

BRIEF COMMUNICATION

Treatment for hereditary angioedema with normal C1-INH and specific mutations in the *F12* gene (HAE-FXII)

K. Bork¹, K. Wulff², G. Witzke¹ & J. Hardt³

¹Department of Dermatology, Johannes Gutenberg University, Mainz; ²University Medicine, Ernst Moritz Arndt University, Greifswald;

³Department of Medical Psychology and Medical Sociology, Johannes Gutenberg University, Mainz, Germany

To cite this article: Bork K, Wulff K, Witzke G, Hardt J. Treatment for hereditary angioedema with normal C1-INH and specific mutations in the *F12* gene (HAE-FXII). *Allergy* 2016; DOI: 10.1111/all.13076.

Keywords

hereditary angioedema; hereditary angioedema type III; hereditary angioedema with normal C1 inhibitor; specific mutations in the *F12* gene; treatment.

Correspondence

Konrad Bork, MD, Department of Dermatology, Johannes Gutenberg University, Langenbeckstr. 1, 55131 Mainz, Germany.

Tel.: +49 6131 17 7290

Fax: +49 6131 17 6614

E-mail: bork@hautklinik.klinik.uni-mainz.de

Accepted for publication 31 October 2016

DOI:10.1111/all.13076

Edited by: Werner Aberer

Abstract

Hereditary angioedema with normal C1 esterase inhibitor and mutations in the *F12* gene (HAE-FXII) is associated with skin swellings, abdominal pain attacks, and the risk of asphyxiation due to upper airway obstruction. It occurs nearly exclusively in women. We report our experience treating HAE-FXII with discontinuation of potential trigger factors and drug therapies. The study included 72 patients with HAE-FXII. Potential triggers included estrogen-containing oral contraceptives (eOC), hormonal replacement therapy, or angiotensin-converting enzyme inhibitors. Drug treatment comprised plasma-derived C1 inhibitor (pdC1-INH) for acute swelling attacks and progestins, tranexamic acid, and danazol for the prevention of attacks. Discontinuation of eOC was effective in 25 (89.3%) of 28 women and led to a reduction in the number of attacks (about 90%). After ending hormonal replacement therapy, three of eight women became symptom-free. Three women with exacerbation of HAE-FXII during intake of quinapril or enalapril had no further HAE-FXII attacks after discontinuation of those drugs. Eleven women were treated with pdC1-INH for 143 facial attacks. The duration of the treated facial attacks (mean: 26.6 h; SD: 10.1 h) was significantly shorter than that of the previous 88 untreated facial attacks in the same women (mean: 64.1 h; SD: 28.0 h; $P < 0.01$). The mean reduction in attack frequency was 99.8% under progestins after discontinuing eOC (16 women), 93.8% under tranexamic acid (four women), and 100% under danazol (three women). For patients with HAE-FXII, various treatment options are available which completely or at least partially reduce the number or duration of attacks.

In 2000, a new type of hereditary angioedema was described that was not associated with a deficiency of C1-INH. It was termed 'HAE with normal C1-INH' (HAEnCI) or 'HAE type III' (1). Four different mutations in the gene coding for the factor XII (*F12*) were identified in patients affected with HAEnCI and were assumed to be specific for and involved in the development of angioedema (2–4). This subtype of HAE was termed 'HAEnCI and mutations in the *F12* gene' or 'HAE-FXII' (5).

Data about treatment of patients with HAE-FXII are sparse and comprise only case reports or small case series. This holds true for both on-demand treatment with plasma-derived C1-INH (pdC1-INH) (5–7), icatibant (7–9), tranexamic acid (TXA) (7, 9), and for long-term prevention (LTP) with progestins (5), TXA (5–7, 9–12), and attenuated androgens (1, 11). Death by asphyxiation due to obstruction of the

upper airways has been reported in 2.9% of patients (13). Due to this risk, data about treatment of patients with HAE-FXII are important. The aim of this study was to present which therapeutic measures are helpful in HAE-FXII.

