

Hereditary Angioedema Associated with Heterozygous Factor V Leiden Mutation in a Patient with Purpura Fulminans

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Key Words

Hereditary angioedema • Purpura fulminans • Factor V Leiden mutation • Thrombosis

Abstract

Background: Hereditary angioedema (HAE) is an autosomal dominant, quantitative or functional defect of the C1 esterase inhibitor. The main role of the C1 esterase inhibitor is to regulate the activation of the complement system, the contact phase of the intrinsic coagulation system. On the other hand, factor V Leiden is the most common cause of primary and recurrent venous thromboembolism and displays a strong interaction with oral contraceptives. Here we report the case of a patient with HAE associated with the factor V Leiden mutation who had purpura fulminans when put on an oral contraceptive therapy. **Case:** A 42-year-old woman presented to the emergency room with a history of livid skin changes on her legs during a flight. On physical examination, the vital signs were normal, but there were edemas in her legs. The livid skin changes tended to increase, eventually leading to skin necrosis on the next day. She had a history of a similar episode two months before and experienced both episodes of necrotic skin lesions just after she had been put on a hormone replacement therapy due to irregular menstruations. She also had a history of recurrent angioedema attacks since her childhood, triggered by stress and

physical stimulants such as pressure and heat. Subsequent investigations revealed heterozygous factor V mutation, activated protein C resistance and reduced C1 inhibitor levels. **Conclusion:** Thrombosis is a multifactorial disease. The co-existence of multiple hereditary and acquired factors eases its occurrence. Women with HAE should be screened for the factor V Leiden mutation before pregnancy or the start of a hormone replacement therapy.

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by episodes of local edema, localized in the face, extremities, upper airways and gastrointestinal tract, which might sometimes be life threatening. Because there is a genetically quantitative and/or functional defect of the C1 esterase inhibitor (C1 INH), HAE generally begins during childhood and may continue throughout life. The main role of C1 INH is to regulate the activation of the complement system and the contact phase of blood coagulation [1].

Purpura fulminans (PF) is a rare disease characterized by rapidly evolving skin gangrene most frequently in the buttocks, thighs, extremities and abdomen [2]. The pathophysiological mechanism of the disease involves an

acute thrombotic occlusion of dermal vessels and hemorrhagic skin necrosis. PF is clearly related to some clinical conditions. Sepsis, disseminated intravascular coagulation, homozygous protein C or S deficiencies in neonates, and early periods of warfarin treatment in persons with deficiencies of protein C or S are classical clinical conditions associated to PF. Varicella, as well as streptococcal and viral upper respiratory tract infections in children are also described to cause PF.

We report a woman with HAE and heterozygous factor V Leiden mutation who suffered PF shortly after hormone replacement therapy. According to our opinion, this case provides clues for the understanding of coagulation activation in patients with HAE. This example may also have clinical implications for the management of women with HAE.

Case

A 42-year-old woman presented to the emergency room with a history of acute livid skin changes on the lower medial left knee and the lateral right thigh after a flight of 45 min. On physical examination, the vital signs were normal, there were edemas in her left leg and around the skin lesion on the right thigh. The laboratory tests, including white blood cell count and blood biochemistry, were within normal limits. The sedimentation rate was 31 mm/h. A Doppler ultrasound of the leg and abdominal vessels disclosed no abnormalities. She was empirically put on antibiotics. After 12 h at the emergency room, the livid skin changes tended to increase, eventually leading to skin necrosis the next day and she was diagnosed as having PF. Heparin and warfarin were started sequentially.

She did not describe any recent infection. Her medical history revealed a similar episode 2 months before, involving the medial surface of her left thigh. She was operated with suspected necrotizing fasciitis at another hospital. During the operation, normal fascia but necrotic subcutaneous soft tissue were observed. So only debridement and after a while skin grafting were performed.

She also had a history of recurrent angioedema attacks triggered by stress and physical stimulants such as pressure and heat since her childhood. She took antihistaminic medications irregularly for years. She had ablation therapy for ventricular tachycardia 2 years before and used beta-blockers after the intervention. In addition, she underwent a hormone replacement therapy (ethinylestradiol 20 µg and desogestrel 150 µg) due to irregular menses for 7–10 days before this skin necrosis episode, similarly to the previous episode.

Activated partial thromboplastin time, prothrombin time and fibrinogen levels were normal. D-dimer was 2.69 mg/ml (normal range: 0–0.5). The tests for antiphospholipid antibodies, lupus anticoagulant and antinuclear antibodies were negative. Antithrombin III activity was within normal limits. Protein C activity was 77% (normal range: 70–130) and protein S activity was 88% (normal range: 60–130), but activated protein C resistance was 42%

(normal range: 69–156). A polymerase chain reaction analysis of the factor V gene demonstrated a heterozygous factor V Leiden mutation. Prothrombin 20210A polymorphism was absent.

Because of recurrent angioedema attacks not responding to antihistaminics and steroids, HAE was suspected. The C1 INH level was diminished (0.03 g/l, normal range: 0.15–0.35), immune complex C1q was normal (45 µg/ml, normal range: 0–50) and because her son's C1 INH level was low as well (0.023 g/l, normal range: 0.15–0.35), her condition was diagnosed as type I HAE.

She could be managed without debridement and grafting. She has now been doing well for 3 years since the PF attacks. She is still on warfarin anticoagulation.

