, are relatively more frequent
The tongue is considerably more often affected; recurrent tongue swelling is observed in many patients and is a cardinal symptom of the condition
Many patients have only skin swellings
Many patients have only recurrent skin swellings and tongue swellings
Abdominal attacks are less frequent
Suffocation may be preceded and caused by a tongue swelling
There is no erythema marginatum (gyrated erythematous rash), which is highly characteristic of HAE due to C1-INH deficiency
Hemorrhages into skin swellings were observed in hereditary angioedema with normal C1-INH

C1-INH—C1 inhibitor; HAE—hereditary angioedema.

with HAE-C1-INH. These results show that estrogens play a role in both conditions, and that the negative influence of estrogens is not a specific sign for HAE type III.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors are associated with the occurrence of angioedema in about 0.7% of individuals who receive this medication [14,15]. It has been reported that angiotensin-converting enzyme inhibitors can induce an exacerbation of symptoms in patients with HAE-C1-INH [16]. We observed a 60-year-old man from a family with HAE with normal C1-INH who has had arterial hypertension since age 30 and had four tongue swellings following treatments with captopril and enalapril [5]. The last episode occurred when the patient received only hydrochlorothiazide and metoprolol. The patient has not exhibited other symptoms of HAE. Our observation demonstrates that angiotensin-converting enzyme inhibitors may have a trigger function with regard to HAE type III. HAE type III shares this feature with HAE-C1-INH. This state of affairs points to an important role of bradykinin in the pathogenesis of HAE type III (see below).

Angiotensin II type 1 receptor antagonists

Two unrelated patients with preexisting HAE type III were described who experienced severe exacerbation of symptoms associated with using angiotensin II type 1 receptor antagonists [17]. A possible pathogenetic relationship between the underlying disease and the drug-associated angioedema was suggested.

Gender

The disease has been observed predominantly in women [1–4,11•,12•]. In two families, however, the existence of clinically unaffected male carriers has been deduced [2,3]. In 2006, we described a family with dominantly inherited angioedema and normal C1 inhibitor activity in which not only five female but also three male family members were clinically affected [5]. Later, more male patients with HAE III were reported, among them were patients with HAE-FXII [8•,12•]. The familial angioedema observed by Gupta et al. [18] in three brothers appears to be an HAE with normal C1-INH in men; however, a possibly recessive inheritance pattern and a favorable response to treatment with antihistamines may indicate that the condition of the three brothers is different from that of the family we observed [5]. In a study of 25 patients with idiopathic nonhistaminergic angioedema, Cicardi et al. [19] noted that four of these patients had affected relatives. In at least three of these families, all affected individuals were male.

Inheritance

Within the 43 families described in 2007 [12•], between two and 10 members per family were affected. The examination of the pedigrees of the 43 families revealed that two successive generations were affected in 30 families, three successive generations were affected in nine families, and four successive generations were affected in four families. These results support the assumption of a dominant inheritance pattern.

Genetic Results

Normal C1-INH activity and C4 in plasma were found in all patients; therefore, right from the beginning it seemed to be improbable that the cause of the disease would be a mutation in the C1-INH gene. Binkley and Davis [2] found no abnormalities in either the 5′ regulatory region or the coding sequences of the C1-INH gene in affected individuals. In

four of our affected patients, we also looked for mutations in the C1-INH gene and found none. Binkley and Davis [2] also sequenced the *5′* regulatory region of the FXII gene because it contains a known estrogen-response element. However, they found no abnormalities in that region.

As previously mentioned, a recent genetic examination revealed new insight into HAE type III [11•]. We hypothesized that an abnormal coagulation FXII molecule may lead to inappropriate activation of the kinin-forming cascade, of which FXII is a major constituent [20]. Therefore, we performed a search for mutations in the FXII (Hageman factor; *F12*) gene and studied 20 unrelated patients, all female and of German origin [11•]. All patients had experienced recurrent angioedema attacks, had one or more affected relatives (also exclusively women), and showed normal C1-INH measurements. For several of these index patients, various numbers of family members could be included in the study.

