

Hereditary Angioedema with Normal C1 Inhibitor

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KEYWORDS

- Hereditary angioedema with normal C1 inhibitor • Hereditary angioedema type III
- Coagulation factor XII • Kallikrein-kinin pathway • Mutations in the *F12* gene

KEY POINTS

- A hereditary angioedema with normal C1 inhibitor (HAE type III) should be considered if 2 or more patients per family with recurrent angioedema and normal C1 inhibitor are identified.
- The disease affects mostly women, mainly in high estrogen states, like intake of oral contraceptives and pregnancy.
- Two subgroups of hereditary angioedema with normal C1 inhibitor can be differentiated, one with a mutation in the gene encoding coagulation factor XII (HAE-FXII) and one without such a mutation (HAE-unknown).
- Hereditary angioedema with normal C1 inhibitor has an autosomal-dominant inheritance.

INTRODUCTION

Hereditary angioedema (HAE) is characterized by recurrent edema episodes in various organs, leading predominantly to skin swellings, abdominal pain attacks, and potentially life-threatening laryngeal edema. Until recently, it was assumed that HAE constitutes a single disease entity and that all patients have a genetically determined deficiency of C1-esterase inhibitor (C1-INH) due to mutations in the gene coding for C1-INH. In acute attacks in patients with HAE due to C1-INH deficiency (HAE-C1-INH), the kallikrein-kinin system (KKS) is activated, with production of bradykinin at the end of the cascade. The coagulation factor FXII (Hageman factor) is assumed to play a central role in early activation steps of the KKS.

In 2000, a novel type of HAE was described that was not associated with C1-INH deficiency and occurred mainly in women.¹ Ten families with this disease were reported. In these families a total of 36 women, but not one man, were affected with recurrent angioedema. 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

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HAE type II).¹ In the same year, an additional family was described, with 7 affected women.^{2,3} This hitherto unknown disease was proposed to be termed as “hereditary angioedema with normal C1 inhibitor” (HAEnCI) or “hereditary angioedema type III”.¹ In a recent consensus of an international expert panel it was recommended to use the name “hereditary angioedema with normal C1-INH”.⁴ HAEnCI is autosomally inherited with incomplete phenotypical penetrance.¹

In 2006, 2 different missense mutations in a nonconservative gene region were identified in German patients, located in exon 9 of the gene coding for the coagulation factor XII (Hageman factor).⁵ The point mutations c.1032C>A (p.Thr328Lys) (old nomenclature: p.Thr309Lys) were observed in 5 unrelated families and the mutations c.1032C>G (p.Thr328Arg) (old nomenclature: p.Thr309Arg) were observed in one family. In 2011 a further HAE mutation was identified, a large deletion of 72 base pairs (c.971_1018+24del72).⁶

Until now, numerous families have been reported that include members having HAE with normal C1-INH, with affected women bearing these mutations (**Table 1**).

In most families with HAEnCI patients, a mutation in the *F12* gene could not be found. The author have proposed the name “HAE-unknown” for this variant of disease.⁷ Therefore 2 subgroups of HAEnCI can be differentiated, HAEnCI with one of the 3 known mutations in the coagulation factor XII gene (HAE-FXII) and HAEnCI without a mutation in the *F12* gene (HAE-unknown) (**Box 1**).

CLINICAL PRESENTATION

Clinical Symptoms

The clinical symptoms of HAEnCI include recurrent skin swellings, abdominal pain attacks, tongue swellings, and laryngeal edema. In 2000, it was reported that 36 patients had 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 affected the trunk less frequently. The abdominal attacks likewise lasted 2 to 5 days and were manifested as severe cramplike pains. In a more recent study, a total of 138 patients with HAEnCI who belonged to 43 unrelated families were examined.⁸ Most 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 HAE-C1-INH. Erythema marginatum was not observed. Hence, HAEnCI shows a characteristic pattern of clinical symptoms. There are many differences in the clinical symptoms and course of disease between HAEnCI and HAE-C1-INH (**Box 2**).

The clinical manifestation of HAEnCI is highly variable, and penetrance of the disease might be low; thus, obligate female carriers, even in their seventh decade, without any clinical symptoms were observed.^{1,9} Therefore, a considerable number of asymptomatic carriers may exist in the population.