Material and methods

This was an observational study examining various treatments in 72 patients with HAE-FXII coming from 24 unrelated families. Estrogens and angiotensin-converting enzyme inhibitors (ACE-I) seem to increase the number of HAE attacks. The efficacy of discontinuation of such potential trigger factors was determined by an intraindividual comparison of the frequency of attacks under intake and after discontinuation of the agents. In patients having acute facial and abdominal attacks, the efficacy of pdC1-INH was determined

by an intraindividual comparison of the attack duration of treated and untreated attacks. The efficacy of LTP was determined by an intraindividual comparison of the frequency of attacks before and during LTP. Statistics were performed using STATA (version 12, StataCorp, College Station, Texas, USA).

Plasma levels of C1-INH function and protein, C4, and C1q were assayed, and HAE-specific *F12* mutations were identified as described elsewhere (14).

Results

Of 72 HAE-FXII patients, 71 were female (mean age: 48 years) and one was a 10-year-old boy. C1-INH activity was normal or subnormal (mean: 86.6%; SD: 17.7%; normal values (reference range, rr) 70–130%), and C1-INH protein (mean: 25.2 mg/dl; SD: 6.7 mg/dl; rr: 15.5–33.8 mg/dl), C4 (mean: 26.3 mg/dl; SD: 9.7 mg/dl; rr: 16.4–31.3 mg/dl), and C1q (mean: 18.8 mg/dl; SD: 4.4 mg/dl; rr: 10–25 mg/dl) were normal. Mutations in the *F12* gene (p.Thr328Lys in 20 families, p.Thr328Arg, and the large deletion c.971_1018+24del72 each in two families) could be identified in all patients plus in some symptom-free family members.

Of 71, 54 (76.1%) women had taken estrogen-containing oral contraceptives (eOC). During the period of eOC intake, 49 (90.7%) of 54 women had HAE attacks; 28 (57.1%) of 49 women discontinued eOC without any following LTP. After discontinuation, 22 (78.6%) of the 28 women had no further

attacks (attack reduction 100%) and 2 (7.1%) of the remaining women had rare attacks (attack reduction 98.5% and 96.5%). One woman (3.6%) still had further attacks, but the number of attacks was markedly reduced (attack reduction 47.9%). One woman (3.6%) had an attack reduction of only 6.4%, and in two women (7.1%), discontinuation of eOC had no effect. Hence, discontinuation of eOC was effective in 25 (89.3%) of 28 women. Calculated on a per-attack basis, the attack reduction was 87.5% on average.

Eight women had received estrogen-containing hormonal replacement therapy (HRT). After discontinuation, the swelling attacks stopped in three (37.5%) of eight women, continued with a reduced number of attacks in one woman (12.5%), and remained unchanged in four (50%) of eight women. Calculated on a per-attack basis, the attack reduction was 22.2% after discontinuation of HRT.

After symptom-free phases, three women received ACE-I for 3 years, 13 months, and 3 months, respectively, because of arterial hypertension. After starting quinapril, one woman had 14 severe skin and tongue swellings and an upper airway obstruction that required an emergency tracheotomy. Another woman had a series of six tongue swellings within a period of 3 months under quinapril. The third woman had four severe tongue swellings during intake of enalapril. After discontinuation of ACE-I, all three women had no further swelling attacks.

Table 1 shows the efficacy of treatment with pdC1-INH for 145 acute facial and abdominal attacks in 11 patients.

Table 1 Effect of pdC1-INH in 143 facial (patients no. 1–11) and two abdominal (patients no. seven and eight) attacks compared to 108 untreated attacks in the same 11 individuals suffering from HAE-FXII

