

Type III hereditary angio-oedema: clinical and biological features in a French cohort

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angioedema; C1inhibitor; oestrogen; pregnancy.

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Abstract

Background: Hereditary angio-oedema (HAE) has been associated with C1inhibitor deficiency. The first cases of type III HAE were described in patients with normal C1Inh antigenic protein level and function and normal C4 levels in 2000. This finding has been reported mostly in women with a family history and may be influenced by exogenous oestrogen exposure.

Objectives: The purpose of this article is to describe the clinical, biological and genetic characteristics of a French population suffering from type III HAE.

Patients and Methods: We conducted a retrospective analysis of angio-oedema (AE) cases seen in the National Reference Centre of AE between 2000 and 2009.

Results: We found 26 patients (from 15 unrelated families) with type III HAE. All but four were women and presented with typical AE attacks, exacerbated by pregnancy or oral contraceptives containing oestrogens (OC). We also found that 54.5% of women were worsened with oestrogen and 23% were oestrogen dependent. All patients improved on long-term prophylactic tranexamic acid treatment; some acute attacks improved with C1Inh concentrate infusion. All of the patients had normal C1Inh and C4 levels. C1Inh function was also normal, except in women receiving OC or during a pregnancy: transient, moderately low levels (32–74% of the normal range) were found in 18 patients tested (67%). No *SERPINE1* gene mutation was found. Six patients from three unrelated families were heterozygous for an *F12* gene variant.

Conclusion: Diagnosis of type III HAE should be based on clinical (typical attacks, often hormonally influenced), laboratory (normal C1Inh antigenic protein) and genetic (*F12* gene mutation) evidence.

Hereditary angio-oedema (HAE) is a rare disorder characterised by recurrent episodes of localised swelling without urticaria, which may involve the face, extremities or larynx (with a risk of asphyxiation) (1–3). Gastro-intestinal tract involvement leads to recurrent episodes of severe abdominal pain. The main mediator of oedema is bradykinin, because of activation of the kallikrein-kinin system (4, 5). Two genetic forms are well established, both associated with C1inhibitor (C1Inh) abnormalities: type I HAE in which there is reduced production of C1inhibitor and type II HAE which involves functional deficiency (2). These two types refer to a single genetic disease. A new type of HAE has

recently been reported associated with normal C1Inh. Type III HAE was initially described by Bork et al. (6), 'Binkley & Davis' (7) and Martin et al. (8) in 2000–2001 as recurrent angio-oedema (AE) without quantitative or functional C1Inh abnormalities, mostly affecting women, particularly during pregnancy or in those receiving oral contraceptives containing oestrogens (OC). In 2006, Dewald et al. (9) and Cichon et al. (10) identified two missense mutations in the *F12* gene (gene encoding for Hageman factor) associated with type III HAE.

The purpose of this article is to describe the clinical, biological and genetic characteristics of a French population

suffering from type III HAE and to describe the tools available for the diagnosis and treatment strategy for this disease.

Patients and methods

Study design

We conducted a retrospective analysis of AE cases seen in the National Angio-oedema Reference Centre located in Grenoble and Paris, between 2000 and 2009. The patients included had typical recurrent episodes of mucosal or submucosal tissue swelling involving several clinical features including localised oedema lasting at least 24 h without pruritus, at various sites including laryngeal oedema, possibly combined with severe abdominal symptoms (Table 1). To exclude histamine-induced AE, only those patients whose attacks were not improved by adequate corticosteroid therapy (≥ 1 mg/kg oral prednisone or methylprednisolone) and long-term antihistaminergic treatment (3 months) were included. We excluded patients with a history of urticaria or asthma concomitant to the AE. Types I and II HAE and acquired AE were excluded on specific clinical and laboratory grounds. The diagnosis of type III HAE was based on the following criteria:

- Clinical characteristics of AE,
- Corticosteroids ineffective in improving attacks
- Normal antigenic protein level and function of C1Inh.
- Family history (similar cases reported in the family).

