Prevalence of hereditary angioedema in untested first-degree blood relatives of known subjects with hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal-dominant disease characterized by recurring attacks of nonpruritic, nonpitting edema caused by an inherited deficiency or dysfunction of C1 esterase inhibitor (C1 INH). Symptoms can present years before an accurate diagnosis is made. The objective of this study, the Angioedema Clinical Epidemiology Testing Initiative for the Study of Hereditary Angioedema, was to determine the prevalence and clinical manifestations of HAE in untested first-degree blood relatives of known patients with HAE. Patients with a confirmed diagnosis of HAE recruited first-degree relatives who had not been evaluated for HAE. Enrolled subjects underwent complement testing (C4, C1 INH antigen, and functional C1 INH). If the lab tests were abnormal, the enrolled subjects returned to the site for a follow-up visit and questionnaire. Overall, 31 patients with HAE and 46 first-degree relatives enrolled in the study. Of 46 enrolled relatives, 30 (65%) had lab test results that ruled out a diagnosis of HAE, two (4%) were categorized as "HAE not ruled out," and 14 (30%) were newly diagnosed with HAE. Of 14 newly diagnosed subjects, nine (64%) reported having experienced symptoms that may have been related to HAE, such as swelling in the throat, face, or extremities or abdominal pain. When reported, median age of symptom onset in these 14 subjects was nine years whereas newly diagnosed asymptomatic subjects had a median chronological age of six years. These 14 subjects reported a historic mean standard deviation rate of 2.51 (5.59) swelling episodes per month with a mean standard deviation duration of 1.6 (0.74) days. This study's findings reinforce the importance of testing family members of patients with HAE to detect this hereditary condition.

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Hereditary angioedema (HAE) is a rare disorder caused by an inherited deficiency or dysfunction in the plasma protein C1 esterase inhibitor (C1 INH)¹ and is characterized by recurring attacks of nonpruritic, nonpitting subcutaneous edema, or submucosal edema of the bowel or upper airway.² Symptoms typically present during childhood; however, diagnoses can be delayed for a decade or more.^{1,3–5} HAE is an autosomal-dominant condition; the offspring of a par-

ent with a mutation of the C1 inhibitor gene will have a 50% chance of inheriting HAE. Due to the rarity of the disease (~1:50,000 persons), physicians may not consider HAE in their differential diagnosis.⁶ In addition, despite its familial predisposition, many family members of HAE patients are not screened for the condition. In fact, patients with HAE responding to a survey reported that only 48% of immediate family members and 26% of extended family members had been tested for HAE.³ With the recent advent of effective therapies, screening of family members has increasingly been emphasized as a means to reduce the substantial morbidity and mortality associated with HAE.

The Angioedema Clinical Epidemiology Testing Initiative for the Study of Hereditary Angioedema was designed to determine the prevalence of HAE in previously unevaluated first-degree blood relatives of known patients with HAE in the United States and to evaluate the occurrence of clinical manifestations of HAE in untested relatives.

METHODS

Study Subjects

All subjects were required to be more than or equal to one year of age. Adults were informed of the nature of the study and provided written informed consent. A

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parent/legal guardian was required to provide written informed consent for a child (not yet at the legal age for consent) to participate in the study with assent from the child as appropriate. This was a multisite study, and the protocol was approved by the institutional review board at each investigator's site.

The study population comprised patients with a confirmed diagnosis of HAE (type I or II) and relatives untested for HAE. Subjects with a confirmed diagnosis of HAE were required to have at least one first-degree blood relative (defined as a parent, sibling, or offspring) who would be eligible for the study. These relatives met eligibility requirements for enrollment as long as they had no history of previous evaluation for HAE.

Subjects were excluded if they received antifibrinolytics within 30 days of enrollment, fresh frozen plasma within 15 days of enrollment, or C1 INH concentrate (human or recombinant), bradykinin receptor antagonist, or plasma kallikrein inhibitor within 72 hours of the blood collection for complement testing. These exclusions were implemented to ensure that therapeutic agents would not interfere with the results of complement testing. Women in their second or third trimesters of pregnancy or within one month postpartum were also excluded. Subjects were excluded if they had any clinically significant medical condition that the investigator deemed could possibly complicate the diagnosis. Untested relatives were excluded if they had received attenuated androgens within 30 days of enrollment or had a previous diagnosis of HAE type I or II.