Patient No.	Untreated attacks* (n)	Mean duration of untreated attacks (h)	Treated attacks (n)	Attacks treated with 500 IU/1000 IU pdC1-INH (n)	Mean time to first symptom relief (h)	Mean duration of treated attacks (h)	Mean shortening of treated vs. untreated attacks (%)	Attacks shortened for >50% (n)	Attacks shortened for 20–50% (n)	Attacks shortened for <20% (n)
Facial attacks										
1	10	36.3	51	49/2	1.1	30.8	15.2	0	0	51
2	10	36.1	1	1/0	1	32	11.4	0	0	1
3	10	120.2	1	1/0	1	6	95	1	0	0
4	7	60.3	1	1/0	0.5	10	83.4	1	0	0
5	10	47.6	35	31/4	1.2	18.4	61.3	35	0	0
6	2	48	1	1/0	1	22	54.2	1	0	0
7	4	25.3	7	7/0	1.1	11	56.5	7	0	0
8	5	84.4	21	19/2	1	24.1	71.4	21	0	0
9	10	83.8	4	4/0	0.5	43	48.7	3	1	0
10	10	64.1	20	17/3	3.6	37.9	40.9	8	12	0
11	10	71.8	1	1/0	1	12	83.3	1	0	0
Abdominal attacks										
7	10	36.4	1	1/0	1	12	67.0	1	0	0
8	10	60.2	1	1/0	1	24	60.1	1	0	0
Total No.	108	–	145	134/11	–	–	–	80	13	52

pdC1-INH, plasma-derived C1-INH; HAE-FXII, hereditary angioedema (HAE) with normal C1-INH and HAE-specific mutation in the *F12* gene.

*Last 10 attacks before treatment or all if <10.

The mean duration of the 143 treated facial attacks (mean: 26.6 h; SD: 10.1 h) was significantly shorter than that of the previous 88 untreated facial attacks (mean: 64.1 h; SD: 28.0 h; $P < 0.01$), and thus, application of pdC1-INH was shortening the facial swellings by 58.5% on average.

Laryngeal attacks were reported by 15 of (20.8%) 72 patients and totaled 82 attacks. Of them, 67 were untreated and lasted for 77.7 h (SD: 19.8 h) on average. The remaining 15 laryngeal attacks were treated and occurred in five patients. Mean duration of treated attacks was 32.4 h (SD: 13.7 h). Time to first relief was 1.3 h (SD: 1.1 h) on average ($P < 0.01$).

Sixteen women discontinued eOC and received progestins for LTP of HAE-FXII and for continuing oral contraception, 15 of them desogestrel (progestin-only pill, POP) and one woman an etonogestrel implant. During this treatment, 15 (93.7%) of 16 women were symptom-free (Table 2). Only one woman had three mild lip swellings during the first month of desogestrel intake. The mean reduction in attack frequency was 99.8% (from 1220 attacks before to three attacks under progestins).

Four women received TXA for an average of 3.5 years having a mean reduction in attack frequency of 93.8%. Three women received danazol for LTP. All women became symptom-free when treated with danazol (attack reduction 100%, see Table 2).

Discussion

In the present study, we could demonstrate various management options effective in most or all patients with HAE-FXII. After discontinuation of eOC, about 90% of women with HAE-FXII had no further attacks reflecting the variations in estrogen impact. Hence, discontinuation of eOC or HRT is the most important and an easy measure among the recommended measures in women with HAE-FXII. Similar results were obtained after discontinuation of ACE-I.

The treatment with pdC1-INH for acute attacks was effective in most patients with HAE-FXII for the majority of attacks. According to our observations, however, the response to pdC1-INH was more variable than in patients with HAE-C1-INH in which treatment with pdC1-INH

Table 2 Attack frequency in women with HAE-FXII before and during long-term prophylaxis with progestins, tranexamic acid, and danazol

Patient No.	Medication	Symptomatic years before LTP (n)	Attacks during symptomatic years before LTP (n)	Years with LTP (n)	Attacks during LTP (n)	Reduction in attack frequency (%)
Progestins*						
2	Desogestrel	15	150	5	0	100
4	Desogestrel	5	126	2	0	100
5	Desogestrel	14	33	1	0	100
7†	Desogestrel	4	29	1	3	58.9
10	Desogestrel	2	97	2	0	100
14	Desogestrel	1	3	3	0	100
15	Desogestrel	5	52	1	0	100
16	Desogestrel	1	12	12	0	100
17	Desogestrel	1	4	7	0	100
18	Desogestrel	12	248	14	0	100
19	Desogestrel	31	180	4	0	100
20	Desogestrel	9	29	4	0	100
21	Desogestrel	10	3	12	0	100
22	Desogestrel	7	94	6	0	100
23†	Desogestrel	1	15	4	0	100
24†	Etonogestrel	4	145	7	0	100
Antifibrinolytics						
3	TXA	13	118	6	10 (mild)	81.3
7	TXA	9	44	3	0	100
11	TXA	6	72	1	3	75
23	TXA	3	105	4	8	94.2
Attenuated androgens‡						
1	Danazol	52	1330	12	0	100
24	Danazol	11	25	6	0	100
25	Danazol	3	28	15	0	100

