

Hereditary Angioedema with Normal C1 Inhibitor Activity Including Hereditary Angioedema with Coagulation Factor XII Gene Mutations

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Recurrent angioedema of the skin is a commonly diagnosed clinical symptom that can be found in various clinical entities [1,2]. Some types of angioedema of the skin are associated with episodes of upper airway obstruction that may be life threatening. Death by asphyxiation from laryngeal edema is well known in hereditary angioedema (HAE) due to C1 inhibitor deficiency [3,4] and in recurrent angioedema induced by angiotensin-converting enzyme (ACE) inhibitors [5–9]. Therefore, it is important to determine the exact type of angioedema in each patient.

In many patients angioedema is associated with urticaria. If relapsing urticaria occurs simultaneously or alternately with angioedema, both conditions are assumed to be symptoms of the same disease. This assumption is true in chronic idiopathic urticaria/angioedema, IgE-mediated reactions (to foods, drugs, insect toxins, and other substances), serum sickness, urticaria/angioedema induced by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDS) or azo dyes and benzoates, and in reactions caused by substances that induce direct histamine release from mast cells.

Recurrent angioedema may occur in patients without urticaria. In these cases various disease entities due to a number of different pathogenetic mechanisms have to be considered. Recurrent angioedema without urticaria can be due to an inherited or acquired C1 inhibitor deficiency [10–13] or may be induced by ACE inhibitors. HAE due to C1 inhibitor deficiency is not associated with urticaria, whereas ACE inhibitors may cause recurrent angioedema alone or in association with urticaria. Other types of angioedema without urticaria

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include local angioedema secondary to physical stress such as vibratory angioedema. A group of patients remains with recurrent angioedema whose clinical symptoms cannot be ascribed to one of these disorders; this type of angioedema is referred to as “idiopathic angioedema” [2,14].

Until recently it was assumed that hereditary angioedema is a disease that results exclusively from a deficiency of the C1 inhibitor. In 1985, the author of this article 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 inhibitor function. One of the family members had asphyxiated secondary to sudden laryngeal edema. Since then the author has paid special attention to similar patients. In 2000, 10 families with this disease were described [15]. In these families a total of 36 women, but not a single man, were affected. All patients had normal C1 inhibitor 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 might 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 [16,17]. Recently, clinical data on an additional 29 women with HAE type III were presented [18]. 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 inhibitor in which not only five female but also three male family members were clinically affected [19].

Our recent results of molecular genetics revealed mutations in the coagulation factor XII (Hageman factor) gene in the affected women in some families with “hereditary angioedema with normal C1 inhibitor” [20]. These patients have “hereditary angioedema with coagulation factor XII gene mutations” and represent a subgroup of “hereditary angioedema with normal C1 inhibitor.” Other patients from additional families (see Genetic results) do not have these mutations; we assume a genetic heterogeneity in patients with “hereditary angioedema with normal C1 inhibitor” [20].

Clinical presentation

Clinical symptoms

The clinical symptoms include 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 or

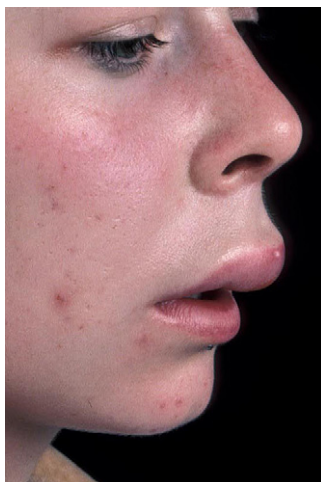


Fig. 1. Lip swelling in a patient with hereditary angioedema with normal C1 inhibitor (HAE type III). This was the third lip swelling during the 1-year-long intake of an oral contraceptive.

attacks of abdominal pain or recurrent laryngeal edema [15]. 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 cramplike pains.

The clinical manifestation of hereditary angioedema type III is highly variable, and penetrance of the disease might be low; thus, we have observed obligate female carriers, even in their seventh decade, without any clinical symptoms [15,18]. 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 2000 [15], one female had asphyxiated at the age of 16 during her first laryngeal edema attack. A second female asphyxiated at the age of 36 after 10 episodes of upper airway obstruction, and a third at the age of 38 during her eighth airway attack.

