Original Article

Hereditary Angioedema with Normal C1 Inhibitor and *F12* Mutations in 42 Brazilian Families

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What is already known about this topic? Hereditary angioedema (HAE) with mutations in the *F12* gene (FXII-HAE) is a rare genetic disease with characteristics similar to those of angioedema with C1 inhibitor deficiency, which mainly affects female patients, increasing the expression and severity of symptoms.

What does this article add to our knowledge? The higher frequency of symptomatic male patients in the Brazilian population suggests that the gender penetrance previously described for FXII-HAE should be reconsidered. We report the highest number of families with FXII-HAE outside the European continent.

How does this study impact current management guidelines? Our results demonstrate the usefulness of genetic testing to diagnose patients presenting with clinical features of HAE with normal C1 inhibitor, including male patients, even in the absence of a family history or estrogen influence.

BACKGROUND: Hereditary angioedema (HAE) with normal C1 inhibitor (C1-INH) is a rare condition with clinical features similar to those of HAE with C1-INH deficiency. Mutations in the *F12* gene have been identified in subsets of patients with HAE with normal C1-INH, mostly within families of European descent.

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Abbreviations used
ACEI- Angiotensin-converting enzyme inhibitor
C1-INH- C1 inhibitor
C1-INH-HAE- Hereditary angioedema with C1 inhibitor deficiency
eOC- Estrogen-containing oral contraceptive
FXII- Coagulation factor XII
FXII-HAE- Hereditary angioedema with F12 *gene mutations*
HAE- Hereditary angioedema
HRT- Hormonal replacement therapy
U-HAE- HAE with normal C1-INH of unknown cause

OBJECTIVES: Our aim was to describe clinical characteristics observed in Brazilians from 42 families with HAE and *F12* gene mutations (FXII-HAE), and to compare these findings with those from other populations.

METHODS: We evaluated a group of 195 individuals, which included 102 patients clinically diagnosed with FXII-HAE and their 93 asymptomatic relatives.

RESULTS: Genetic analysis revealed that of the 195 subjects, 134 individuals (77.6% females) carried a pathogenic mutation in *F12*. The T328K substitution was found in 132 individuals, and the c.971_1018+24del72 deletion was found in 2 patients. The mean age at onset of symptoms in patients with FXII-HAE was 21.1 years. The most common symptoms were subcutaneous edema (85.8% of patients), abdominal pain attacks (69.7%), and upper airway edema (32.3%). Of male individuals carrying *F12* mutations, 53.3% (16 of 30) were symptomatic. Compared with reports from Europe, fewer female patients (68.6%) reported an influence of estrogen on symptoms.

CONCLUSIONS: Our study included a large number of patients with FXII-HAE, and, as the first such study conducted in a South American population, it highlighted significant differences between this and other study populations. The high number of symptomatic males and patients with estrogen-independent FXII-HAE found here suggests that male sex and the absence of a hormonal influence should not discourage clinicians from searching for *F12* mutations in cases of HAE with normal C1-INH. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Hereditary angioedema; Normal C1 inhibitor;* F12 *mutations; Estrogen; Brazilian population*

Hereditary angioedema (HAE) is a rare condition characterized by uncontrolled activation of the contact system with excessive bradykinin production and recurrent episodes of angioedema.[1] In most patients, HAE is associated with mutations in *SERPING1*, the gene encoding C1 inhibitor (C1-INH). C1-INH deficiency renders the contact system prone to activation, resulting in increased production of bradykinin. HAE with normal C1-INH was first described in 2000[2,3] and, in subsets of patients,[4-6] it has subsequently been associated with mutations in *F12*, the gene encoding coagulation factor XII (FXII-HAE).[7-10] Patients are designated as cases of unknown HAE when they display clinical features of HAE and belong to families with no identified mutation in *SERPING1* or the *F12* gene.[1]

Patients with HAE and normal C1-INH present clinical features that are similar to those of HAE caused by C1 inhibitor deficiency (C1-INH-HAE), including subcutaneous, gastrointestinal, and laryngeal edema. However, different characteristics are also apparent in patients with FXII-HAE, including a lower frequency of abdominal pain attacks and a higher frequency of facial and tongue swelling, a higher number of symptomatic female patients, marked estrogen sensitivity, and delayed onset of disease.[11,12] In addition, hemorrhagic lesions at the sites of angioedema, which develop 1 to 2 days after the onset of swelling, have been reported in HAE with normal C1-INH, but they have not yet been described in patients with C1-INH-HAE.[11,13]

To date, all mutations described in patients with FXII-HAE are located in exon 9 of the *F12* gene, and affect a proline-rich region of coagulation factor XII. The missense mutations T328K and T328R are associated with a defect in O-linked glycosylation of FXII, which has been shown to increase contact activation of zymogen FXII. This loss of glycosylation ultimately increases activation of the kallikrein-kinin pathway, leading to higher levels of bradykinin, without affecting C1-INH binding to FXII.[14,15] New pathways leading to excessive bradykinin formation in patients with HAE that involve plasmin activation of factor XII have been reported recently, which could have implications for diagnosis and treatment of the disease,[16,17] although further studies are needed to confirm these mechanisms.

More than 60 families with FXII-HAE have been described worldwide; however, the prevalence of FXII-HAE in a South American population has not been established. A recent study estimated the prevalence of FXII-HAE to be 1:400,000.[6] In the Brazilian population, few families with HAE with normal C1-INH have been reported. Those reported include 2 unrelated FXII-HAE families with members carrying a homozygous T328K mutation.[18-22] In the present study, we describe the clinical characteristics of 134 Brazilian individuals with FXII-HAE, who are from 42 unrelated families, and compare their clinical features to those reported in patients from other countries.

METHODS

Subjects

After genetic testing, 102 Brazilian patients with recurrent episodes of subcutaneous edema without wheals, normal quantitative and/or functional C1-INH plasma levels, and no clinical response to high doses of antihistamines according to the criteria established by Cicardi et al[1] were included in this study. All patients who showed mutations in the *F12* gene known to be related to HAE were characterized as having FXII-HAE, a criterion for entering the study. Family history was a relevant factor for inclusion in the study; however, its absence was not an exclusion criterion. Clinical data regarding angioedema sites, triggering factors, and therapy were recorded using an established protocol (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Symptomatic and asymptomatic family members were also evaluated. Patients were referred to this study from 9 different medical centers in Brazil. Approval for this study was obtained from the Ethics Committee of the Federal University de São Paulo (CAAE: 04032912.6.0000.5505), the Clinical Hospital of Ribeirão Preto Medical School (HCRP 14000521/2012), and the School of Medicine of ABC (CAAE: 51896015.0.1001.0082). All participants provided informed consent.