Death by asphyxiation due to upper airway obstruction

In a patient series described in 2007,⁸ one woman asphyxiated at the age of 16 during her first laryngeal edema attack. A second woman 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.

Table 1

Hereditary angioedema with mutations in the coagulation factor XII gene: Number of families reported until now, mutations, and gender of patients

	Reported Families with HAE-FXII	Families with the p.Thr328Lys Mutation in the Factor XII Gene	Families with the p.Thr328Arg Mutation in the Factor XII Gene	Families with the Deletion Mutation in the Factor XII Gene	Number of Women Clinically Affected with HAE-FXII	Number of Men Clinically Affected with HAE-FXII
Dewald & Bork, ⁵ 2006	6	5	1	0	23	0
Cichon et al, ¹⁸ 2006	1	1	0	0	4	0
Bouillet et al, ¹⁹ 2007	1	1	0	0	2	0
Martin et al, ¹⁶ 2007	1	1	0	0	2	2
Bell et al, ²⁰ 2008	1	1	0	0	1	0
Prieto et al, ²¹ 2009	1	1	0	0	4	0
Duan et al, ²² 2009	1	1	0	0	7	0
Nagy et al, ²³ 2009	1	1	0	0	3	0
Hentges et al, ²⁴ 2009	1	1	0	0	2	0
Bork et al, ⁷ 2009, further families	7	6	1	0	30	0
Picone et al, ²⁵ 2010	2	2	0	0	3	0
Vitrat-Hincky et al, ²⁶ 2010	3	3	0	0	6 (?)	0 (?)
Baeza et al, ²⁷ 2011	1	1	0	0	3	0
Bork et al, ⁶ 2011	1	0	0	1	2	0
Marcos et al, ¹⁷ 2012	13	13	0	0	26	3

Box 1**Classification of hereditary angioedema**

- I. Hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH)
 - A. Type I (low C1 inhibitor activity and concentration in plasma)
 - B. Type II (low C1 inhibitor activity but normal or increased C1 inhibitor concentration in plasma)
- II. Hereditary angioedema with normal C1 inhibitor (HAEnCI, HAE type III)
 - A. Hereditary angioedema with one of the known mutations in exon 9/intron 9 of the coagulation factor XII gene (Thr328Lys or Thr328Arg or the large deletion) (HAE-FXII)
 - B. Hereditary angioedema without one of the known mutations in exon 9/intron 9 of the coagulation factor XII gene (HAE-unknown)

Onset of clinical symptoms

In a series of 138 patients, the mean age at onset of the disease was 26.8 years ($SD \pm 14.9$ years, range 1–68 years).⁸ 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 HAEnCI compared with HAE-C1-INH.

Box 2**Features of hereditary angioedema with normal C1-INH that serves to differentiate it from hereditary angioedema due to C1-INH deficiency**

- Patients have normal C1-INH protein and activity.
- Mainly 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 than in hereditary angioedema because of C1-INH deficiency.
- There are more disease-free intervals during the course of the disease.
- Symptoms are less frequent compared with hereditary angioedema because of C1-INH deficiency.
- Facial swellings, mainly lip swellings, are relatively more frequent.
- The tongue is considerably more often affected: Recurrent tongue swelling is more common than in HAE because of C1-INH deficiency.
- 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) as is highly characteristic of HAE because of C1-INH deficiency.
- Hemorrhages into skin swellings were observed in hereditary angioedema with normal C1-INH.

POTENTIALLY PROVOKING FACTORS

Role of Estrogens

In many women clinical symptoms either begin or are exacerbated after the intake of oral contraceptives (OC) or hormone replacement therapy (HRT) or during pregnancy.^{1–3,9} Binkley and Davis^{2,10} observed patients with typical symptoms of recurrent angioedema that were restricted to conditions of high estrogen levels (estrogen-dependent HAE). However, in an analysis of 228 angioedema patients receiving OC or HRT, it was demonstrated that in only 24 (62%) of 39 women with HAE_{EnCI} were the clinical symptoms induced or exacerbated after starting OCs or HRT; correspondingly, 15 (38%) of 39 women tolerated exogenous estrogens without any influence on their disease.⁹ It was shown that estrogens play a considerable role in most women with HAE-FXII.⁷ However, the influence of estrogens is variable (**Table 2**). The negative influence of estrogens is also well known in HAE-C1-INH and, therefore, not a specific sign for HAE_{EnCI}.