Onset of clinical symptoms

In our series of 36 patients [15], the onset of clinical symptoms ranged from the 1st to the 63rd year of life. In seven patients from four families, symptoms started before the age of 10 years. In 22 of the 36 females, the clinical symptoms began between the ages of 10 and 23, in 3 between the ages of 30 and 40, and in 4 between 47 and 63 years. In all patients the edema episodes occurred at irregular intervals, in most cases 3 to 12 times a year.

Potentially provoking factors

Exogenous estrogens

Oral contraceptives

In our first study [15], 10 of the 36 women with hereditary angioedema type III took estrogen-containing oral contraceptives and reported either the first appearance of clinical symptoms or a severe exacerbation of the disease in association with this treatment. In one female the skin swelling and abdominal symptoms appeared after starting the intake of oral contraceptives at the age of 18 and continued until the end of her second pregnancy at the age of 27. Since then, the patient has remained symptom-free for more than 15 years. Binkley and Davis reported two women who had swelling episodes after starting oral contraceptives [16]. Clinical symptoms were restricted to the time period of taking oral contraceptives. In the family reported by Martin and colleagues [17], four females had attacks of facial and acral edema, upper airway obstruction, and abdominal pain attacks (partly with ascites) after they took estrogens or during pregnancy. In 2003, data were presented concerning 39 women with HAE type III [18] who received oral contraceptives or estrogen replacement therapy. In 17 of the women, recurrent angioedema occurred for the first time after starting intake of oral contraceptives, and in 5 women a preexistent recurrent angioedema was exacerbated by oral contraceptives.

Estrogen replacement therapy

Binkley and Davis [16] gave an account of three females who had recurrent angioedema after starting estrogen replacement therapy. These females also had clinical symptoms during previous pregnancies but were symptom-free in the interval between pregnancies and onset of estrogen replacement therapy. In 2003, we described one woman from a family with HAE without C1-INH deficiency who experienced her first symptoms after onset of estrogen replacement therapy [18]. Furthermore, we cited three women whose symptoms were exacerbated by estrogen replacement therapy.

Pregnancies

One of our patients had relapsing skin swelling and abdominal pain attacks only during pregnancy. In another patient, skin swelling and abdominal attacks occurred after oral contraceptives were started and continued until the end of her second pregnancy [15]. Binkley and Davis [16] observed two patients who had clinical symptoms exclusively when pregnant. In three other women, symptoms were restricted to the periods of pregnancy and estrogen replacement therapy. Martin and colleagues noted four patients of one family who experienced edema episodes limited to times of oral contraceptive use or pregnancies [17].

Recurrent angioedema in women not taking oral contraceptives, receiving estrogen replacement therapy, or being pregnant

According to our study in 2000 [15], 24 patients in 10 families suffered from recurrent angioedema without receiving exogenous estrogens (oral contraceptives or estrogen replacement therapy) or being pregnant. In the family described by Binkley and Davis [16], all seven affected women reported that their symptoms were restricted to the times of oral contraceptive use, estrogen replacement therapy, or pregnancy. Martin and colleagues reported on one woman who had clinical symptoms without taking oral contraceptives, receiving estrogen replacement therapy, or being pregnant [17]. In a later patient series, we reported that 15 (38%) of 39 patients with HAE type III angioedema received oral contraceptives or estrogen replacement therapy without experiencing angioedema symptoms. A similar percentage (37%) of women receiving hormone therapy without angioedema was demonstrated for patients with HAE type I [18].

Angiotensin-converting enzyme inhibitors

It is well known that ACE inhibitors are associated with the occurrence of angioedema in about 0.7% of individuals who receive this medication [21,22]. It has been reported that ACE inhibitors can induce an exacerbation of symptoms in patients with hereditary angioedema caused by C1 inhibitor deficiency [23]. We observed a 60-year-old man from a family with “hereditary angioedema with normal C1 inhibitor” who has had arterial hypertension since age 30 and was initially treated with hydrochlorothiazide and various β -receptor blockers [19]. The patient had four tongue swellings, one each in 1993, 1995, 1997, and 1999. Each swelling lasted for about 24 hours. Three of the swellings occurred 2 weeks after the patient had started taking a new antihypertensive drug (1993 and 1995, captopril; 1997, enalapril). The last episode, in 1999, occurred during the period from 1997 until now, when the patient received only hydrochlorothiazide and metoprolol. The patient has had no other symptoms of hereditary angioedema. Our observation demonstrates that ACE inhibitors might have a trigger function with regard to hereditary angioedema type III.