The 14 exons and splice junctions of the *F12* gene were screened in 20 unrelated patients by polymerase chain reaction amplification and bidirectional sequencing [21]. Aside from several known polymorphic variants, two different nonconservative missense mutations were identified in exons [9]. Both mutations are located in exactly the same position, namely in the second position of the codon (ACG) encoding amino acid residue 309 of the mature protein, a threonine residue. "Mutation 1" (1032C→A), encountered in five unrelated patients, results in an AAG triplet encoding a lysine residue (Thr309Lys). "Mutation 2" (1032C→G), observed in one patient, predicts a threonine-to-arginine substitution (Thr309Arg). Thus, with respect to both mutations, the wild-type threonine residue is substituted by a basic amino acid residue. In accordance with the dominant inheritance pattern of the disease, patients are heterozygous for the respective mutations.

Neither of the two mutations was detected in 145 healthy control individuals in this control panel. Thus, missense mutations affecting Thr309 were seen in six of 20 patients, but in none of 145 controls ($P = 0.0000015$; Fisher's exact test).

In six of the 20 families, 20 individuals, all female, were clinically diagnosed with HAE with normal C1-INH. All of these women were found to be heterozygous carriers of either the Thr309Lys or the Thr309Arg mutation. Two additional women carried the Thr309Lys mutation but have not experienced any angioedema symptoms as of yet. Finally, there were eight male heterozygous carriers of a missense mutation of Thr309, all symptom-free [11•]. More recently, one of these mutations (Thr309Lys) has been reported in additional patients with HAE with normal C1-INH activity, each in one family [6,7,8•,22].

Potential Pathogenetic Mechanisms

Genetics

The results of our molecular genetic investigation revealed that HAE type III is not a homogeneous disease entity. Mutations in the *F12* gene were found in six families; however, the index patients of 14 other families did not show such mutations [11•]. In the six families, the mutations of the *F12* gene were present in all affected women, in none of the men, and in some of the nonaffected women (in whom clinical symptoms may occur in the future). These results show that HAE with normal C1-INH (HAE type III) includes two or more conditions with different genetic causes. We assume a genetic heterogeneity in patients with HAE with normal C1 inhibitor. One of these conditions, "hereditary angioedema with coagulation FXII gene mutations and normal C1 inhibitor" (HAE-FXII), now has been identified [11•].

Regarding both the patients and families in whom the present mutation screen remained negative, future studies will have to examine whether mutations eventually will be located within the noncoding regions of *F12* or whether other gene loci are involved.

Potential role of FXII gene mutations in HAE-FXII

The predicted structural and functional impact of the mutations in the FXII gene, their absence in healthy controls, and their cosegregation with the phenotype all provide strong support for the idea that these mutations cause disease. The remarkable observations that 1) two different mutations seen in patients but not controls both affect the identical DNA position, and 2) both lead to substitution of the wild-type threonine residue by a positively charged residue, lend further support to the assumption that these mutations play a disease-causing role.

It is not clear how the mutations in the FXII gene cause HAE-FXII (ie, the tendency to develop recurrent and self-limiting edema attacks in various organs). There are several arguments for the assumption that the kallikrein-kinin system (KKS), also known as the *contact system* or *contact activation system*, may be involved in the pathogenesis: 1) the causative mutations are in the FXII gene, and FXII is part of KKS; 2) KKS activation with the release of bradykinin at the end of the cascade is known to cause the acute attacks of HAE due to C1-INH deficiency; and 3) corticosteroids and antihistamines are therapeutically ineffective for the treatment of swelling in HAE-FXII; therefore, histamine does not seem to play a major role in HAE-FXII.

