ALLERGY, ASTHMA & CLINICAL IMMUNOLOGY

REVIEW Open Access

# Hereditary angioedema in women

Laurence Bouillet

**Abstract**

Women with hereditary angioedema (HAE) are more likely to be symptomatic that men. Hormonal factors (puberty, contraception, pregnancy,....) play a significant role in the precipitation or worsening of the condition in women. So, combined contraceptive pills are not indicated and progestogen pill must be preferred. During pregnancy, attack rate can increase (38-48% of women). C1Inhibitor concentrate and tranexamic acid can be used during pregnancy. Attenuated androgens for long term prophylaxis are effective but side effects appear more often in female patients. These side effects are dose dependant and can be attenuated by titrating the dose down the lowest effective level.

## Review

Hereditary angioedema (HAE) is inherited in an autosomal dominant manner: consequently both women and men can be affected. However, published series of hereditary angioedema report a clear female predominance (60%) [1,2]. This might be explained by the fact that women are more likely to be symptomatic than men. In HAE associated with C1 Inh deficiency, Professor Bork has shown that women have more clinical episodes than men ($p < 0.02$) [2].

Hormonal factors play a significant role in the precipitation or worsening of the condition in women. There appear to be variation in overall frequency of angioedema symptoms according to the different female life stages of childhood, puberty, menses, pregnancies and menopause. Reports have noted a close relationship between female hormones and angioedema: a mother and her daughter whose HAE-related symptoms appeared to be sex hormone dependent [3]. Their first attack happened around puberty; angioedema worsened premenstrual and when they took combined oral contraceptives. The case of a woman [4] with HAE and Turner's syndrome is also very interesting: starting physiological oestrogen replacement at the age of 34 years old, this woman experienced a worsening both in the severity and in the frequency of angioedema attacks. McGlinchey and al [5] described a patient whose symptoms of HAE emerged after starting hormone replacement therapy (HRT).

Correspondence: lbouillet@chu-grenoble.fr
National French Reference Centre of Angioedema, Internal Medicine Department, Grenoble University Hospital, France

Female sex hormones are known to affect the synthesis of many proteins. In the context of bradykinin mediated angioedema, they act on the kallikrein-kinin system by increasing synthesis of bradykinin. In ovariectomized rats, studies showed that 17β-estradiol increases Hageman factor levels by stimulation of gene transcription [6-9]. This hormone also increases kininogen and kallikrein levels [10]. Additionally oestrogens regulate B2 receptor gene expression and function: the vasodepressor response to bradykinin and the B2 receptor mRNA levels are reduced in ovariectomized rats, and restored by oestrogen substitution [11]. Progesterone does not modify Hageman factor levels but seems to raise kallikrein cDNA levels [12].

In healthy women taking oral contraception, there is an increase of fibrinolytic proteins: elevation of plasmin, factors VII, X, IX and a decrease of plasminogen activator inhibitor (PAI) [12-14]. These effects appear to be oestrogen-dependant [13]. The plasma of these women shows enhanced in vitro fibrinolysis [15]. The contact system is also affected: Hageman factor, prekallikrein, kallikrein and high molecular weight kininogen increase [16-19]. This results in consumption of C1Inh; the decrease of C1Inh levels correlating with the increase in Hageman factor [15,16]. Hormone replacement therapy (HRT) appears to have the same effect, despite lower oestrogen dose: fibrinolytic proteins (plasminogen and tissue-type plasminogen activator) rise, PAI decreases [19-21], Hageman factor, prekallikrein and C3, C4 levels rise [14,20,21]. Moreover, some studies have shown an influence of HRT on the bradykinin system: angiotensin converting enzyme activity decreases whereas bradykinin

levels increase [22-24]. Visy and al [25] measured serum sex hormone levels in 44 females with HAE: they found a positive correlation between the rate of attacks and oestradiol and progesterone levels. However we don't have any information about clinical hormone sensibility women profile in this study.