We collated clinical data (family history, frequency, duration and site of the attacks, age at onset, oestrogen sensitivity), laboratory results (C1Inh protein antigenic level and function, C4, C3) and genetic investigations (*SERPING1* and *F12* genes) in all those patients. All patients with abdominal attacks had laboratory and radiological investigations to exclude other causes of abdominal emergencies.

Laboratory methods

Laboratory data: complement investigations

C1Inh, C1q, C4 and C3 protein concentrations were assayed by fixed-time nephelometry (BNII; Dade Behring, Liederbach, Germany), and C1Inh function using the chromogenic substrate BAEc (11). When C1Inh function was found to be reduced, the quality of circulating serpin was assessed after anti-C1Inh immunoblot, as described previously (12). Complement haemolytic activity was measured using the conventional CH50 haemolysis time (13).

Table 1 Clinical features of bradykinin-mediated angio-oedema

Recurrent swelling
Absence of urticaria
Circumscribed
Deformed
Duration >24 h
Recurrent abdominal pain
Corticosteroids ineffective in improving an attack
Long term antihistaminergics ineffective in preventing attacks

Genetic investigations

Patients were investigated for *SERPING1* gene mutations by sequencing or multiplex ligation dependant probe amplification (MPLA) methods (14). Two missense mutations in the *F12* gene (p.Thr309Lys and p.Thr309Arg) were screened by bidirectional sequencing (10).

Results

Clinical characteristics

We have seen and studied 26 patients from 15 unrelated families (Table 2). All of the patients had cases suggestive of AE in their family according to the features of type III HAE. The majority were female (22/26, 85%), with only four men affected. All the patients had recurrent episodes of swelling typical of AE, with peripheral skin swelling and facial (18/26, 69%) or laryngeal (58%) attacks. Abdominal involvement was common, 21/26 (81%) of patients having experienced at least one abdominal attack of pain. Attacks occurred at a frequency of twice weekly to once annually and lasted for 48–72 h. Clinical features began in early adulthood in most patients, with a mean age at onset of the disease of 24 (from 3 to 42).

Oestrogen sensitivity

Most of the women (17/22, 77%) reported worsening during pregnancy or with OC. Four of the twenty women who had used OC did not experience any worsening of their disease (two sisters from two unrelated families). The time between starting the OC and the first attack varied from a few months to 8 years. Eleven women had had at least one pregnancy. The disease worsened during pregnancy in five of these women. Four of these women also had attacks with OC (two sisters from two unrelated families). Attacks persisted after stopping oestrogen administration in seven women exposed to exogenous oestrogens.

Five women, belonging to five unrelated families, presented oestrogen-dependent attacks, symptoms only appearing during pregnancy and/or when taking OC. Otherwise these women were asymptomatic.

Complement investigations

All but one of the patients had normal C1Inh antigenic protein levels (Table 3). One woman had a transient moderate fall in C1Inh antigenic protein when taking oestrogen–progestogen contraception. All had normal C4 and C3 levels. C1Inh function was normal in all the patients tested when measured out of a period of oestrogen administration or pregnancy. Twelve of the 18 symptomatic patients tested (67%), however, displayed a moderate transient fall in C1Inh function to between 32% and 74% of normal. Three patients underwent C1Inh function testing during pregnancy: this was reduced in all three. One woman, however, reported fewer attacks during pregnancy. Interestingly, the sister of one patient (2.x) had low C1Inh function (46% of normal)

