Uncommon Signs Associated With Hereditary Angioedema With Normal C1 Inhibitor

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Hereditary angioedema (HAE) is a rare disease with an autosomal dominant inheritance pattern that is characterized by edema affecting the subcutaneous and submucosal tissues, preferentially the skin, gastrointestinal tract, and upper airways. HAE with C1 esterase inhibitor deficit (HAE-C1INH) due to a quantitative defect (type I) or anomalous protein (type II) has been described. In 2000, both Bork et al [1] and Binkley and Davis [2] described HAE with normal C1-INH (HAE-n-C1INH) and with similar clinical manifestations to other types [1,2]. The formation of bradykinin at high levels has been associated with the symptoms of these diseases [3].

The mechanism involved in HAE-n-C1INH is not fully understood. However, mutations in coagulation factor XII have been reported [4]. Hyperactivity and stimulation of the contact system and fibrinolysis have been assumed, not only in FXII-HAE, but also in unknown HAE [5]. Other mutations have been associated with the phenotype of HAE, including the mutation in the angiopoietin 1 gene, which is associated with interference in vascular permeability and, more recently, mutations in the plasminogen and kininogen genes [4]. In some patients with HAE-n-C1INH, the genetic cause remains unknown, although the clinical characteristics may be like those of patients with a known mutation.

Prodromes for swelling attacks have been described in patients with C1-INH deficiency. These include erythema marginatum, nausea, irritability, and tiredness [6]. Patients with HAE-n-C1INH have been reported to experience intense fatigue and even chest discomfort and palpitations [7]. Bruising has also been reported in patients with HAE-n-C1INH [7-9]. In contrast with our description of hemorrhages or bruising, Firinu et al [9] reported bruising only in *F12*-mutated HAE-n-C1INH [9].

Considering the high prevalence of HAE-n-C1INH in Brazil [10], the occurrence of hemorrhages or bruising in patients seen at our clinic led us to report the following cases to enable better recognition of this condition.

The first patient (daughter of consanguineous parents) was diagnosed at the age of 46. Her initial symptoms were abdominal attacks at 8 years and upper airway edema. At age 14 years, she experienced facial edema and wheezing associated with her menstrual cycle. Her symptoms worsened at 37 years of age. She had 4 miscarriages and 1 episode of coma owing to a severe attack. The patient reported wheezing and local hemorrhages or bruising preceding or at the onset of the attacks, which disappeared without scarring as soon as the edema appeared (Figure). The patient's parents had died of a severe angioedema attack. Of 9 siblings, 5, including the patient, had manifestations consistent with HAE with no identified mutations. The patient took tranexamic acid and progestins for prophylaxis. Icatibant (Firazyr) and plasma-derived C1 inhibitor (Berinert) were used to treat attacks, although recently, she was treated with fresh frozen plasma owing to unavailability of other medications.

The second patient was a 37-year-old woman who had been diagnosed 10 years earlier with edema (eyelids, lips, and feet), abdominal distension and pain, vomiting, and pressure pain in the hands. The symptoms started after treatment for an unsuccessful pregnancy. The intensity of the attacks decreased with aminocaproic acid, although they were triggered by her menstrual cycle. Danazol was introduced during the same year, and, even at a low dosage, she developed several adverse effects. She reported that the attacks had been triggered by stress and trauma. Edema was preceded by bruising (Figure). The patient reported the spontaneous disappearance of the lesions without residual marks. She was receiving tranexamic acid and progestin as prophylaxis and was using icatibant for attacks. Her family history was positive for angioedema.

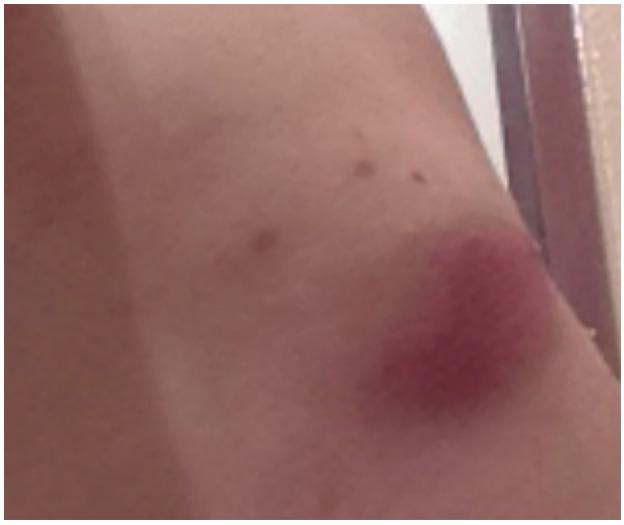

Figure. Hemorrhage/bruising reported by a patient with hereditary angioedema and normal C1 inhibitor.

Neither patient was shown to carry any of the mutations associated with HAE-n-C1INH to date.

Prodromes occur in approximately 50% of symptomatic HAE-C1INH patients. Erythema marginatum, paresthesia, gastrointestinal complaints, fatigue/malaise, and changes in mood/emotions have been reported [6]. However, except for fatigue/malaise, prodromes have not been well established in HAE-n-C1INH. We observed the presence of local hemorrhages and/or bruising followed immediately by edema, which is difficult to define as a prodrome or is actually the first sign to be detected in some cases. Interestingly, neither patient presented any of the previously described mutations, with the result that the condition was classified as unknown HAE. A clear correlation with hormonal factors as triggers was reported and verified in both patients. Several affected family members had HAE-n-C1INH.

Edema results from increased vascular permeability without capillary injury via a mechanism other than bruising. However, the absence of residual marks in the cases we report suggests the same pathophysiology.

No prospective studies have evaluated the symptoms and/or signs associated with attacks of HAE-n-C1INH. Hemorrhage or bruising could represent an additional sign to consider in some HAE-n-C1INH patients. We suggest systematic questioning of patients with this type of HAE regarding manifestations such as hemorrhage and bruising. The recognition of new mutations associated with HAE and these signs may clarify the underlying mechanism or even differentiate the mechanism of this clinical form from others already identified in HAE-n-C1INH.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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