The reason for the negative impact of estrogens in HAE-FXII remains unclear. Binkley and Davis² also sequenced the 5' regulatory region of factor XII gene because it contains a known estrogen response element. However, they found no abnormalities in that region in families with the p.Thr328Arg mutation in the factor XII gene.

Angiotensin-Converting Enzyme Inhibitors

It is well known that angiotensin-converting enzyme inhibitors (ACE-I) are associated with the occurrence of angioedema in about 0.7% of individuals who receive this medication.^{11,12} It has been reported that ACE-I can induce an exacerbation of symptoms in patients with HAE-C1-INH.¹³ A 60-year-old man from a family with HAE_{EnCI} was reported who has had arterial hypertension since age 30 and had 4 tongue swellings following treatments with captopril and enalapril.¹⁴ The last episode occurred when the patient received only hydrochlorothiazide and metoprolol. The patient has had no other symptoms of HAE. Two further patients with an exacerbation of HAE_{EnCI} after commencing ACE-I intake have been reported.⁷ These observations demonstrate that ACE-I might have a trigger function with regard to HAE_{EnCI}. HAE_{EnCI} shares this feature with HAE-C1-INH. This state of affairs points to an important role of bradykinin in the pathogenesis of HAE_{EnCI}.

Angiotensin II Type 1 Receptor Antagonists

Two unrelated patients with preexisting HAE_{EnCI} were described who experienced severe exacerbation of symptoms associated with using angiotensin II type 1 receptor

Table 2
Influence of OC, pregnancies, and HRT on HAE-FXII in 35 women

	Intake of OC, n (%)	Pregnancy, n (%)	Receiving HRT, n (%)
Induction of the first clinical symptoms of HAE-FXII	17 (63.0)	3 (12)	0 (0)
Exacerbation of the preexisting symptomatic HAE-FXII	8 (29.6)	7 (28)	3 (42.9)
No influence	2 (7.4)	10 (40)	4 (57.1)
Improvement of symptoms	0 (0)	5 (20)	0 (0)
Total	27 (100)	25 (100)	7 (100)

Data from Bork K, Wulff K, Hardt J, et al. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 2009;124:129–34.

antagonists (ARB).¹⁵ A possible pathogenetic relationship between the underlying disease and the drug-associated angioedema was suggested.

GENDER

The disease has been observed predominantly in women.^{1–3,5,8,9} In 2 families, however, the existence of clinically unaffected male carriers has been deduced.^{2,3} In 2006 a family with dominantly inherited angioedema and normal C1 inhibitor was described in which not only 5 female but also 3 male family members were clinically affected.¹⁴ Later additional male patients with HAE_{NCI} were reported, among them also patients with HAE-FXII.^{8,16,17}

INHERITANCE

Within the 43 families described in 2007,⁸ between 2 and 10 members per family were affected. The examination of the pedigrees of the 43 families revealed that 2 successive generations were affected in 30 families, 3 successive generations were affected in 9 families, and 4 successive generations were affected in 4 families. These results support the assumption that HAE_{NCI} is autosomally inherited with incomplete phenotypical penetrance.¹ An autosomal-dominant inheritance was also shown in HAE-FXII.⁷