Angiotensin II type 1 receptor antagonists

Two unrelated patients with preexisting hereditary angioedema type III were described who experienced severe exacerbation of symptoms associated with using angiotensin II type 1 receptor antagonists [24]. A possible pathogenetic relationship between the underlying disease and the drug-associated angioedema was suggested.

The first patient was a 65-year-old woman, one of seven women in her family with recurrent angioedema and normal C1-inhibitor and C4. From ages 30 to 32 years, she had approximately 50 episodes of abdominal pain. An episode of facial swelling occurred at age 57 and again at age 61.

At age 63 she began treatment with losartan 50 mg/d for hypertension. Six months later she began to experience facial swelling—26 episodes in total within 17 months, with the final episodes occurring every 2 weeks. She received no other medication while taking losartan. After discontinuing losartan the patient has remained symptom-free for the past 18 months.

The second patient was a 70-year-old woman; she, as well as her daughter and granddaughter, had recurrent angioedema with normal C1 inhibitor and C4. Beginning at age 29, she had recurrent swelling of the tongue about five times a year. Approximately 10 episodes of facial swelling occurred from ages 29 to 40 years. At age 69, she began taking 80 mg of valsartan once daily for hypertension without any additional medication. Three weeks after starting treatment with valsartan, her angioedema attacks began to increase in frequency and severity; within the following 7 months, she had 10 episodes of facial swelling and 25 episodes of tongue swelling, 13 of which progressed to laryngeal edema. After discontinuing valsartan the patient has had no further swelling episodes for the past 9 months.

Of all the women reported to have hereditary angioedema type III that the author is aware of, the two patients described here are the only ones who received an angiotensin II receptor antagonist. Thus, these cases may indicate that patients with hereditary angioedema type III are at risk of severe exacerbation of their disease when exposed to this medication.

Laboratory results

In our study of 36 patients with HAE type III, laboratory results from the symptom-free intervals between edema attacks were available for 24 patients [15]. All patients had normal values for C1 inhibitor protein and activity and C4 concentration. In all patients with HAE type III, these tests were repeated two to five times at intervals of at least 2 months, and the results were confirmed consistently. In a subset of patients with HAE type III ($n = 9$), C1q was determined. All values were within normal range. In a further subset of the patients ($n = 14$), a variety of coagulation and fibrinolysis parameters in the symptom-free intervals were evaluated without evidence of activation. Specifically, thromboplastin time, activated partial thromboplastin time, fibrinogen, D-dimer, thrombin antithrombin complex, plasminogen, and antiplasmin plasmin complex were all within the normal range.

Laboratory results recorded from the acute edema episodes were obtained from 4 of the 26 patients originating from four different families. The four patients were tested during a total of eight acute attacks of skin swelling, one patient during an episode of abdominal swelling, and another during two laryngeal edema attacks. All patients had a normal plasma concentration of C1 inhibitor protein (mean 29 mg/dL; normal range (NR) = 15–35 mg/dL) and normal activity of plasma C1 INH (mean 94%; NR = 70%–130%) and C4 (mean 32 mg/dL; NR = 20–50 mg/dL).

Gender

The disease has been observed predominantly by far in women [15–18,20]. Fig. 2 shows a pedigree with affected women in four generations. In two families, however, the existence of clinically unaffected male carriers has been deduced [16,17]. Because all 76 patients from the initial 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 inhibitor in which not only five female but also three male family members were clinically affected [19]. Fig. 3 shows the family pedigree in which eight affected members are present in four successive generations. Laboratory results for five patients demonstrated normal values for C1 inhibitor activity and protein and C4 in plasma. Two of the three affected men have already died; however, reliable information about their clinical symptoms has been obtained through several other family members. The third affected man had three attacks when he was taking ACE inhibitors and one attack without such medication. Concerning the role of hormone medications, the initial manifestation of one woman's disease occurred 4 weeks after starting an oral contraceptive, whereas in another woman a remarkable improvement of symptoms was observed after she changed from an estrogen-containing contraceptive pill to a pill containing only a progestin.