Coagulation FXII is a serine protease circulating in human plasma as a single-chain inactive zymogen at a concentration of approximately 30 μg/mL [20–24]. Upon contact with negatively charged surfaces, FXII is activated by autoactivation and by plasma kallikrein, which itself is generated from prekallikrein by activated FXII, high-molecular-weight kininogen serving as a cofactor for reciprocal activation of FXII and prekallikrein. FXII is a typical mosaic protein: following a leader peptide of 19 residues, the mature plasma protein consists of 596 amino acids and is organized in an N-terminal fibronectin type-II domain, followed by an epidermal growth factor–like domain, a fibronectin type-I domain, another epidermal growth factor–like domain, a kringle domain, a proline-rich region, and the C-terminal catalytic serine protease domain [23]. The

amino acid substitutions that we described are located in the poorly characterized proline-rich region of FXII [11•]. This region appears to play some role in the binding of FXII to negatively charged surfaces [24,25]. Thus, one may speculate that those mutations may influence mechanisms of contact activation and may eventually inappropriately facilitate FXII activation.

A recent report of patients with HAE-FXII demonstrated a more than fourfold increase in FXIIa amidolytic activity on S-2302 compared with healthy controls [6]. The increased enzymatic activity was blocked completely by H-D-Pro-Phe-Arg-chloromethylketone (PCK), and the report stated that PCK specifically inhibited FXII activation in human plasma. Based on these findings, it was suggested that the FXII Thr309Lys mutation (referred to as Thr328Lys by adding the leader protein) is a gain-of-function mutation that markedly increases FXII amidolytic activity but does not alter FXII plasma levels [6]. In a more recent study, elements of the KKS (contact system) and the downstream-linked coagulation, complement, and fibrinolytic systems in the plasma of six patients with HAE caused by the Thr309Lys mutation and healthy probands were examined [26]. The mean FXII clotting activity was 90% in patients with the FXII mutation and the concentration of FXIIa was 4.1 ng/mL; this did not differ from healthy probands. Mean prekallikrein amidolytic activity and high-molecular-weight kininogen clotting activity were 130% and 144%, respectively, both higher than in healthy probands. The mean kallikrein-like activity of the HAE patients was 11.4 U/L and did not differ from the healthy probands. There was no difference in FXII surface activation by silicon dioxide or in kallikrein-like activity with and without activation by dextran sulfate. Contrary to the results of the study mentioned before [6], no indication that the Thr309Lys mutation causes a gain-of-function of FXIIa was observed in this investigation. Hence, the functional role of the observed FXII gene mutations in HAE III still remains unclear.

Possible mediator responsible for angioedema formation

The mediator responsible for edema formation in HAE type III is not known. However, consider the following facts: 1) there are many similarities concerning clinical symptoms of hereditary angioedema types I and III; 2) the percentages of women whose disease is negatively affected by estrogen-containing medications are similar in both conditions; 3) angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists may lead to an increase in frequency and severity of attacks in HAE type III (according to the observations mentioned earlier) similar to HAE due to C1 inhibitor deficiency (HAE type I and II); and 4) the response to antihistamines and corticosteroids is lacking, at least in the patients reported up to now. These facts permit the speculation that edema formation in HAE type III also may be related to the kinin pathway. It is possible that bradykinin is the most important mediator in HAE type III, similar to HAE type I and II.

Diagnosis

Until now, the clinical diagnosis of "hereditary angioedema with normal C1 inhibitor" has required that patients have the above-mentioned clinical symptoms, one or more family members also affected with these symptoms, the exclusion of familial and hereditary chronic urticaria with urticaria-associated angioedema, and normal C1-INH activity and protein in plasma. The diagnosis "hereditary angioedema with coagulation factor XII gene mutation" (HAE-FXII) requires the corresponding demonstration of the mutation.