Study Design

Patients with confirmed diagnoses of HAE due to C1 INH deficiency enrolled in the study and reported to the study site, where the investigator completed a questionnaire that collected information on demographics, employment, HAE history, medications related to HAE management, medical history, and information about first-degree blood relatives. During this site visit, these patients also underwent blood sample collection for complement testing.

Untested first-degree relatives of patients with HAE were identified and invited to enroll in the study. Relatives who agreed to enroll in the study visited the study site, where the investigator completed a separate questionnaire that collected information on demographics, HAE status of first-degree blood relatives, medication use, and medical history, including specific questions about swelling and symptoms that could be consistent with an angioedema attack. Symptom questions were general, and reported symptoms could potentially be due to causes other than an angioedema condition. First-degree relatives also underwent blood sample collection for complement testing.

If the results of complement testing for the first-degree relatives were normal (normal levels of antigenic and functional C1 INH) and a diagnosis of HAE was ruled out, those subjects were notified, and participation in the study was concluded. If lab results were abnormal (indicative of HAE, or indeterminate such that HAE could not be ruled out), subjects were asked to return to the study site for a follow-up visit within 30 days, and the investigator completed a second questionnaire that collected information on unexplained or recurrent swelling (including any swelling that had occurred since the first study visit) and updates of medication use and medical history.

Complement Testing

Fresh serum blood samples were collected into a red top Vacutainer tube for complement testing. Within six hours of collection, more than or equal to 3 mL of fresh serum was obtained from enrolled patients, frozen into six equal aliquots of more than or equal to 0.5 mL, and stored at -20°C . Frozen serum samples were shipped within 24 hours; two aliquots to the reference laboratory (National Jewish Medical and Research Center, Denver, CO) and four to the central laboratory (LabCorp, Burlington, NC). Samples collected from HAE patients were tested for functional C1 INH at both laboratories. Samples collected from untested relatives were tested for C4 and antigenic and functional C1 INH levels at the central laboratory; in addition, functional C1 INH testing was performed at the reference laboratory. C4 was tested using an immunoturbidimetric method (reference range, 9–36 mg/dL), and C1 INH antigen was measured using nephelometry (reference range, 21–39 mg/dL). Functional C1 INH enzyme-linked immunosorbent assay (ELISA) results were categorized as low (less than 41% of normal), equivocal (41%–67%), or normal (more than 67%), and functional C1 INH chromogenic results were categorized as low (less than 74% of mean normal) or normal (74%–174% of mean normal).

Statistical Analysis

Data from all sites were pooled and presented as summary statistics in the form of group means, rates, and proportions.

RESULTS

Disposition

A total of 31 patients with HAE due to C1 INH deficiency enrolled in the study, including four patients who did not identify first-degree relatives and did not contribute to the subject population of untested relatives. The patients with HAE identified 189 first-

Figure 1. Flow of participation from the index cases (patients with HAE) to the identification of first-degree relatives with laboratory results consistent with a diagnosis of HAE.

degree relatives, 42 of whom had previous diagnoses of HAE. Of the remaining 147 relatives, 46 elected to enroll in the study and underwent complement testing. Normal lab results ruled out HAE in 30 relatives. Of the remaining 16 relatives, 14 had lab results indicative of HAE (Fig. 1).

In the remaining two subjects, HAE could not be ruled out during the study due to equivocal lab results. One subject was 36 years of age and had normal C1 INH antigen and C4 levels; functional C1 INH results were equivocal according to ELISA and normal according to the chromogenic method. Complement testing was repeated after study completion, and the ELISA test result indicated normal functional C1 INH. Thus, HAE was ultimately ruled out in this subject. The other subject was two years of age and had low C1 INH antigen and normal C4, with equivocal functional C1 INH results according to ELISA and normal results according to the chromogenic method. The subject did not have a history of symptoms suggestive of HAE; however, symptoms would be unlikely to develop at such a young age. Based on the laboratory results and family history, HAE remains possible in this subject.