LTP, long-term prevention; TXA, tranexamic acid.

*After discontinuing estrogen-containing oral contraceptives.

†Patients having received two types of long-term prevention without overlap in time.

‡Dose range 100 mg to 200 mg danazol daily.

usually is promptly and consistently effective (15). Still, pdC1-INH is effective in most patients with HAE-FXII although patients with HAE-FXII have no C1-INH deficiency in plasma during the attack-free interval. A supposed consumption of C1-INH in the beginning of an acute attack in HAE-FXII patients may be an explanation. This consumption might be compensated by treatment with pdC1-INH, at least partially.

Treatment with progestins after discontinuing eOC was highly effective in our patients. However, it is impossible to distinguish the effects between discontinuing eOC and treatment with progestins, here. The effectiveness of progestins is not specific for HAE-FXII, but has also been observed in patients with HAE-C1-INH and idiopathic angioedema (16). The exact mode of action of progestins in those types of angioedema is unknown.

We treated four patients with HAE-FXII with TXA for a total of 14 years and observed a good to excellent efficacy in all patients supporting the assumption that fibrinolysis is involved in the pathogenesis of HAE-FXII. Recently, it has been shown that the plasminogen activator inhibitors 1 and 2 were lower in plasma of some patients with HAE-FXII (13, 17, 18). This decrease might be a sign for complex formation of plasminogen activators with plasminogen activator inhibitors and an indication for plasmin formation and fibrinolysis (19). Plasmin can activate the kallikrein–kinin system and may thus lead to bradykinin formation (20). This activation could be blocked by TXA, partially or completely, and might explain the clinical efficacy of TXA in HAE-FXII.

Danazol belongs to the 17-alpha alkylated androgens that have been effective in HAE-C1-INH. Our results demonstrate a high effectiveness in three patients with HAE-FXII treated for a total of 33 years with danazol.

Up to now, icatibant has been used for the treatment of one laryngeal attack (1/1 patient, effective) (7), abdominal attacks (3/3 patients, effective) (8, 9), and facial swellings (2/3 patients, effective, one patient, not effective) (7, 9).

The main limitation of our study is that it is an uncontrolled observational study. No prospective, randomized placebo-controlled double-blind study has been performed so far in patients having this rare disease. But information about treatment is important to avoid asphyxiation as observed in HAE-FXII and to avoid or mitigate HAE attacks. Given these limitations, the results of the relatively large patient series reported here show that there are various treatment options available which completely or at least partially reduce the symptoms in patients with HAE-FXII.

In sum, we recommend treatment measures for patients with HAE-FXII in the following order: (i) for acute attacks pdC1-INH or icatibant if required; (ii) discontinuation of eOC or HRT; (iii) discontinuation of ACE-I; (iv) intake of progestin (POP) for LTP (as a treatment measure and not only for contraception); (v) Tranexamic acid or danazol for LTP.

Author contributions

KB designed the study, performed data acquisition and analysis, and wrote the manuscript. KW designed the study, interpreted and analyzed the data, and drafted the manuscript. GW performed data analysis and interpretation and drafted the manuscript. JH contributed to conception and design of the study and performed data analysis and interpretation. All authors contributed to drafting the article and revising the manuscript and approved the final version.

Funding

There was no financial support for the study.

Conflicts of interest

Dr. Bork reports consulting fees from CSL Behring and Shire, outside the submitted work. The other authors have no conflicts of interest to disclose.

