

## **Uncommon Signs Associated with Hereditary Angioedema with Normal C1**

### **Inhibitor**

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Hereditary Angioedema (HAE) is a rare disease with autosomal dominant inheritance, characterized by edema that affects the subcutaneous and submucosal tissues, preferentially affecting the skin, gastrointestinal tract and upper airways. HAE with deficit of C1 esterase inhibitor (HAE-C1INH) due to quantitative defect (type I) or anomalous protein (type II) have been described. In 2000, both Bork *et al.* and Binkley & Davis 3<sup>rd</sup> 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 for unknown-HAE [5]. Still, there are further mutations associated with the phenotype of HAE, including the mutation in angiotensin-converting enzyme 1 gene 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 is still unknown, although they have clinical characteristics similar to those with a known mutation.

Several prodromes of swelling attacks have been described in patients with C1-INH deficiency, such as erythema marginatum, nausea, irritability, tiredness, among others [6]. In patients with HAE-n-C1INH, there are reports of intense fatigue and even chest discomfort or palpitations [7], and the description of bruising has been reported in a few patients with HAE-n-C1INH [7,8,9]. In contrast with our description of hemorrhages or bruising, Firinuet *al.* described it only in *F12* mutated HAE-n-C1INH [9].

Considering the high prevalence of HAE-n-C1INH in our country (Brazil) [10], we observed the occurrence of hemorrhages or bruising in the patients of our clinic and we describe below for better recognition.

The first female patient was diagnosed at the age of 46 and she is the daughter of consanguineous parents. Her first symptoms started with abdominal attacks at 8 years of age and glottis edema. At 14 years of age, she had edema on her face and wheezing associated with menstrual cycle and symptoms worsened at 37 years of age. She had 4 miscarriages and one episode reported as coma, owing to a severe attack. The patient reports wheezing and local hemorrhages or bruising preceding or at the beginning of the attacks, disappearing without scars as soon as the edema is installed (Figure 1A). The patient's parents died of a severe angioedema attack. From 9 siblings, 5, including the patient, had manifestations consistent with HAE without identified mutations. The patient used tranexamic acid and progestins for prophylaxis. Icatibant (Firazyr®) and plasma-derived C1 inhibitor (Berinert®) was used for treating attacks, but recently, she had to treat with fresh frozen plasma due to unavailability of other medications.

The second patient was evaluated at 37 years old, female, diagnosed 10 years earlier by edema in the eyelids, lips and feet, distension and abdominal pain, vomiting and pressure pain in the hands. The symptoms started after treatment for unsuccessful pregnancy. With the use of aminocaproic acid, the intensity of the attacks decreased; however, they were triggered by the menstrual cycle. In the same year, danazol was introduced and, even with low dosage, she developed several adverse effects. She reported that stress and trauma have been triggering the attacks. Bruising was reported preceding edema (Figure 1B and 1C). The patient described the spontaneous disappearance of the lesions without residual marks. The patient was receiving tranexamic acid and progestin as prophylaxis and was using icatibant for attacks. Family

history is positive for angioedema. Both patients did not have any of the mutations associated with HAE-n-C1INH to date.

Prodromes occur in approximately 50% of HAE-C1INH symptomatic patients. Erythema *marginatum*, paresthesia, gastrointestinal complaints, fatigue/malaise, and changes in mood/emotions have been reported [6]. However, the observation of prodromes in HAE-n-C1INH is still not well established except for fatigue/malaise. We observed the presence of local hemorrhages and/or bruising just followed by edema, which is difficult to define as a prodrome or actually the first sign to be detected in some cases. Interestingly, both patients do not present any of the mutations previously described and, consequently, were classified as Unknown-HAE. A clear correlation with hormonal factors as triggers of attacks was reported and verified in both patients. Several affected family members had HAE-n-C1INH.

Edema is resultant of an increasing in the vascular permeability without capillary injury, in a different mechanism from bruising. However, the absence of residual marks in our patients suggests the same pathophysiology.

There is no prospective study evaluating symptoms and/or signs associated with attacks of HAE-n-C1INH. Hemorrhage or bruising in these patients could represent an additional sign to take into account in some HAE-n-C1INH patients. We suggest the systematic questioning of patients with this type of HAE regarding these manifestations. The recognition of new mutations associated with HAE and those signs may clarify or even differentiate the mechanism of this clinical form from others already identified in HAE-n-C1INH.

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## Conflict of Interest

No conflicts of interest regarding this manuscript.

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**Figure 1.** Picture with the hemorrhage/bruising reported by one patient with Hereditary Angioedema and normal C1 inhibitor.