Prevalence of HAE in Relatives

Of 46 relatives who enrolled in the study and underwent complement testing, 14 (30%) had lab results indicative of HAE.

Demographics

The majority of patients with known HAE were female (24, 77%) and Caucasian (25, 81%) (Table 1). The mean standard deviation age of this group was 35.8 (13.67) years, and the greatest number of patients was aged 31–40 years (14, 45%). Twenty-five enrolled relatives (54%) were female, and 42 (91%) were Caucasian. Enrolled relatives were generally younger than patients with HAE, with a mean standard deviation age of 25.9 (23.65) years. The most common age range for enrolled relatives was 2–11 years (21, 46%). Among the 14 enrolled relatives whose lab results were consistent with HAE, six (43%) were female.

History of Swelling and Abdominal Pain

Table 2 is a summary of enrolled relatives' history of symptoms that are similar to those experienced during an angioedema attack, including abdominal pain and swelling of the throat, skin, genitourinary region, face,

Table 1. Demographics

	Patients with HAE	Enrolled Relatives				
		All	HAE Ruled Out	Abnormal Lab Results		
				All	Results Indicative of HAE	HAE Not Ruled Out by Study
Subjects, n	31	46	30	16	14	2
Female, n (%)	24 (77)	25 (54)	17 (57)	8 (50)	6 (43)	2 (100)
Caucasian race, n (%)	25 (81)	42 (91)	26 (87)	16 (100)	14 (100)	2 (100)
Age (years), mean (SD)	35.8 (13.67)	25.9 (23.65)	32.0 (25.05)	14.5 (15.92)	13.9 (15.63)	19.0 (24.04)
Age distribution (years), n (%)						
2 to 11	3 (10)	21 (46)	12 (40)	9 (56)	8 (57)	1 (50)
12 to 17	1 (3)	3 (7)	0	3 (19)	3 (21)	0
18 to 30	3 (10)	7 (15)	5 (17)	2 (13)	2 (14)	0
31 to 40	14 (45)	2 (4)	1 (3)	1 (6)	0	1 (50)
41 to 50	7 (23)	3 (7)	3 (10)	0	0	0
51 to 65	3 (10)	7 (15)	6 (20)	1 (6)	1 (7)	0
>65	0	3 (7)	3 (10)	0	0	0

HAE = hereditary angioedema; SD = standard deviation.

Table 2. History of swelling and abdominal pain in enrolled relatives

	Enrolled Relatives	Enrolled Relatives With HAE Ruled Out	Enrolled Relatives With Abnormal Lab Results		
			All	Results Indicative of HAE	HAE Not Ruled Out by Study
Subjects, n	46	30	16	14	2
Ever experienced symptoms, n (%)	22 (48)	12 (40)	10 (63)	9 (64)	1 (50)
Ever experienced the next symptoms, n (%)					
Extremity swelling	14 (30)	4 (13)	10 (63)	9 (64)	1 (50)
Abdominal pain	11 (24)	8 (27)	3 (19)	2 (14)	1 (50)
Facial swelling	7 (15)	2 (7)	5 (31)	4 (29)	1 (50)
Skin swelling	7 (15)	2 (7)	5 (31)	4 (29)	1 (50)
Throat swelling	3 (7)	2 (7)	1 (6)	1 (7)	0
Genitourinary swelling	3 (7)	0	3 (19)	3 (21)	0
Visited emergency room, n (%)	3 (7)	2 (7)	1 (6)	1 (7)	0
Throat swelling	1 (2)	0	1 (6)	1 (7)	0
Abdominal pain	3 (7)	2 (7)	1 (6)	1 (7)	0
Admitted to hospital, n (%)	3 (7)	1 (3)	2 (13)	2 (14)	0
Throat swelling	1 (2)	0	1 (6)	1 (7)	0
Facial swelling	1 (2)	0	1 (6)	1 (7)	0
Abdominal pain	2 (4)	1 (3)	1 (6)	1 (7)	0

HAE = hereditary angioedema.

or extremity. Overall, 22 enrolled relatives (48%) reported experiencing these symptoms. The most commonly reported symptom was extremity swelling (14 subjects, 30%) followed by abdominal pain (11 subjects, 24%).