In this family [19], women and men were clinically affected by recurrent angioedema. The familial angioedema observed by Gupta and colleagues

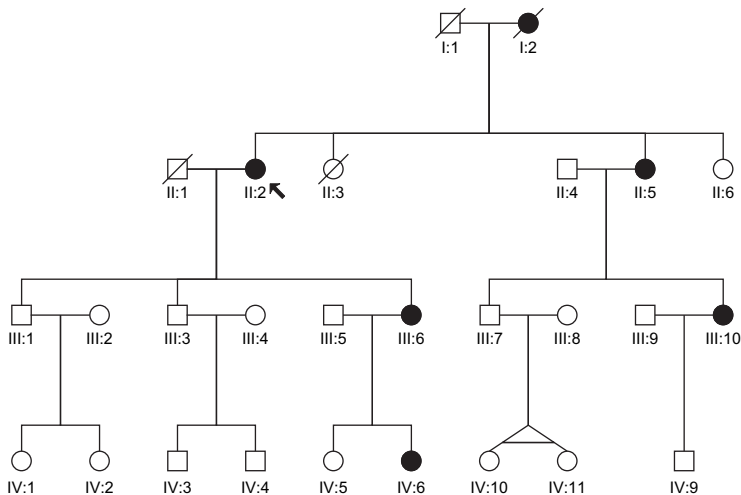


Fig. 2. Pedigree of a family with hereditary angioedema with normal C1 inhibitor. Six women from four generations are or were affected. The index patient is indicated by an arrow. ●, affected female; ○, unaffected female; □, unaffected male; ■, affected male; Slashed line, deceased family member.

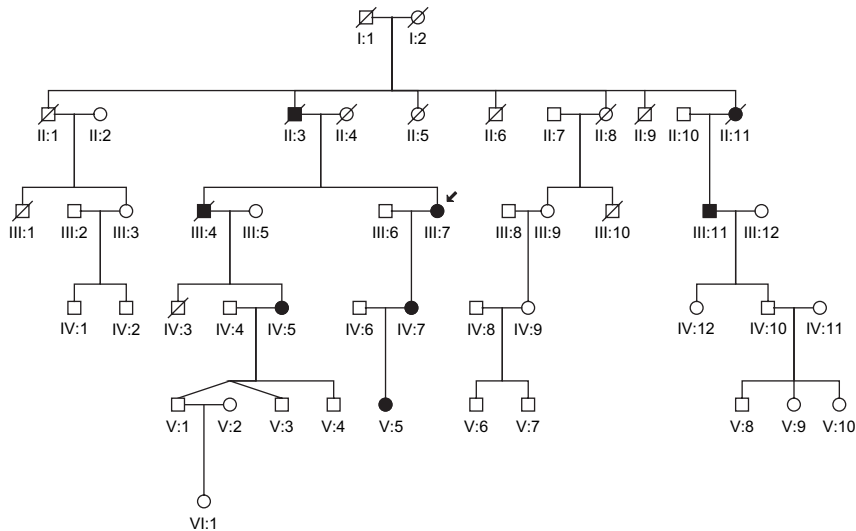


Fig. 3. Pedigree of a four-generation family with dominantly inherited angioedema with normal C1 inhibitor in which not only five females but also three male family members were clinically affected. The index patient is indicated by an arrow. ●, affected female; ○, unaffected female; □, unaffected male; ■, affected male; Slashed line, deceased family member.

[25] in three brothers appears to be HAE with normal C1 inhibitor in men; however, a possibly recessive inheritance pattern and a favorable response to treatment with antihistamines may indicate that the three brothers' condition is different from that of the family we observed [19]. In a study of 25 patients with idiopathic nonhistaminergic angioedema, Cicardi and colleagues [14] mentioned that four of these patients had affected relatives. In at least three of these families, all affected individuals were male. It is possible that these observations may be related to the type of HAE described in our family [19].

Inheritance

Within the families described in 2000 [15], between two and seven members per family were affected. In five families the disease had occurred in three successive generations and in the other five families in two successive generations. In two families we noted skipping, ie, one woman in each family transmitted the disease to offspring but showed no symptoms herself. When analyzing offspring of affected mothers including the last, often still disease-free generation, we counted in the pedigrees 27 males, 23 affected women and 17 unaffected women, resulting in a sex ratio (M:F) of 1:1.48. The presence of the disease in successive generations and the apparent male-to-male transmission [17] clearly favor the assumption of an autosomal dominant inheritance.

Genetic results

Normal C1 inhibitor 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 inhibitor gene. Binkley and Davis [16] found no abnormalities in either the 5' regulatory region or the coding sequences of the C1 inhibitor gene in affected individuals. In four of our affected patients we also looked for mutations in the C1 inhibitor gene and did not find any. Binkley and Davis 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.