Table 2 Clinical features of the 26 cases of type III hereditary angio-oedema

	Sex	Familial history cases	Age at onset (years)	Attack duration (h)	Oestrogen sensitivity	Site of attack
1.1	F	Sister, son (1.2)	21	72–96	OC	Limb, face, abdominal attack
1.2	M	Son (1.1)	3	24	NA	Abdominal attack
2.1	F	Sister (2.2)	19	48	OC, PG	Face
2.2	F	Sister (2.1)	18–19	24–48	OC, PG Dependent	Face, abdominal attack
2.x	F	Sister (2.1 and 2.2)	Asymptomatic	Asymptomatic		Asymptomatic
3.1	F	Sister (3.2)	21	96	OC, PG Dependent	Limb, face, abdominal attack
3.2	F	Sister (3.1)	7	96–168	OC, PG	Face, abdominal attack
4.1	F	Grandfather, sister (4.2), aunt (4.3)	22	24–48	None	Limb, face, abdominal attack
4.2	F	Grandfather, sister (4.1), aunt (4.3)	18	24–48	None	Abdominal attack
4.3	F	Aunt (4.1 and 4.2)	Adolescence	24	None	Abdominal attack
5.1	F	Cousin (5.2)	28	24	OC	Abdominal attack
5.2	F	Cousin (5.1)	Childhood	24–48	OC Dependent	Abdominal attack
6.1	F	Son (6.2) and daughter (6.3)	38	24–48	None	Face, abdominal attack
6.2	M	Mother (6.1) and sister (6.3)	40	24	NA	Limb, face
6.3	F	Mother (6.1) and brother (6.2)	Childhood	24	OC Dependent	Abdominal attack
7.1	F	Son (7.2)	42	48	OC	Limb, face
7.2	M	Mother (7.1)	16	48	NA	Face, abdominal attack
8	F	Grandfather, father, aunt, cousin	23	24	OC	Limb, face
9	F	Aunt	38	48	OC	Abdominal attack
10	F	Grandmother and aunt	4	24	None	Abdominal attack
11.1	F	Grandfather, father (11.2), aunt, brother	10	72	OC Dependent	Face, abdominal attack
11.2	M	Father, brother, sister, daughter (11.1), son	40	10–48	NA	Face
12	F	Father	30	48–72	OC	Face, abdominal attack
13	F	Father	41	48–72	OC	Face, abdominal attack, chest
14.1	F	Sister (14.2)	NS	48–72	OC	Face, abdominal attack
14.2	F	Sister (14.1)	NS	48–72	OC	Face, abdominal attack
15	F	2 Sons	Childhood	48–72	PG	Limb, face, abdominal attack

F, female; M, male; NS, not specified; NA, not applicable; OC, oral contraceptives containing oestrogen; PG, pregnancy.

on the contraceptive pill and was entirely asymptomatic (Tables 2 and 3). For patients with functional C1Inh abnormalities, anti-C1Inh immunoblotting revealed spontaneous C1Inh cleavage in 6/8 patients. C1Inh function and anti-C1Inh immunoblotting were normal after stopping the OC pill or on completion of the pregnancy in all but one patient.

Genetic data (Table 3)

All of the patients underwent genetic investigations and had a normal *SERPING1* gene. Six patients (23%) from three unrelated families (20% of the families) had causal mutations in the *F12* gene.

Treatment

As defined by the inclusion criteria, none of the attacks improved with corticosteroids, and antihistaminergic treat-

ments were ineffective as long-term preventative therapy. Tranexamic acid provided effective long-term prophylaxis in all of patients suffering from type III HAE (one gram three times daily, every day). All patients reported at least 50% of reduction in the severity or frequency of the attacks when they were taking tranexamic acid. C1inhibitor concentrate was administered for two cases of severe laryngeal attacks and for three short-term prophylactic treatments for childbirth. All these treatments were successful.

Discussion

Type III HAE was first described as HAE with normal C1Inh only affecting women (6). Since 2000, several authors have reported families suspected of having type III HAE (Table 4) (6–9, 15–18). The clinical characteristics of type III HAE attacks are the same as for types I and II, although Bork et al. suggested that facial swelling occurred considerably more often in type III (15, 18–20). About the effect of

Table 3 Laboratory and genetic features of the 24 cases of type III hereditary angio-oedema