Management

Danazol

One of our patients with HAE-FXII had frequent skin swellings and abdominal pain attacks and received a daily, oral dose of 100-mg danazol. Under this treatment, the patient became symptom-free for 9 years. Then the treatment with danazol was discontinued in order to see whether the patient could do without it. Two weeks later, an exacerbation with skin swellings and bowel angioedema occurred. Therefore, treatment with danazol was resumed 4 weeks later; the symptoms have not recurred since then (7 years as of now). Another patient received 100-mg danazol per day for 2 weeks and then 200 mg daily for an additional 4 months without any therapeutic effect [1]. Martin et al. [3] reported one patient whose symptoms improved when she was treated with danazol, 200 mg, every other day. The dosage was progressively tapered to 200 mg per week without relapse after 2.5 years. Herrmann et al. [27] described a 31-year-old woman who suffered from HAE with normal C1 inhibitor. They initially treated the patient with 600-mg danazol daily. No further attacks occurred subsequently; the dosage of danazol was reduced at 2-week intervals to 100 mg daily and then over subsequent weeks to 50 mg twice weekly. At the latter dose, the patient has been free of symptoms for more than 2 years. Side effects included an initial weight gain of around 8 kg, a mild papulopustulous acne, and amenorrhea.

Corticosteroids and antihistamines

In 23 of our patients, previous edema attacks had been treated by antihistamines and corticosteroids (at a dosage of 100–250 mg one or more times daily). This treatment was ineffective in all 23 cases [1]. Likewise, the patients cited by Herrmann et al. [27] and Serrano et al. [10] did not respond to corticosteroids and antihistamines.

Other types of treatment

The experience with C1-INH concentrate or the antifibrinolytic agent tranexamic acid published until now is limited to a few patients, with contradictory results. Presently, the bradykinin B2 receptor antagonist icatibant and the kallikrein inhibitor DX88 (ecallantide) have not been used in HAE type III.

Conclusions

HAE with normal C1-INH occurs mainly in women and shows a characteristic pattern of clinical symptoms. The main clinical features include skin swellings, tongue swellings, and abdominal pain attacks. There are many differences in the clinical symptoms and course of disease between this type of HAE and classic HAE due to a genetic C1-INH deficiency. In some families with HAE and normal C1-INH, mutations in the FXII gene have been found in the affected patients. The cosegregation of those mutations with the disease phenotype demonstrates the causative role of the mutations. The influence of estrogens in HAE with normal C1-INH may be great but is highly variable. Diverse treatment options are available. Treatment with danazol was effective in some women. The mechanism is unclear because C1-INH activity in plasma is normal.

Disclosure

No potential conflict of interest relevant to this article was reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bork K, Barnstedt SE, Koch P, Traupe H: **Hereditary angioedema with normal C1-inhibitor activity in women.** *Lancet* 2000, **356:**213–217.
2. Binkley KE, Davis A 3rd: **Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema.** *J Allergy Clin Immunol* 2000, **106:**546–550.
3. Martin L, Degenne D, Toutain A, et al.: **Hereditary angioedema type III: an additional French pedigree with autosomal dominant transmission.** *J Allergy Clin Immunol* 2001, **107:**747–748.
4. Bork K, Fischer B, Dewald G: **Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy.** *Am J Med* 2003, **114:**294–298.
5. Bork K, Gul D, Dewald G: **Hereditary angio-oedema with normal C1 inhibitor in a family with affected women and men.** *Br J Dermatol* 2006, **154:**542–545.
6. Cichon S, Martin L, Hennies HC, et al.: **Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III.** *Am J Hum Genet* 2006, **79:**1098–1104.
7. Bouillet L, Ponard D, Rousset H, et al.: **A case of hereditary angio-oedema type III presenting with C1-inhibitor cleavage and a missense mutation in the F12 gene.** *Br J Dermatol* 2007, **156:**1063–1065.
8. • Martin L, Raison-Peyron N, Nothen MM, et al.: **Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene.** *J Allergy Clin Immunol* 2007, **120:**975–977.

A man with clinical symptoms of hereditary angioedema and the p.Thr328Lys mutation in the *F12* gene is described in this article. All patients reported earlier were females.