A recent genetic examination revealed new insight into HAE type III [20]. We hypothesized that an abnormal coagulation factor XII molecule may lead to inappropriate activation of the kinin-forming cascade of which factor XII is a major constituent [26]. Therefore, we performed a search for mutations in the factor XII (hageman factor) (*F12*) gene [20].

We studied 20 unrelated patients, all female and of German origin. All patients had experienced recurrent angioedema attacks, had one or more affected relatives (also exclusively women), and showed normal C1 inhibitor 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 [27] were screened in 20 unrelated patients by polymerase chain reaction (PCR) amplification and bi-directional sequencing. Aside from several known polymorphic variants, two different nonconservative missense mutations were identified in exon 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 6 of 20 patients, but in none of 145 controls ($P = .0000015$; Fisher's exact test).

In 6 of the 20 families, 23 individuals, all female, were clinically diagnosed with "hereditary angioedema with normal C1 inhibitor." Twenty-two of these women could be examined and 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 up to now. Finally, there were eight male heterozygous carriers of a missense mutation of Thr309, all symptom-free [20].

Potential pathogenetic mechanisms

Hereditary angioedema type III is a rare disease that is characterized by recurrent angioedema and occurs mainly in women. It is not associated with a deficiency of C1 inhibitor activity.

Genetics

The results of our recent 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 [20]. In the six families, the mutations of the *F12* gene were present in all affected women, in some of the men, and in some of the non-affected women (in whom clinical symptoms might occur in the future).

These results show that “hereditary angioedema with normal C1 inhibitor occurring mainly in women” (HAE type III) includes two or more conditions with different genetic causes. One of these conditions, “hereditary angioedema with coagulation factor XII gene mutations and normal C1 inhibitor,” now has been identified [20].

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.

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 [27–29]. Upon 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 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 [28]. The amino acid substitutions described here are located in the poorly characterized proline-rich region of factor XII. This region appears to play some role in the binding of factor XII to negatively charged surfaces [29,30]. Thus, one may speculate that the mutations described by us [20] may influence mechanisms of contact activation and may eventually inappropriately facilitate factor XII activation.

The present findings are expected to have an immediate impact on the diagnostic evaluation and management of patients with recurrent angioedema but normal C1 inhibitor. Further studies will address, for example, the functional consequences of the described mutations, in particular with respect to kinin formation, the hormonal influence on trait expression, and the

assumed genetic heterogeneity of hereditary angioedema with normal C1 inhibitor.

Reduced penetrance and sex-limited manifestation are well in agreement with previous clinical and pedigree observations [15,16]. It is known that the severity of clinical manifestation of hereditary angioedema with normal C1 inhibitor can vary widely, and that a large number of patients experience onset of symptoms only at an advanced age [15]. Thus, it seems possible that the two female mutation carriers mentioned above (their present ages being 16 years and 43 years, respectively) will still develop angioedema-related symptoms in the future.

Our data [20] demonstrate for the first time a highly significant relationship between a distinct human pathology—namely “hereditary angioedema with normal C1 inhibitor”—and mutations of the coagulation factor XII gene.

The predicted structural and functional impact of the mutations, 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.

Possible mediator responsible for angioedema formation

The mediator responsible for edema formation in hereditary angioedema 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 is similar in both conditions; (3) ACE 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 above) 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 hereditary angioedema type III may also be related to the kinin pathway. It is possible that bradykinin is the most important mediator in HAE type III, similar to HAE types I and II.

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. This observation has led to the assumption that the

clinical manifestation of this new type of hereditary angioedema is estrogen-dependent. Binkley and Davis observed patients with typical symptoms of recurrent angioedema that were restricted to conditions of high estrogen levels; Binkley and Davis thereby created the (misleading) conception of an “estrogen-dependent” or “estrogen-associated” HAE [16,31,32]. In a recent analysis of 228 angioedema patients receiving oral contraceptives or hormone replacement therapy, it was demonstrated that in only 24 (62%) of 39 women with hereditary angioedema type III were the clinical symptoms induced or exacerbated after starting oral contraceptives or hormone replacement therapy; correspondingly, 15 (38%) of 39 women tolerated exogenous estrogens without any influence on their disease [18]. Almost identical numbers were observed with respect to women diagnosed with HAE due to C1 inhibitor deficiency. These results show that estrogens play a similar role in both conditions and that the negative influence of estrogens is not a specific sign for HAE type III [33]. Table 1 reveals, according to the information reported until now, that only in 16 of 81 women affected with HAE type III the attacks occurred exclusively during high estrogen level states ie, during pregnancy, during intake of oral contraceptives, or during estrogen replacement therapy. In the remaining 65 women the attacks occurred either independently of these states or they were present also before or after these states. In some of the patients the disease exacerbated during pregnancy, intake of oral contraceptives, or estrogen replacement therapy. Whether the influence of estrogen-containing oral contraceptives or hormonal