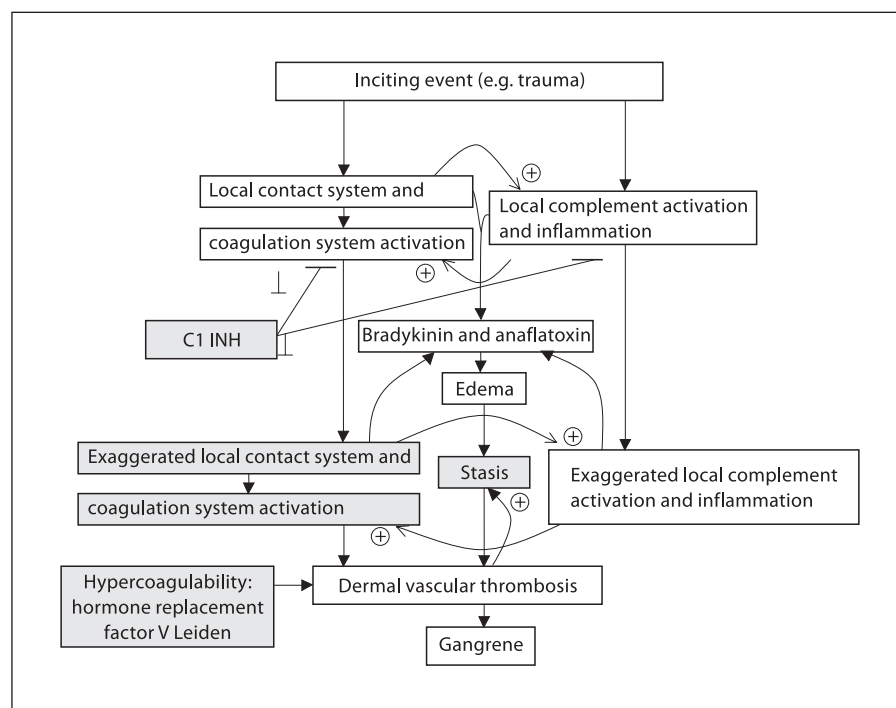
Discussion

Complement activation, inflammation and activation of the contact phase of blood coagulation are biologically related processes [3, 4]. C1 INH has a pivotal role in regulation of all these molecular pathways [5]. It prevents exaggerated tissue responses to the activation of these systems. C1 INH deficiency is classically associated with angioedema attacks due to an excessive bradykinin generation secondary to inappropriate complement and contact phase activations [6]. Local traumas (e.g. dental extraction) frequently precede the attacks.

The involvement of the contact phase of blood coagulation in hemostasis is debated. Deficiencies of the contact phase proteins are not associated with bleeding except for factor XI. Factor XI is known to be activated by thrombin, which is an activator of factor IX [7, 8]. According to the revised scheme of blood coagulation, the thrombin feedback activation of factor XI plays a role in the amplification of the clotting process. Biochemical clues for coagulation system activation have been detected in patients with HAE, especially during the attacks [9–11]. This observation led to the assumption that contact phase activation may lead to a downstream activation of coagulation in HAE [11] probably due to an inefficient inhibition of the contact phase proteins including factor XI. Factor VII activation has also been observed in patients with HAE [9, 11]. Although the coagulation system is activated in patients with HAE, an increased prevalence of thromboembolism has not been detected, probably because of unknown counteracting factors such as hyperfibrinolysis [11].

Here we report a type I HAE patient with an exceptional manifestation of hypercoagulability. Recently, a new type of HAE called type III HAE (estrogen-influenced HAE) has been described. This type of HAE affects only women and their attacks are precipitated when estrogen concentrations increase because of pregnancies,

Fig. 1. Possible mechanism of PF in the patient. C1 INH deficiency, local contact system and coagulation system activations, stasis and hypercoagulability were assumed to contribute to dermal vascular thrombosis as specified. ⊕ = Enhancement; ⊥ = inhibition.



oral contraceptives or hormone replacement therapy. No genetic defects or C1 abnormalities have been reported in this entity so far [12, 13]. Although our patient had a history of hormone replacement therapy, type III HAE was not considered in the differential diagnosis as the C1 INH levels of both the patient and her son were low.

We suggest that this association between HAE and PF is not coincidental. PF, a rare manifestation, was associated with HAE, a rare disease, in at least one other patient [14]. This other patient, like ours, was also in a systemic hypercoagulable state. Pregnancy-related hyperestrogenemia and activated protein C resistance as hypercoagulability factors are similar to the underlying factors in our patient.

The question is why these patients suffered from PF. Local coagulation and complement activations due to an inciting event such as a mild trauma may be enhanced due to a C1 INH deficiency, not only leading to edema but also to dermal vascular thrombosis involving edema-induced stasis and systemic hypercoagulability (fig. 1). According to this hypothesis, edema-induced dermal vascular stasis and local coagulation activation in HAE are the key factors directing a thrombotic tendency to the skin. Although coagulation activation has been reported in HAE, whether this enhancement is a local or systemic event is not evident. The occurrence of PF, but not venous

thromboembolism, in HAE suggests that coagulation activation during the attacks is predominantly localized to areas of angioedema.

These two very similar observations have clinical implications. Oral contraceptives, hormone replacement therapy and pregnancy have been reported to worsen some cases of HAE [12]. Therefore, estrogen preparations must not be used liberally in these patients. The risk of PF may represent another indication to avoid these agents. Women with HAE should be screened for the factor V Leiden mutation, the most common genetic aberration related to hypercoagulability, before pregnancy or the start of a hormone replacement therapy.

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