

Hereditary angioedema: Screening of first-degree blood relatives and earlier diagnosis

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ABSTRACT

Background: Hereditary angioedema (HAE) with C1 inhibitor (C1INH) deficiency is an inherited disease characterized by sudden, recurrent episodes of edema that involve the skin, gastrointestinal tract, respiratory tract, and other organs.

Objective: Because it takes a long time from the first symptoms to diagnosis, we aimed to identify HAE in untested first-degree blood relatives among some of our patients with HAE in our outpatient clinic at Hospital Universitário Clementino Fraga (HUCFF), Federal University of Rio de Janeiro.

Methods: Untested first-degree relatives of patients with HAE C1INH, even those who were asymptomatic, were identified and invited to participate. Those who agreed to participate answered a specific questionnaire and had a blood sample collected for complement testing.

Results: Fifty untested first-degree relatives of 30 index patients with HAE C1INH were identified, and both groups were analyzed. The mean $\pm$ standard deviation (SD) age of the index patients group was 37.08 ± 16.56 years (range, 13–73 years), with a high frequency in women ($n = 24$ [80.0%]). Most of them had severe ($n = 23$ [76.7%]) and moderate ($n = 7$ [23.3%]) attacks. None were asymptomatic. The mean $\pm$ SD time between the first symptoms and diagnosis was 20.2 ± 11.06 years (range, 0–48 years) in that group. In the first-degree relatives group, 30 new cases of HAE C1INH (60%) were identified.

Conclusion: We found that there was a long time between early manifestations and a diagnosis of HAE. First-degree relatives of patients with HAE patients are at risk for having the disease. Sixty percent were newly diagnosed with HAE and with C1INH deficiency in our study. So, screening of family members, including individuals who were asymptomatic, is the key for earlier diagnosis and effective treatment.

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Hereditary angioedema (HAE) with C1 inhibitor (C1INH) deficiency is a rare, underdiagnosed inherited disease characterized by recurrent abdominal pain or swelling, which can be fatal if it involves the larynx. The current estimate is of a prevalence of $\sim 1:50,000$ in the general population.¹ There is no obvious ethnic variation in the disorder. Typically, symptoms begin in late childhood and become worse after puberty. Therefore, the disorder has a much higher morbidity and mortality in adults compared with children.

HAE is listed as an immunodeficiency disorder because the mutated gene functions as an inhibitor of the complement cascade.² Type 1 and type 2 HAEs are caused by mutations of the serpin family G member (SERPING1) gene. In type 1 HAE, C1INH levels are very low or absent in the blood. In type 2 HAE, levels

of C1INH are normal or elevated. Type 2 HAE is thought to be a dominant-negative disorder caused by a circulating dysfunctional protein, which competitively inhibits wild-type C1INH. Some patients with type 2 HAE also produce aggregates of mutant C1INH multimers, which have the potential to directly activate the contact phase and which leads to further bradykinin production.³

All patients suspected of having HAE-1/2 (*i.e.*, recurrent angioedema in the absence of a known cause) should be assessed for blood levels of C4, C1INH protein, and C1INH function, and these tests, if the results are abnormally low, should be repeated to confirm the diagnosis. C4 is the single best screening test, and repeating the C4 during an attack increases the probability that a low C4 will be found. We can streamline treatment and reduce the risks of physical suffering and even fatal consequences if we have the correct diagnosis for patients and their families. We must also emphasize improvement of their quality of life.

METHODS

The study population comprised patients with a confirmed diagnosis of HAE (type 1 or 2) and relatives unevaluated for HAE. The subjects with a confirmed diagnosis of HAE were required to have at least one

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first-degree blood relative defined as a parent, sibling, or offspring, who was eligible for the study. These relatives met eligibility requirements for enrollment as long as they had no history of evaluation for HAE. The study was previously approved by our hospital's ethics committee.

Adult patients were informed of the nature of the study and provided written informed consent, whereas, for children and adolescents, a term of agreement was signed by a parent or legal guardian as well as the adolescent. Untested first-degree relatives of patients with HAE, even those who were asymptomatic, were identified and invited to enroll in the study. Relatives who agreed to enroll in the study completed a questionnaire about angioedema attack symptoms. First-degree relatives also underwent blood sample collection for complement testing (C4, antigenic, and functional C1INH).

Complement Testing

Fresh serum blood was collected for complement testing. Samples collected from first-degree relatives were tested for C4 and for antigenic and functional C1INH levels at the Hospital Universitário Clementino Fraga Filho - Universidade Federal do Rio de Janeiro (HUCFF-UFRJ)'s immunology laboratory. C4 was tested by using a nephelometry method (BN II System; Siemens, Siemens Healthineers, São Paulo, Brazil) (reference range, 10–40 mg/dL), and C1INH antigen was measured by using nephelometry (BN II System) (reference range, 20–35 mg/dL). Functional C1INH chromogenic (Technochrom, Technoclone Herstellung von Diagnostika und Arzneimitteln GmbH, Vienna, Austria) results were categorized as low (<70% of the mean normal) or normal (70%–130% of the mean normal).