	C1 Inhibitor protein concentration N: 210–345 mg/l	C1 inhibitor functional activity (N: 17.2–27.4 U/ml) (% of normal range) during contraception or pregnancy	C1 inhibitor functional activity (N: 17.2–27.4 U/ml) without exposure to oestrogen	C1Inh Immunoblot with pill or pregnancy
1.1	265	15.8 (71%) during pregnancy	21.9	NA
1.2	367	NA	30.8	NA
2.1	222	Progressive fall during pregnancy until 7.3 (33%)	20.8	Cleaved C1Inh
2.2	238	16.7 (75%)	20	NA
2.x	222	14.5 (50%)		Cleaved C1Inh
3.1	206	14.7 (66%)	23	NA
3.2	239	NA	19.9	NA
4.1	286	7 (30%) with oral contraception, 7.2 (32%) during pregnancy	20.5	Cleaved C1Inh
4.2	280	10.2 (46%)	20.8	Cleaved C1Inh
4.3	254	NA	19	NA
5.1	174 with oral contraception 248 without	11.8 (53%)	20.7	Normal
5.2	225	16.1 (72%)	18.6	Cleaved C1Inh
6.1	310	NA	24.8	NA
6.2	315	NA	27.8	NA
6.3	221	16 (72%)	20	Normal
7.1	346	16.2 (73%)	29.8	Cleaved C1Inh
7.2	212	NA	18.7	NA
8	312	24.1	NA	NA
9	308	25	NA	NA
10	289	25.1	NA	NA
11.1	341	27.7	NA	NA
11.2	281	26.3	NA	NA
12	336	10.9 (49%)	29.6	Cleaved C1Inh
13	216	16.6 (74.6%)	29.6	NA
14.1	236	20.1	NA	NA
14.2	212	17	NA	NA
15	306	NA	22.6	NA

NA, not applicable; C1Inh, C1inhibitor; N, normal.

Table 4 Comparison of the features of the different cases of type III hereditary angio-oedema published in the literature

Author	Binkley (7, 31)	Martin (8, 23)	Bork (18, 19)	Prieto (17)	Serrano (16)	This report
Country	Canadian (Family from Italy)	France	Germany	Spain		France
Year of publication	2000–2009	2001–2007	2007 2009	2009	2007	2009
Number of reported cases	7	7	138 35	4	6	26
Number of symptomatic men	0	1	11 0	0	0	4
Percentage of patients with low C1Inh function (50–80% of NR)	0%	14%	0% 29%	0%	17%	50%
Percentage of oestrogen-dependent patients	100%	40%	NS 30%	100%	100%	50%
Percentage of patients with <i>F12</i> gene mutation	100%	100%	17% 100%	100%	NS	23%

NS, not specified.

oestrogens, AE attacks occurred preferentially in women taking the OC pill or during pregnancy (19–21), they can also develop in men (15). Whilst the attacks appeared to be oestrogen dependent in Binkley's series (in which attacks began in the 15 days following starting oral contraception) (7), they

were only oestrogen sensitive in the cases reported by Bork et al. (6) and Martin et al. (8) (oestrogen exposure could induce attacks but after varying periods of time). Most of the cases in our series are women, 54.5% are oestrogen sensitive and 23% are oestrogen dependent, confirming the potential

involvement of oestrogen, although the time between oestrogen exposure and onset of the disease could vary from a few months to 8 years. There are two possible explanations for the influence of oestrogen on AE attacks: first, oral contraception reduces C1Inh antigenic protein and increases Hageman factor and prekallikrein expression, even in women with no features of AE (21). Secondly, Farsetti et al. (22) found an oestrogen-responsive component in the *F12* gene promoter. Some attacks, however, can even develop in children who are not exposed to oestrogen and in men as recently described by Bork et al. (19) and Martin et al. (23). We found four symptomatic men including a 3-year-old boy with abdominal attacks and the *F12* gene mutation. Oestrogen, therefore, does influence type HAE III attacks although the effect varies greatly between individuals, suggesting that oestrogen could be an adjuvant component of the disease rather than the exclusive cause. In addition, while attacks because of oestrogens are one of the features of type III HAE, this is also seen in types I and II HAE: Bork et al. reported that 63% (20/32 patients) of type I HAE reported a worsening of attacks with oestrogens (contraceptive pill or pregnancy) (24).