It is generally accepted that there are distinct patterns of HAE in women. We delineate three of them below:

- Oestrogen dependent: these patients reveal the condition only when they are exposed to the combined contraceptive pill or during pregnancy. They usually have type III HAE.
- Oestrogen sensitive: the symptoms in these subjects are worsened by taking combined contraceptive medication or during pregnancy. Any type of HAE can present in this way.
- Oestrogen-independent: the use of the combined contraceptive pill or pregnancy does not exacerbate the symptoms. These individuals represent a minority of HAE patients.

The relationship between female hormones and angioedema appeared to be even clearer when the type III hereditary angioedema was recognised. This HAE mostly affects women. It was initially described by Bork et al, Binkley et al, and Martin et al in 2000 as recurrent angio-oedema without quantitative or functional C1Inh abnormalities [26-28]. In 2006, Dewald G (et al.) and Cichon (et al.) identified two mutations in the *F12* gene (gene encoding for Hageman factor) associated with type III HAE [29,30]. Only 15-20% of the patients suffering from type III HAE had one of these mutations.

The clinical characteristics of type III HAE attacks are the same as for types I and II, although Bork suggested that facial swelling occurred considerably more often [31,32]. In terms of the effect of estrogens, although, AE attacks occurred preferentially in women taking the OC pill or during pregnancy [33,34]. Whilst the attacks appeared to be estrogen-dependent in Binkley's series (in which attacks began in the 15 days following starting oral contraception), they were only estrogen sensitive in the cases reported by Bork and Martin (estrogen exposure could induce attacks but after varying periods of time) [26-28]. We reported that 54.5% of women are estrogen sensitive and 23% are estrogen dependent, confirming the potential involvement of estrogen, although the time between estrogen exposure and onset of the disease could vary from a few months to eight years [35].

When a physician takes care of women with a HAE, some issues have to be addressed: the choice of contraception, management of pregnancies and deliveries and the selection of an effective prophylactic treatment without side effects.

### Contraception

Combined contraceptive pills exacerbate symptoms in 63-80% of women [3,36-38]. This method of contraception is, therefore, contra-indicated in women with hereditary angioedema. A progestogen pill (mini or full dose) should be advised in this situation. However, if a patient is not having problems with the combined pill, there is no need to stop it. An intra-uterine device is a good alternative method and is generally very well tolerated [36].

### Pregnancy

Fertility and the rate of spontaneous abortion are the same as those found in the normal population. In one third of cases, pregnancy worsens symptoms, but in another third the symptoms are improved [36]. Attack rates increase during pregnancy especially during the third trimester [39,40]. During pregnancy it is acceptable to continue background treatment with tranexamic acid [41]. Danazol is contra-indicated. Treatment of severe attacks is based on the use of C1Inh concentrate [40-42].

The management of labour depends on how the pregnancy has progressed. If the patient has suffered worsening of the condition with frequent severe episodes, then labour must be covered with C1 Inh concentrate (20U/kg by IV infusion). If the disease has been less severe, there is no need for prophylaxis with C1 Inh concentrate. However, this should be available in the delivery room in case it is required. Epidural analgesia is not only acceptable, but is strongly recommended. The Caesarean section rate is no higher in these patients than in the general population.

### Lactation

There is no problem with breast-feeding. However, tranexamic acid and danazol should not be taken as they are secreted in maternal milk. For the same reason icatibant should be avoided and only C1Inh concentrate should be used in the treatment of severe episodes [39].

### Menopause

In most patients (55%) the menopause does not alter the disease. One third is worse while only 13% improve [36]. Menopausal hormone replacement therapy should not be given because oestrogen can exacerbate the condition [5].

### Breast cancer

The incidence of breast cancer is no higher than in the rest of the population. Tamoxifen should not be used as it may worsen symptoms [43].

Women need also specific management for treatment of HAE.

Short term prophylaxis: three options are available: attenuated androgens, tranexamic acid or C1Inh concentrate. There is no specific problem for the use of theses drugs for short course in female patients. In case of short term prophylaxis with attenuated androgens, no virilisation has been observed [44,45].

Acute attack treatment: there is no specific problem for the use of C1inh concentrate, tranexamic acid, icatibant; or ecallantide in female patients.