9. Fiz Matias J, Ferrer Ceron SM, Garcia Perez C, Marcos Vidal JM: **Analgesia obstetrica en un caso de edema angioneurotico hereditario tipo III.** *Rev Esp Anestesiol Reanim* 2007, **54:**253–254.
10. Serrano C, Guilarte M, Tella R, et al.: **Oestrogen-dependent hereditary angio-oedema with normal C1 inhibitor: description of six new cases and review of pathogenic mechanisms and treatment.** *Allergy* 2008, **63:**735–741.
11. • Dewald G, Bork K: **Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor.** *Biochem Biophys Res Commun* 2006, **343:**1286–1289.

This was the initial report about the detection of mutations in the factor XII gene in patients with hereditary angioedema with normal C1 inhibitor. The mutations were found in 22 women from six families. The cosegregation of those mutations with the disease phenotype was shown.

12. • Bork K, Gul D, Hardt J, Dewald G: **Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course.** *Am J Med* 2007, **120:**987–992.

Clinical features of hereditary angioedema with normal C1 inhibitor are described extensively in this study.

13. Binkley KE, Davis AE 3rd: **Estrogen-dependent inherited angioedema.** *Transfus Apher Sci* 2003, **29:**215–219.
14. Sabroe RA, Black AK: **Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema.** *Br J Dermatol* 1997, **136:**153–158.
15. Vleeming W, van Amsterdam JG, Stricker BH, de Wildt DJ: **ACE inhibitor-induced angioedema. Incidence, prevention and management.** *Drug Saf* 1998, **18:**171–188.
16. Agostoni A, Cicardi M: **Contraindications to the use of ace inhibitors in patients with C1 esterase inhibitor deficiency.** *Am J Med* 1991, **90:**278.
17. Bork K, Dewald G: **Hereditary angioedema type III, angioedema associated with angiotensin II receptor antagonists, and female sex.** *Am J Med* 2004, **116:**644–645.
18. Gupta S, Yu F, Klaustermeyer WB: **New-variant hereditary angioedema in three brothers with normal C1 esterase inhibitor level and function.** *Allergy* 2004, **59:**557–558.
19. Cicardi M, Bergamaschini L, Zingale LC, et al.: **Idiopathic nonhistaminergic angioedema.** *Am J Med* 1999, **106:**650–654.
20. Kaplan AP, Joseph K, Shibayama Y, et al.: **The intrinsic coagulation/kinin-forming cascade: assembly in plasma and cell surfaces in inflammation.** *Adv Immunol* 1997, **66:**225–272.
21. Cool DE, MacGillivray RT: **Characterization of the human blood coagulation factor XII gene. Intron/exon gene organization and analysis of the 5'-flanking region.** *J Biol Chem* 1987, **262:**13662–13673.
22. Bell CG, Kwan E, Nolan RC, Baumgart KW: **First molecular confirmation of an Australian case of type III hereditary angioedema.** *Pathology* 2008, **40:**82–83.
23. Cool DE, Edgell CJ, Louie GV, et al.: **Characterization of human blood coagulation factor XII cDNA. Prediction of the primary structure of factor XII and the tertiary structure of beta-factor XIIa.** *J Biol Chem* 1985, **260:**13666–13676.
24. Citarella F, Aiuti A, La Porta C, et al.: **Control of human coagulation by recombinant serine proteases. Blood clotting is activated by recombinant factor XII deleted of five regulatory domains.** *Eur J Biochem* 1992, **208:**23–30.
25. Citarella F, Ravon DM, Pascucci B, et al.: **Structure/function analysis of human factor XII using recombinant deletion mutants. Evidence for an additional region involved in the binding to negatively charged surfaces.** *Eur J Biochem* 1996, **238:**240–249.
26. Bork K, Kleist R, Hardt J, Witzke G: **Kallikrein-kinin system and fibrinolysis in hereditary angioedema due to the factor XII gene mutation Thr309Lys.** *Blood Coagul Fibrinolysis* 2009 (in press).
27. Herrmann G, Schneider L, Krieg T, et al.: **Efficacy of danazol treatment in a patient with the new variant of hereditary angio-oedema (HAE III).** *Br J Dermatol* 2004, **150:**157–158.