Bork et al. first described this new type of HAE with no association with C1Inh deficiency in 2000 (6) and recently published a report on 35 patients with type III HAE associated with the mutations in the factor XII gene (18). Of these patients, 17% had decreased C1Inh function (<70% of the normal range). The report does not specify whether the assays were performed during oestrogen exposure. We reported the case of a single woman with type III HAE and transient C1Inh dysfunction during her pregnancy and with the OC pill (21). We found the same abnormalities in 67% of the women in this series. To determine whether transient C1Inh dysfunction can help to diagnose type III HAE, we would need data from healthy women taking the OC pill or during pregnancy. Indeed, transient and moderate C1Inh dysfunction does not systematically induce AE attacks. In our series, the sister of one symptomatic patient had low C1Inh function (46%) as she was asymptomatic (Tables 2 and 3, patient 2.x). So the only C1Inh decrease is probably not sufficient to diagnose HAE III. On a physiopathology way, other factors such as polymorphisms in the bradykinin receptor or in the contact-system proteins or variations in the kinin catabolism could probably explain the high variation of severity of the disease between individuals (25).

Cichon et al. (10) reported that one of the known mutations was associated with factor XII gain of function. Investigation on the kinin formation could represent a new tool for the diagnosis of type III HAE. Nevertheless, a recent study has reported mean FXII clotting activity and FXIIa concentration to be normal in patients with type III HAE and a known mutation of the *F12* gene. Mean kallikrein-like activity in the HAE patients did not differ from healthy probands (26). Blood samples were taken during the symptom-free period between attacks. The high kinin formation could be directly causative for the attacks and would need to be measured.

Genetic investigations could also help to diagnose type III HAE, particularly when a *F12* gene mutation is found. So

far, two missense mutations have been reported (9). Only 23% of the patients suffering from type III HAE had one of these mutations in our study. This suggests that other, as yet unknown mutations of the *F12* gene or mutations in the genes of other relevant proteins (prekallikrein, etc.), may exist. The percentage of the abnormalities of *F12* gene has been found lower in the present study than usually reported in the literature. This finding is not unexpected as we defined HAE III on clinical data, whereas most of the authors in the literature reported HAE III cases established by the presence of the *F12* gene mutation.

In conclusion, the diagnosis of this new syndrome of type III HAE should be based on clinical, laboratory and genetic evidence:

- First, with exclusion of histaminergic AE on clinical grounds (Table 1) and the ineffectiveness of prophylactic antihistaminergic agents or lack of response of an attack to corticosteroids.
- Secondly, with exclusion of types I and II HAE (C4 or C1Inh are abnormal) and acquired AE, in which C1q, C4 or C1Inh are abnormal.
- Finally, with confirmation of the suspected type III HAE from clinical evidence (influence of oestrogen), laboratory findings (moderate transient fall in C1Inh function) or genetic information (*F12* gene mutation).

There is no consensus for the treatment of type III HAE, which relies on experience with types I and II HAE. Tranexamic acid could be used to prevent (2–3 g/day) or improve (1–2 g/6 h) AE attacks (27, 28). An alternative is danazol, which appears to be more effective in type III HAE according to some authors (3, 25). Because of danazol toxicity and profile tolerance, our experience was essentially based on tranexamic acid treatments. All of the patients in our study improved with tranexamic acid, which was also very well tolerated. Some severe attacks (such as laryngeal or abdominal attacks) may require C1Inh concentrate. We have reported the efficacy of it in the case of one affected woman (21). Bork et al. reported six patients who received C1Inh concentrate for 62 attacks. The treatment was very or moderately effective (18). This could also be helpful in pregnant women preparing for delivery. Finally, the new bradykinin β_2 receptor antagonist (icatibant) may be useful. This has been tested in types I and II HAE in two double-blind, randomised, multicentre, phase 3 trials, FAST 1 and 2 (29). We have found this treatment to be effective in three type III HAE women (30). Nevertheless, the safety and efficacy of icatibant needs to be examined in more patients.

As described earlier, type III HAE diagnosis relies on multiple elements, but there is no specific criterion to establish the HAE III. Further studies will propose the rationale for new tools to develop in the diagnosis of type III HAE such as kinin formation or identification of new mutations in the *F12* gene or in genes encoding pro-proteases of strategic interest (prekallikrein, etc.).