GENETIC RESULTS

In 2001 the author of this article initiated a microsatellite scan of the total genome (performed by Dr C. Hennies, Max-Delbrück Center, Berlin) in 4 HAE_{NCI} families that revealed major linkage signals for chromosomes 6 and 16 but not for chromosome 5 (Hennies C, personal communication, 2003). By following a functional hypothesis that the genetic defect might be located in the gene encoding the coagulation factor XII (F12) gene, the *F12* gene on chromosome 5 was then selectively investigated.⁵ In May 2006, genetic mutations in 6 index patients of 20 families and in 22 patients of the corresponding 6 families were identified: 2 different missense mutations have been verified that were assumed to be responsible for the disease according to the cosegregation pattern.⁵ The location of these mutations is the same locus, 5q33-qter of the Hageman factor or coagulation FXII gene (Online Mendelian Inheritance in Man no. 610619). Both mutations are located in exactly the same position, namely, in the second position of the codon (ACG) encoding amino acid residue 328 (or, if the leader peptide of FXII is not included in the numbering of amino acids, 309) of the mature protein, a threonine residue. One mutation leads to a threonine-to-lysine substitution (p.Thr328Lys), and the other to a threonine-to-arginine substitution (p.Thr328Arg). The mutations were located on exon 9. It was also found that the index patients of 14 further families with HAE and normal C1-INH did not show these mutations.⁵ In accordance with the dominant inheritance pattern of the disease, patients were heterozygous for the respective mutations. Neither of the 2 mutations was detected in 145 healthy control individuals in this control panel. In 6 of the 20 families, 20 individuals, all female, were clinically diagnosed with HAE_{NCI}. All these 20 women were found to be heterozygous carriers of either the Thr328Lys or the Thr328Arg mutation. Two additional women carried the Thr328Lys mutation but have not experienced any angioedema symptoms until now. Finally, there were 8 male heterozygous carriers of a missense mutation of Thr328, all symptom-free.⁵

Until now, the Thr328Lys mutation has been reported in numerous families (see **Box 2**).^{5,7,16–27} The Thr328Arg mutation has been described only twice, both families coming from the patient series of Mainz.^{5,7}

In 2011, a novel mutation, the deletion of 72 base pairs (c.971_1018+24del72), was identified in 3 members of a family originating from Turkey. The family included 2 sisters having HAE_nCI and their symptom-free father displaying the same mutation (**Fig. 1**). The deletion started at c.971A (coding p.Lys324) in exon 9 and finished 24 base pairs downstream of intron 9. In the mutant *F12* alleles, the authentic donor splice site of exon 9 was deleted. The *F12* gene deletion was located in the gene region coding the proline-rich region of the FXII protein, which comprises the amino acids 315 to 368.

The novel mutation (ie, the deletion of c.971_1018+24del72) was heterozygous in the *F12* gene of the 2 sisters and their symptom-free father. All other members of this family were symptom-free and did not have the *F12* deletion. Three *F12* gene