RESULTS

A total of 50 first-degree relatives (defined as a parent, sibling, or offspring) of 30 index patients with HAE due to C1INH deficiency, 29 type 1 and one type 2, were elected to enroll in the study and underwent complement testing. In 20 relatives, normal laboratory results ruled out HAE. Thirty relatives (60%) had laboratory results indicative of HAE C1INH, all type 1: 16 females (53.3%) and 14 males (46.7%). The mean $\pm$ standard deviation (SD) age at the end of the study was 35.5 ± 12.7 years (range, 2–72 years). The mean $\pm$ SD age of symptom onset was 12.9 ± 8.9 years and of the diagnosis was 30.0 ± 18.8 years. The time between early manifestations and diagnosis ranged from 0 (early diagnosis) to 61 years (mean $\pm$ SD, 17.8 ± 14.6 years) (Table 1).

Three relatives were asymptomatic (10.0%); 9 (30.0%) had mild attacks, 7 (23.3%) had moderate attacks, and

Table 1 Sociodemographic and clinical features of 30 Brazilian first-degree relatives of patients with HAE newly diagnosed with HAE type 1

Sociodemographic Features and Clinical Patterns	Findings
Female relative, no. (%)	16 (53.3)
Male relative, no. (%)	14 (46.7)
Age, mean $\pm$ SD, y	35.5 ± 12.7
Time from symptom to diagnosis, mean $\pm$ SD, y	17.8 ± 14.6
Asymptomatic, no. (%)	3 (10.0)
Symptomatic, no. (%)	27 (90.0)

HAE = Hereditary angioedema; SD = standard deviation.

Table 2 Clinical patterns of 27 symptomatic first-degree relatives of patients with HAE newly identified

Clinical Patterns of Subjects with Symptoms	Findings, no. (%)
HAE attacks	
Mild	9 (33.3)
Moderate	7 (26.0)
Severe	11 (40.7)
Location of swelling	
Cutaneous edema	23 (85.2)
Abdominal pain	20 (70.1)
Laryngeal edema	10 (37.0)
Intensive care unit	3 (11.1)

HAE = Hereditary angioedema.

11 (36.7%) had severe attacks. The duration of edema was reported as between 3 and 5 days in most of these attacks (56.7%) (Table 1). Twenty-seven enrolled relatives (90.0%) had a history of symptoms of angioedema attacks, including cutaneous edema (76.7%), mainly face, hands, and feet; abdominal pain (66.7%); and laryngeal edema (33.3%). Three (10.0%) had a history of intensive care unit hospitalization (Table 2). Among 30 subjects newly diagnosed with HAE, 4 were <12 years old. However, it took 61 years until there was an HAE diagnosis in one of the subjects.

DISCUSSION

HAE is considered a rare disease that may not be familiar to health-care professionals. Most patients with HAE have symptoms for an extended period before receiving an accurate diagnosis and appropriate treatment.¹ During the period that patients are undiagnosed, they experience angioedema attacks, with no response to conventional treatment and high morbidity, and have a substantial risk of mortality. After

patients are diagnosed with HAE, they are more likely to have access to effective treatment options, and HAE attacks are appropriately treated, which shortens and lessens the severity of the attacks.^{4–8} Patients who are undiagnosed and with abdominal pain from an angioedema attack may undergo unnecessary surgery.⁹ Early recognition and diagnosis of HAE may reduce the morbidity and mortality associated with the disease. HAE is an autosomal-dominant genetic disease in which an affected individual has a 50% chance of transmitting the disease to his or her offspring, and the importance of testing family members of patients with HAE has previously been recognized.¹

Riedl *et al.*¹⁰ performed a similar study in which they confirmed HAE in 30% of the enrolled relatives. In our study, we confirmed HAE in a higher frequency of the enrolled relatives (60%). These abovementioned results endorsed the importance of familial testing of patients with HAE to detect this hereditary disease, which allowed those who are at risk of an angioedema attack to have access to specific and effective treatment. Remarkably, 90% of newly diagnosed relatives reported angioedema attacks, 33.3% of which were laryngeal edema. Riedl *et al.*¹⁰ showed that 64% of newly diagnosed relatives had reported symptoms that were consistent with HAE. This reaffirmed that even individuals with a family history of HAE and suggestive severe clinical symptoms had not had diagnostic testing.

Of the 30 newly diagnosed subjects, 4 were children who presented few or mild symptoms at the time of the study, whereas, in the study by Riedl *et al.*¹⁰, 11 of 14 subjects were children. With an early diagnosis, these children may have access to treatment and improved morbidity and mortality. However, in our study one of the subjects was 68 years old, which demonstrated that it is also important to test elderly relatives of patients with known HAE. These results reinforced the importance of testing family members of patients with a diagnosis of HAE, even in individuals who are asymptomatic.

CONCLUSION

HAE is an inherited disease in which patients experience a delay between symptoms onset and diagnosis.

Testing first-degree relatives should be considered to ensure that individuals who are at risk for an angioedema attack have access to treatment and to prevent morbidity and mortality. Our study encouraged such HAE family screening by demonstrating a 60% rate of confirmed C1INH deficiency in untested family members of patients with HAE.

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