### Long term prophylaxis

Antifibrinolytiques (acid tranexamic) are the first best choice for HAE women because of good tolerance. The limits are a moderate efficacy and adverse effects as nausea, diarrhea and theoretical risk about thromboembolism. These products present no specific effect for women. Only few women have reported mild dysmenorrhea [46,47].

Attenuated androgens are highly effective but are accompanied by side effects. These side effects appear more often in female patients. The result of PREHAET study (presented by Bork) reported a weight gain for 30% of women, virilisation for 6%, menstrual irregularities for 30%, acne for 7%. Women report also alopecia, hirsutism, and mammary hypotrophy [48-50]. The side effects are dose dependant and can be attenuated by titrating the dose down the lowest effective level [51-53]. It is important to note that women who take this treatment may ovulate even if they present menstrual irregularities or amenorrhea. So, it's important to use additional contraceptive method for fertile women taking attenuated androgens. This treatment must be stopped in case of pregnancy and lactation.

#### Competing interests

The authors declare that they have no competing interests.

Received: 25 May 2010 Accepted: 28 July 2010 Published: 28 July 2010

#### References

1. Agostoni A, Cicardi M: **Hereditary and acquired C1 inhibitor deficiency: biological and clinical characteristics in 235 patients.** *Medicine* 1992, **71**:206-215.
2. Bork K, Meng G, Staubach P, Hardt J: **Hereditary angioedema: new findings concerning symptoms, affected organs and course.** *Am J Med* 2006, **119**:26-274.
3. Yip J, Cunliffe WJ: **Hormonally exacerbated hereditary angioedema.** *Australas J Dermatol* 1992, **33**:35-38.
4. Fletcher A, Weetman AP: **Coexistence of hereditary angioedema and Turner's syndrome.** *Postgrad Med J* 1998, **74**:41-42.
5. McGlinchey PG, McCluskey DR: **Hereditary angioedema precipited by estrogen replacement therapy in a menopausal woman.** *Am J Med Sci* 2000, **320**:212-213.
6. Farsetti A, Misiti S, Citarella F, Felici A, Andreoli M, Fantoni A, Sacchi A, Pontecorvi A: **Molecular basis of estrogen regulation of Hageman factor XII gene expression.** *Endocrinolgy* 1995, **136**:5076-83.
7. Citarella F, Misiti S, Felici A, Farsetti A, Pontecorvi A, Fantoni A: **Estrogen induction and contact phase activation of human factor XII.** *Steroids* 1996, **61**:270-6.
8. Gordon EM, Johnoson TR, Schmeidler-Sapiro KT: **Enhanced expression of factor XII (Hageman factor) in isolated livers of estrogen and prolactin treated rats.** *J Lab Clin Med* 1991, **117**:353-8.
9. Gordon EM, Douglas JG, Ratnoff OD, Arafah BM: **The influence of estrogen and prolactin on Hageman factor (factor XII) titer in ovariectomized and hypophysectomised rats.** *Blood* 1985, **66**:602-5.
10. Chen LM, Chung P, Chao S, Chao L, Chao J: **Differential regulation of kininogen gene expression by estrogen and progesterone in vivo.** *Biochim Biophys Acta* 1992, **1131**:145-51.
11. Madeddu P, Emanueli C, Song Q, Varoni MV, Demontis MP, Anania V, Glorioso N, Chao J: **Regulation of bradykinin B2 receptor expression by oestrogen.** *Br J Pharmacol* 1997, **121**:1763-91.
12. Gordon EM, Williams SR, Frenchek B, Mazur CA, Speroff L: **Dose dependant effects of postmenopausal estrogen and progestin on antithrombin III and factor XII.** *J Lab Clin Med* 1988, **111**:52-6.