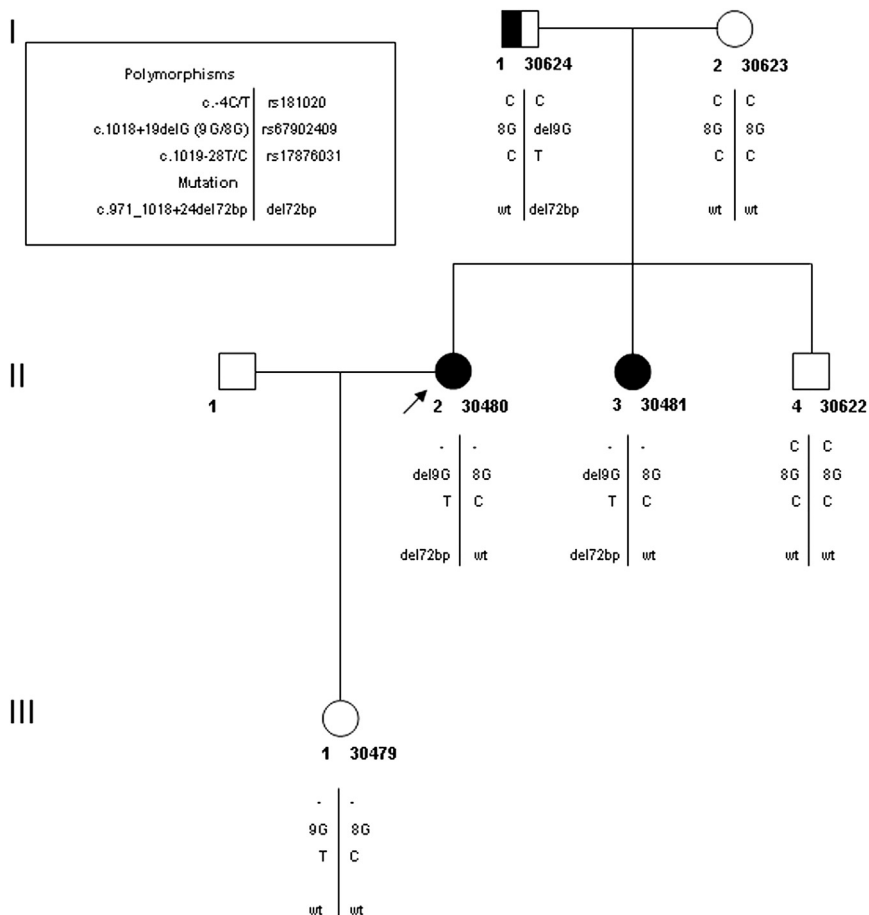


Fig. 1. Pedigree of a family with hereditary angioedema with normal C1-inhibitor. Results of the *F12* mutation analysis and the haplotypes using three *F12* gene polymorphisms are presented. Filled symbols, heterozygous deletion carrier with symptoms of angioedema; half-filled symbol, symptom-free heterozygous deletion carrier; unfilled symbols, symptom-free, without the *F12* deletion. (Data from Bork K, Wulff K, Meinke P, et al. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. Clin Immunol 2011;141:31–5.)

polymorphisms were used for haplotyping of the mutant alleles (see **Fig. 1**). The DNA region of the polymorphism c.1018+18delG (rs67902409) in intron 9 was involved in the deletion. As expected, the haplotype of the novel *F12* deletion allele was different from the haplotype of the well-known HAE-FXII allele p.Lys328.^{5,18}

The deletion of c.971_1018+24del72 was not present in the 183 control subjects (366 independent chromosomes) comprising 84 male and 99 female subjects.

In **Fig. 2**, the FXII protein domains are presented with localization of the novel and the previously described *F12* gene mutations in the proline-rich region.

C1-INH activity and C4 in plasma were normal in most patients and slightly decreased in a small proportion of patients.^{7,8,17,26} Therefore, right from the beginning, in the year 2000, it seemed to be improbable that the cause of the disease would be a mutation in the C1-INH gene. Binkley and Davis² found no abnormalities in either the 5' regulatory region or the coding sequences of the C1-INH gene in affected individuals.

In most families with HAE_{EnCI} patients, a mutation in the *F12* gene could not be found. The author proposed the name "HAE-unknown" for this variant of disease.⁷

POTENTIAL ROLE OF THE MUTATIONS IN THE *F12* GENE IN HAE-FXII

The predicted structural and functional impact of the mutations in the *F12* gene, their absence in healthy controls, and their co-segregation with the phenotype in women provide strong support for the idea that these mutations cause disease. The remarkable observations that (1) 3 different mutations seen in patients but not controls; they affect the identical DNA position, and (2) all 3 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 *F12* gene could 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 KKS, also known as the "contact system" or "contact activation system," might 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-C1-INH; (3) icatibant, a bradykinin B2 receptor antagonist, is effective in acute attacks of HAE_{EnCI}; and (4) 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 factor XII is a serine protease circulating in human plasma as a single-chain inactive zymogen at a concentration of approximately 30 µg/mL.²⁸⁻³¹ On contact with negatively charged surfaces, factor XII is activated by autoactivation and by plasma kallikrein, which itself is generated from prekallikrein by activated factor XII, high-molecular weight kininogen serving as a cofactor for reciprocal activation of factor XII, and prekallikrein. Factor XII, prekallikrein and high molecular weight kininogen form the KKS or "contact" system. Factor XII can be activated by negatively charged surfaces. In addition factor XII can be activated by activated factor XII (autoactivation). Prekallikrein can be activated to kallikrein by activated factor XII and/or cell-released proteases. Kallikrein splits bradykinin from high molecular weight kininogen. Activated factor XII and kallikrein are inactivated by C1 inhibitor. Factor XII 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.³⁰