Table 1
Hereditary angioedema type III: Number of affected women reported until now, in whom the attacks occurred exclusively in high-estrogen states, ie, during pregnancy, intake of oral contraceptives, or estrogen replacement therapy

Authors	Reported families with HAE type III	Women affected with HAE type III	Women who had HAE attacks exclusively in high-estrogen states	Families in which all affected women had HAE attacks exclusively in high estrogen states
Bork et al, 2000 [15]	10	36	2	0
Binkley and Davis, 2000 [16]	1	7	7	1
Martin et al, 2001 [17]	1	4	3	0
Bork et al, 2003 [18]	10	29	4	0
Bork et al, 2006 [19]	1	5	0	0
Total	23	81	16	1

replacement therapy on the kinin pathway actually plays a role in favoring angioedema formation in patients with hereditary angioedema is far from being clear today. The observations available until now suggest that even among patients with underlying hereditary angioedema, administration of estrogen does not always result in the appearance or worsening of symptoms. Other factors that might predispose women with angioedema to new or exacerbated symptoms when treated with estrogens could include, for example, a functionally or quantitatively relevant genetic polymorphism in the kinin system. Information about such polymorphisms might be important in identifying women whose angioedema would be aggravated by administration of estrogen-containing medications.

Role of ACE inhibitors and angiotensin II type 1 receptor antagonists

ACE inhibitors and angiotensin II type 1 receptor antagonists may lead to an increase in the frequency and severity of attacks in HAE III, according to the observations mentioned above. Concerning ACE inhibitors, HAE type III shares this feature with HAE due to C1 inhibitor deficiency. This state of affairs points to an important role of bradykinin in the pathogenesis of HAE type III.

Affected males

Our observation of a family with affected women and men [19] can be interpreted in two ways: men, although having the same genetic defect, might have a highly reduced chance for clinical manifestation of angioedema, because of either the lack of female-specific risk factors (for example, estrogen-containing medications or pregnancy) or the presence of male-specific protective factors; eventually, manifestation may need a further triggering factor. Such a factor could be either endogenous—for example, a certain genetic cofactor—or exogenous, such as treatment of hypertension with ACE inhibitors, as in one of the patients [19].

Alternatively, one may speculate that this family represents another disease entity with a different underlying defect, namely hereditary angioedema with normal C1 inhibitor, but not restricted to the female sex. The identification of further underlying molecular defects in this and other families with hereditary angioedema type III will allow researchers to define various potentially existing forms of hereditary angioedema with normal C1 inhibitor.

Diagnosis

Up to 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 inhibitor activity and protein in plasma. The diagnosis “hereditary angioedema with coagulation factor XII gene mutation” requires the corresponding demonstration of the mutation.

Management

Danazol

One of our patients 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 to see whether the patient could do without it. Two weeks later an exacerbation with skin swellings and bowel angioedema occurred. Therefore, 4 weeks later treatment with danazol was resumed; the symptoms have not recurred since then (7 years as of now). Another patient received 100 mg danazol per day for 2 weeks and later on 200 mg daily for an additional 4 months without any therapeutic effect [15]. Martin and colleagues [17] 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/week without relapse after 2.5 years. Herrmann and colleagues [34] 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.

Tranexamic acid

Two patients were treated with the antifibrinolytic agent tranexamic acid, 1 g three times a day for 4 months, without any success [15].

C1 inhibitor concentrate

Four women having 11 episodes of acute laryngeal edema had received 1000-U doses of C1 inhibitor concentrate (Berinert P, ZLB Behring, Germany) [15]. This treatment had proven ineffective.

Corticosteroids and antihistamines

In 23 of our patients, previous edema attacks had been treated by antihistamines and corticosteroids (at a dosage of 100 to 250 mg one or more times daily). This treatment had been ineffective in all 23 cases [15]. Likewise, the patient cited by Herrmann and colleagues did not respond to corticosteroids and antihistamines [34].

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