13. Norris LA, Bonnar J: **The effect of oestrogen dose and progestogen type on haemostatic changes in women taking low dose oral contraceptives.** *Br J Obstet Gynaecol* 1996, **103**:261-7.
14. Thiery M, Vermeulen A, Baele G, Deslypere JP: **Effects of a very low estrogen oral contraceptive on clotting factors, carbohydrate metabolism, and plasma lipids and lipoproteins.** *Med Sci Res* 1987, **15**:1231-2.
15. Gordon EM, Ratnoff OD, Saito H, Donaldson VH, Pensky J, Jones PK: **Rapid fibrinolysis, augmented Hageman factor (factor XII) titers, and decreased C1 esterase inhibitor titers in women taking oral contraceptives.** *J Lab Clin Med* 1980, **96**:762-9.
16. Hoem NO, Johannesen S, Hauge G, Rud AC, Sandem S, Briseid K: **Contact activation factors in plasma from women using oral contraceptives increased levels of factor XII, kinin free high molecular weight kininogen and acetone activated kallikrein.** *Thromb Res* 1991, **64**:427-34.
17. Wessler S: **Estrogen associated thromboembolism.** *Ann Epidemiol* 1992, **2**:439-43.
18. Campbell SJ, Mackie IJ, Robinson GE, Machin SJ: **Contact factor mediated fibrinolysis is increased by the combined oral contraceptive pill.** *Br J Obstet Gynaecol* 1993, **100**:79-84.
19. Luyer MD, Khosla S, Owen WG, Miller VM: **Prospective randomized study of effects of unopposed estrogen replacement therapy markers of coagulation and inflammation in postmenopausal women.** *J Clin Endocrinol Metab* 2001, **86**:3629-34.
20. Madsen JS, Kristensen SR, Gram J, Bladbjerg EM, Henriksen FL, Gram J, Christensen K, Jespersen J: **Positive impact of hormone replacement therapy on the fibrinolytic system: a long term randomized controlled study in healthy postmenopausal women.** *J Thromb Haemost* 2003, **1**:1984-91.
21. Teede HJ, McGrath BP, Smolich JJ, Malan E, Kotsopoulos D, Liang YL, Peverill RE: **Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis.** *Arterioscler Thromb Vasc Biol* 2000, **20**:1404-9.
22. Sumino H, Ichikawa S, Kumakura H, Takayama Y, Kanda T, Sakamaki T, Kurabayashi M: **Effects of hormone replacement therapy on serum angiotensin converting enzyme activity and plasma bradykinin in postmenopausal women according to angiotensin converting enzyme genotype.** *Hypertens Res* 2003, **26**:53-8.
23. Nogawa N, Sumino H, Ichikawa S, Kumakura H, Takayama Y, Nakamura T, Kanda T, Mizunuma H, Kurabayashi M: **Effect of long term hormone replacement therapy on angiotensin converting enzyme activity and bradykinin in post menopausal women with essential hypertension and normotensive postmenopausal women.** *Menopause* 2001, **8**:210-5.
24. Gallagher PE, Li P, Lenhart JR, Chappell MC, Brosnihan KB: **Estrogen regulation of angiotensin converting enzyme mRNA.** *Hypertension* 1999, **33**:323-8.
25. Visy B, Füst G, Varga L, Szendei G, Takács E, Karádi I, Fekete B, Harmat G, Farkas H: **Sex hormones in hereditary angioneurotic edema.** *Clin Endocrinol (oxf)* 2004, **60**:508-15.
26. Bork K, Barnstedt SE, Koch P, Traupe H: **Hereditary angioedema with normal C1-inhibitor activity in women.** *Lancet* 2000, **356**:213-7.
27. Binkley KE, Davis A: **Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema.** *J Allergy Clin Immunol* 2000, **106**:546-50.