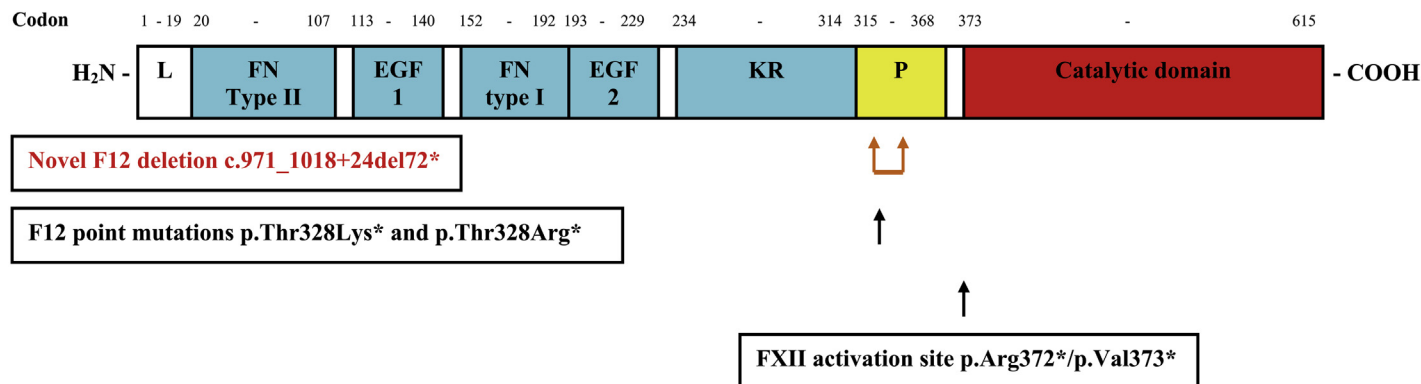


Fig. 2. Schematic presentation of the FXII protein domains with numbering of the amino acids and localization of the novel and previously described *F12* gene mutations in the proline-rich region that differs in HAE-FXII patients (*arrows*). EGF 1 or EGF 2, epidermal growth factor-like 1 or 2 domain; FN type I or FN type II, fibronectin type I or II domain; KR, kringle domain; L, signal or leader peptide; P, proline-rich region; * identify new numbering according to Ensembl. (*Data from* Bork K, Wulff K, Meinke P, et al. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. Clin Immunol 2011;141:31–5.)

The described amino acid substitutions are located in the poorly characterized proline-rich region of factor XII.^{5,6} This region seems to play some role in the binding of factor XII to negatively charged surfaces.^{31,32} Thus, one may speculate that those mutations may influence mechanisms of contact activation and may eventually inappropriately facilitate factor XII activation.

A report of patients with HAE-FXII demonstrated a more than 4-fold increase in FXIIa amidolytic activity on S-2302 compared with healthy controls.¹⁸ The increased enzymatic activity was blocked completely by 2 mM PCK, and the report stated that PCK specifically inhibits FXII activation in human plasma. Based on these findings, it was suggested that the FXII Thr328Lys mutation is a gain-of-function mutation that markedly increases FXII amidolytic activity but that does not alter FXII plasma levels.¹⁸ In a more recent study, elements of the KKS and the downstream-linked coagulation, complement, and fibrinolytic systems in the plasma of 6 patients with HAE-FXII with the Thr328Lys mutation and healthy probands were examined.³³ The mean FXII clotting activity was 90% in patients with the *F12* gene 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-FXII 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 earlier,¹⁸ no indication that the Thr328Lys 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-FXII still remains unclear.

The mediator responsible for edema formation in HAE_{EnCI} is not known. However, consider the following facts: (1) there are many similarities concerning clinical symptoms of HAE-C1-INH and HAE_{EnCI}; (2) in both conditions there is a high percentage of women whose disease is negatively affected by estrogen-containing medications; (3) ACE-I may lead to an increase in frequency and severity of attacks in HAE_{EnCI} similar to HAE-C1-INH (HAE type I and II); and (4) the response to antihistamines and corticosteroids is lacking, at least in the patients reported up until now. These facts permit the speculation that edema formation in HAE_{EnCI} may also be related to the kinin pathway. It is possible that bradykinin is the most important mediator in HAE_{EnCI}, similar to HAE type I and II. This possibility is supported by the efficacy of treatment of HAE_{EnCI} attacks with icatibant, a bradykinin B2 receptor antagonist.

DIAGNOSIS

Up until now the clinical diagnosis of HAE_{EnCI} 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. Until now there was no further laboratory test that could confirm the diagnosis "HAE_{EnCI}."

The question of whether there are sporadic, nonfamilial cases cannot be answered satisfyingly today. For HAE-FXII, a few patients with no further affected family members have been reported.¹⁷ It is not possible to identify sporadic cases of HAE without mutations in the *F12* gene (HAE-unknown) at present because there are no laboratory tests available to confirm the diagnosis of this subtype of HAE_{EnCI}.

DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis of HAE_{NCI} is the other types of recurrent angioedema. Angioedema is a clinical sign that belongs to various clinical entities. Some of them are due to a hereditary or acquired C1-INH deficiency such as HAE types I and II and acquired angioedema due to C1-INH deficiency. Other types are not associated with a C1-INH deficiency. Other than HAE_{NCI}, they include angioedema due to ACE-I and ARB, angioedema associated with an urticaria, allergic or nonallergic angioedema caused by insect stings, food, drugs other than ACE-I and ARB, or certain diseases, and idiopathic angioedema.

MANAGEMENT

Treatment of Acute Attacks

Until now, acute angioedema attacks of HAE_{NCI} were treated with a C1-INH concentrate, icatibant, tranexamic acid, corticosteroids, and antihistamines. In one study, 7 patients with HAE-FXII received a C1-INH concentrate (Berinert, CSL Behring Inc, Marburg, Germany) for 63 angioedema attacks.⁷ One patient who received this agent once for an abdominal attack reported that it was not effective. In the other 6 patients, the agent was very or moderately effective. Several patients with HAE_{NCI} were reported who were treated with icatibant, a bradykinin B2 receptor antagonist used for acute attacks of HAE-C1-INH.^{17,34,35} Time to resolution of symptoms was 1 hour to 6 days. In one attack the symptoms recurred after 6 hours and necessitated a second injection of icatibant. Tranexamic acid was also used for the treatment of acute attacks.¹⁷ Time to first resolution of symptoms ranged from 3 hours to 5 days.

In numerous patients with HAE_{NCI}, angioedema attacks had been treated with corticosteroids and antihistamines (at a dosage of 100–250 mg once or more times daily); however, this treatment was ineffective in all cases.^{1,7,36,37}

Prophylactic Treatment

Progesterone, danazol, and tranexamic acid have been used prophylactically to prevent angioedema attacks.⁷ In one study, 8 patients with HAE-FXII received a progesterone-containing and estrogen-free OC.⁷ Seven of these patients took desogestrel, which is a progestagen, for 1 to 6 years, for a total of 27 years. One of these 7 patients was switched to an implant with etonogestrel for 3 years. The remaining woman received injections of medroxyprogesterone for 3 years. The 8 women were symptom-free during progesterone treatment. One woman with HAE-FXII received danazol (200 mg), an attenuated androgen, daily for 12 years.⁷ While on treatment, she was symptom-free. During these 12 years, she discontinued danazol twice. Each cessation of treatment was followed by a series of severe abdominal attacks, tongue swellings, and skin swellings, and each time the patient resumed treatment. To date, the patient has had no side effects from danazol treatment. A second patient who received danazol (100 mg) daily for 6 years for severe HAE symptoms was also free of symptoms during treatment. The dose was subsequently tapered and discontinued; during the 2 years between discontinuation and the present, no HAE symptoms were observed.⁷ Other studies^{3,37,38} have also shown an improvement in symptoms in patients with HAE_{NCI} during treatment with danazol. One woman with HAE-FXII who started tranexamic acid therapy (4 g/d) has had no attacks with this treatment regimen.⁷ Tranexamic acid was effective or partly effective in long-term prophylaxis in pregnancies.¹⁷

SUMMARY

Hereditary angioedema with normal C1 inhibitor (HAE type III) is clinically characterized by recurrent angioedema affecting the skin, gastrointestinal tract, and larynx. Skin swellings are the most frequent symptoms of HAE type III. Most often they occur on the face, less frequently at the extremities, and only in rare cases at the genitals. Tongue swellings and abdominal pain attacks are less frequent symptoms. Laryngeal edema is rare. Death by asphyxiation as a result of attacks of upper airway obstruction has been observed. Women are more often affected than men. In some women the clinical symptoms of HAE type III occur exclusively in periods of OC, HRT, or pregnancies, indicating that estrogens may have a considerable influence on the phenotypical disease expression. Only limited data on the molecular basis of HAE type III are currently available. In some families with HAE type III, mutations in the *C1INH* gene have been found in the affected patients. The co-segregation of these mutations with the disease phenotype demonstrates the causative role of the mutations. Several treatment options are available for HAE type III, including C1-INH agents, icatibant, progesterone, danazol, and tranexamic acid.

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