Conflict of interest

There is no conflict of interest.

References

- Cicardi M, Agostoni A. Hereditary angioedema. *N Engl J Med* 1996;**334**:1666–1667.
- Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 2004;**3**(Suppl.):S51–S131.
- Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 2008;**359**:1027–1036.
- Bas M, Adams V, Suvorava T, Niehues T, Hoffmann TK, Kojda G et al. Nonallergic angioedema: role of bradykinin. *Allergy* 2007;**62**:842–856.
- Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A et al. Plasma bradykinin in angio-oedema. *Lancet* 1998;**351**:1693–1697.
- Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;**356**:213–217.
- Binkley KE, Davis A III. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000;**106**:546–550.
- Martin L, Degenne D, Toutain A, Ponard D, Watier H. Hereditary angioedema type III: an additional French pedigree with autosomal dominant transmission. *J Allergy Clin Immunol* 2001;**107**:747–748.
- 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.
- Cichon S, Martin L, Hennies HC, Müller F, Van Driessche K, Karpushova A et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet* 2006;**79**:1098–1104.
- Drouet C, Alibeu C, Ponard D, Arlaud GJ, Colomb MG. A sensitive method to assay blood complement C1-inhibitor activity. *Clin Chim Acta* 1988;**174**:121–130.
- Bouillet L, Ponard D, Drouet C, Jullien D, Massot C. Angioedema and oral contraception. *Dermatology* 2003;**206**:106–109.
- Dumestre-Pérard C, Osmundson J, Lemaire-Vieille C, Thielens N, Grives A, Favier B et al. Activation of classical pathway of complement cascade by soluble oligomers of prion. *Cell Microbiol* 2007;**9**:2870–2879.
- Drouet C, Blanch A, Roche O, Monnier N, Duponchel C, Kalmar L et al. Mutation analysis of the C1INH gene. *J Allergy Clin Immunol* 2004;**114**:S66–S74.
- 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.
- Serrano C, Guilarde M, Tella R, Dalmau G, Bartra J, Gaig P et al. Estrogen-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.
- Prieto A, Tornero P, Rubio M, Fernández-Cruz E, Rodríguez-Sainz C. Missense mutation Thr309Lys in the coagulation factor XII gene in a Spanish family with hereditary angioedema type III. *Allergy* 2009;**64**:284–286.
- 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.
- 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.
- Bork K. Hereditary angioedema with normal c1 inhibition. *Curr Allergy Asthma Rep* 2009;**9**:280–285.
- 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.
- Farsetti A, Misiti S, Citarella F, Felici A, Andreoli M, Fantoni A et al. Molecular basis of estrogen regulation of Hageman factor XII gene expression. *Endocrinology* 1995;**136**:5076–5083.
- 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.
- 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.
- Drouet C, Désormeaux A, Robillard J, Ponard D, Bouillet L, Martin L et al. Metalloproteinase activities in hereditary angioedema: effect of androgen prophylaxis on plasma aminopeptidase P. *J Allergy Clin Immunol* 2008;**121**:429–433.
- 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.
- Cicardi M, Bergamaschini L, Zingale LC, Gioffré D, Agostoni A. Idiopathic non-histaminergic angioedema. *Am J Med* 1999;**106**:650–654.
- Bouillet L, Ponard D, Drouet C, Massot C. Non-histaminic angioedema management: diagnostic and therapeutic interest of tranexamic acid. *Rev Med Interne* 2004;**25**:924–926.
- Deeks ED. Icatibant. *Drugs* 2010;**70**:73–81.
- Bouillet L, Boccon-Gibodi I, Ponard D, Drouet C, Cesbron JY, Dumestre-Pérard C et al. Bradykinin receptor 2 antagonist (Icatibant) for hereditary angioedema type III attacks. *Ann Allergy Asthma Immunol* 2009;**103**:448.
- Duan QL, Binkley K, Rouleau GA. Genetic analysis of Factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. *J Allergy Clin Immunol* 2009;**123**:906–910.