References

1. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;**356**:213–217.
2. 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.
3. Bork K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. *Clin Immunol* 2011;**141**:31–35.
4. Kiss N, Barabas E, Varnai K, Halasz A, Varga LA, Prohaszka Z et al. Novel duplication in the F12 gene in a patient with recurrent angioedema. *Clin Immunol* 2013;**149**:142–145.
5. Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 2009;**124**:129–134.
6. Bouillet L, Ponard D, Rousset H, Cichon S, Drouet C. A case of hereditary angioedema type III presenting with C1-inhibitor cleavage and a missense mutation in the F12 gene. *Br J Dermatol* 2007;**156**:1063–1065.
7. Marcos C, Lopez Lera A, Varela S, Linares T, Alvarez-Eire MG, Lopez-Trascasa M. Clinical, biochemical, and genetic characterization of type III hereditary angioedema in 13 Northwest Spanish families. *Ann Allergy Asthma Immunol* 2012;**109**:195–200.
8. Bouillet L, Boccon-Gibod I, Ponard D, Drouet C, Cesbron JY, Dumestre-Perard C et al. Bradykinin receptor 2 antagonist (icatibant) for hereditary angioedema type III attacks. *Ann Allergy Asthma Immunol* 2009;**103**:448.
9. Firinu D, Bafunno V, Vecchione G, Barca MP, Manconi PE, Santacroce R et al. Characterization of patients with angioedema without wheals: the importance of F12 gene screening. *Clin Immunol* 2015;**157**:239–248.
10. Martin L, Raison-Peyron N, Nothen MM, Cichon S, Drouet C. 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.
11. Moreno AS, Valle SO, Levy S, Franca AT, Serpa FS, Arcuri HA et al. Coagulation

- factor XII gene mutation in Brazilian families with hereditary angioedema with normal C1 inhibitor. *Int Arch Allergy Immunol* 2015;**166**:114–120.
12. Wintenberger C, Boccon-Gibod I, Launay D, Fain O, Kanny G, Jeandel PY et al. Tranexamic acid as maintenance treatment for non-histaminergic angioedema: analysis of efficacy and safety in 37 patients. *Clin Exp Immunol* 2014;**178**:112–117.
 13. Bork K, Wulff K, Witzke G, Hardt J. Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations. *Allergy* 2015;**70**:1004–1012.
 14. Bork K, Wulff K, Hardt J, Witzke G, Lohse P. Characterization of a partial exon 9/intron 9 deletion in the coagulation factor XII gene (F12) detected in two Turkish families with hereditary angioedema and normal C1 inhibitor. *Haemophilia* 2014;**20**:e372–e375.
 15. Bork K. Pasteurized and nanofiltered, plasma-derived C1 esterase inhibitor concentrate for the treatment of hereditary angioedema. *Immunotherapy* 2014;**6**:533–551.
 16. Saule C, Boccon-Gibod I, Fain O, Kanny G, Plu-Bureau G, Martin L et al. Benefits of progestin contraception in non-allergic angioedema. *Clin Exp Allergy* 2013;**43**:475–482.
 17. Bork K, Kleist R, Hardt J, Witzke G. Kallikrein-kinin system and fibrinolysis in hereditary angioedema due to factor XII gene mutation Thr309Lys. *Blood Coagul Fibrinolysis* 2009;**20**:325–332.
 18. Joseph K, Tholanikunnel BG, Wolf B, Bork K, Kaplan AP. Deficiency of plasminogen activator inhibitor 2 in plasma of patients with hereditary angioedema with normal C1 inhibitor levels. *J Allergy Clin Immunol* 2016;**137**: 1822–1829.
 19. Agren A, Wiman B, Schulman S. Laboratory evidence of hyperfibrinolysis in association with low plasminogen activator inhibitor type 1 activity. *Blood Coagul Fibrinolysis* 2007;**18**:657–660.
 20. Kleniewski J, Blankenship DT, Cardin AD, Donaldson V. Mechanism of enhanced kinin release from high molecular weight kininogen by plasma kallikrein after its exposure to plasmin. *J Lab Clin Med* 1992;**120**:129–139.