28. 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**:747-8.
29. 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**:1286-9.
30. Cichon S, Martin L, Hennies HC, Müller F, Van Driessche K, Karpushova A, Stevens W, Colombo R, Renné T, Drouet C, Bork K, Nöthen MM: **Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III.** *Am J Hum Genet* 2006, **79**:1098-104.
31. 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**:542-5.
32. Bork K, Wulff K, Hardt J, Witzke G, Staubach P: **Hereditary angiodema caused by missense mutations in the factor XII gene: Clinical features, trigger factors, and therapy.** *J Allergy Clin Immunol* 2009, **124**:129-34.
33. Bork K, Gul D, Hardt J, Dewald G: **Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course.** *Am J Med* 2007, **120**:987-92.
34. Bouillet L, Ponard D, Rousset H, Cichon S, Drouet C: **A case of hereditary angio-oedema type III presenting with C1-inhibitor cleavage and a missense mutation in the F12 gene.** *Br J Dermatol* 2007, **156**:1063-5.
35. Vitrat-Hincky V, Gompel A, Dumestre-Perard C, Boccon-Gibod I, Drouet C, Cesbron JY, Lunardi J, Massot C, Bouillet L: **Type III Hereditary angio-oedema: clinical and biological features in a French cohort.** *Allergy* 2010.
36. Bouillet L, Longhurst H, Boccon-Gibod I, Bork K, Bucher C, Bygum A, Caballero T, Drouet C, Farkas H, Massot C, Nielsen EW, Ponard D, Cicardi M: **Disease expression in women with hereditary angioedema.** *Am J Obst Gynecol* 2008, **11**:484e1-e4.
37. 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**:294-8.
38. Borradori L, Marie O, Ryboad M, Vexian P, Morel P, Morel P, Spath P: **Hereditary angioedema and oral contraception.** *Dermatologica* 1990, **181**:78-9.
39. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, Heller C, Klingebiel T, Kreuz W: **Characterization of acute hereditary angioedema attacks during pregnancy and breast feeding and their treatment with C1 inhibitor concentrate.** *Am J Obstet Gynecol* 2010.
40. Czaller I, Visy B, Csuka D, Füst G, Toth F, Farkas H: **The natural history of hereditary angioedema and the impacrt of treatment with human C1-inhibitor concentrate during pregnancy: a long term survey.** *Eur J Obstet Gynecol Reprod Biol* 2010.
41. Lindoff C, Rybo G, Astedt B: **Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications.** *Thromb Haemost* 1993, **70**:238-40.
42. Hermans C: **Successful management with C1Inhibiteur concentrate of hereditary angioedema during two successive pregnancies: a case report.** *Arch Gynecol Obstet* 2007, **276**:271-76.
43. Rousset-Jablonski C, Thalabard JC, Gompel A: **Tamoxifen contraindicated in women with hereditary angioedema?** *Ann Oncol* 2009, **20**:1281-2.
44. Cicardi M, Castelli R, Zingale LC, Agostoni A: **Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients.** *J Allergy Clin Immunol* 1997, **99**:194-6.
45. Sheffer AL, Fearon DT, Austen KF: **Clinical and biochemical effects of stanozolol therapy for hereditary angioedema.** *J Allergy Clin Immunol* 1981, **68**:181-7.
46. Frank MM, Gelfand JA, Atkinson JP: **Hereditary angioedema: the clinical syndrome and its management.** *Ann Intern Med* 1976, **84**:580-93.
47. Sim TC, Grant JA: **Hereditary angioedema: its diagnostic and management perspectives.** *Am J Med* 1990, **88**:656-64.
48. Zurlo JJ, Frank MM: **The long-term safety of danazol in women with hereditary angioedema.** *Fertil Steril* 1990, **54**:64-72.
49. Dmowski WP: **Danazol-induced pseudomenopause in the management of endometriosis.** *Clin Obstet Gynecol* 1988, **31**:829-3.
50. Heusse JL, Claude O, Lantieri L: **Can one propose aesthetic surgery to one male or female patient with an hereditary angio-oedema?** *Ann Chir Plast Esthet* 2008, **53**:289-92.
51. Cicardi M, Bergamaschini L, Cugno M, Hack E, Agostoni G, Agostoni A: **Long-term treatment of hereditary angioedema with attenuated androgens: a survey of a 13-year experience.** *J Allergy Clin Immunol* 1991, **87**:768-73.
52. Banerji A, Sloane DE, Sheffer AL: **Hereditary angioedema: a current state-of-the-art review, V: attenuated androgens for the treatment of hereditary angioedema.** *Ann Allergy Asthma Immunol* 2008, **1001**:S19-22.
53. Sloane DE, Lee CW, Sheffer AL: **Hereditary angioedema: safety of long term stanozolol therapy.** *J Allergy Clin Immunol* 2007, **120**:654-8.

doi:10.1186/1710-1492-6-17
**Cite this article as:** Bouillet: Hereditary angioedema in women. *Allergy, Asthma & Clinical Immunology* 2010 **6**:17.