Of the 30 subjects whose lab results ruled out HAE, 12 (40%) reported experiencing symptoms, and the most commonly reported symptom was abdominal pain (8 subjects, 27%). Of the 14 subjects whose lab results were indicative of HAE, nine (64%) reported

Table 3. Characterization of swelling in enrolled relatives with abnormal lab results

	All	Results Indicative of HAE	HAE Not Ruled Out by Study
Subjects, n	16	14	2
Experienced unexplained/recurrent swelling, n (%)	10 (63)	9 (64)	1 (50)
Age at onset of swelling symptoms (years)			
Subjects reported	9	8	1
Mean (SD)	16.2 (18.27)	14.8 (18.96)	28.0 (NA)
Median (range)	9.0 (1, 60)	9.0 (1, 60)	28.0 (NA)
Distribution of age at onset of swelling symptoms (years), n (%)			
2 to 11	5 (31)	5 (36)	0
12 to 17	2 (13)	2 (14)	0
18 to 30	1 (6)	0	1 (50)
51 to 65	1 (6)	1 (7)	0
Swelling episodes per month			
Subjects reported	10	9	1
Mean (SD)	2.27 (5.322)	2.51 (5.585)	0.08 (NA)
Median (range)	0.34 (0.08, 17.20)	0.42 (0.08, 17.20)	0.08 (NA)
Receiving the following treatments for swelling, n (%)			
Pain medication	3 (19)	3 (21)	0
Androgen derivatives	2 (13)	2 (14)	0
C1 inhibitor	1 (6)	1 (7)	0
Other	1 (6)	1 (7)	0
Major triggers for swelling, n (%)			
Trauma	9 (56)	9 (64)	0
Stress	6 (38)	6 (43)	0
Not sure	4 (25)	3 (21)	1 (50)
Other	7 (44)	7 (50)	0

HAE = hereditary angioedema; NA = not available; SD = standard deviation.

experiencing symptoms, with extremity swelling (nine subjects, 64%) as the most commonly reported symptom.

Characterization of Swelling History

Sixteen enrolled relatives had abnormal laboratory results that were either indicative of HAE or could not definitively exclude HAE. Within 30 days, these subjects returned to the site for a second visit and underwent further questioning about swelling history (Table 3). Among these 16 subjects, 10 (63%) reported experiencing swelling.

Of the 14 subjects whose lab results were indicative of HAE, nine (64%) reported at the second visit that they had experienced unexplained or recurrent swelling. In the subjects who reported their age at onset of swelling symptoms, the median age was nine years (mean 16.2 years, range 1–60 years), and the median time to diagnosis was two years (mean 4.0 years, range 0–9 years). Swelling occurred in the extremity (nine subjects, 64%), abdomen (four, 29%), face (four, 29%), genitourinary region (three, 21%), and throat (one, 7%).

Five subjects (36%) were asymptomatic and reported experiencing no previous symptoms, despite lab results indicative of HAE. These five asymptomatic subjects had a median (range) age of six (2, 15) years.

Discussion and Conclusions

HAE is a rare disease that may not be familiar to health care professionals evaluating a symptomatic patient. Symptoms of the condition, including nonpruritic swelling or unexplained abdominal pain, are common to a variety of disorders.⁶ As a result, most patients with HAE have symptoms for an extended period before receiving an accurate diagnosis and appropriate treatment.^{1,3,4}

During this period, when undiagnosed patients are experiencing angioedema attacks without treatment, patients experience morbidity and have a substantial risk of mortality. Patients diagnosed with HAE are more likely to have access to effective treatment options, and HAE attacks that are appropriately treated are shorter and less severe than those in which therapy is not promptly administered.^{7–12} Undiagnosed

patients with abdominal pain from an angioedema attack may undergo unnecessary surgery.³ Most importantly, patients with undiagnosed HAE have a much greater risk of mortality from a laryngeal attack than those who have a diagnosis.¹³ Early recognition and diagnosis of HAE may therefore be expected to 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.^{3,14} We conducted this epidemiologic study to determine the incidence of HAE in previously untested first-degree relatives of patients with HAE. The results show that 30% of the enrolled relatives had lab results that were indicative of HAE. These results reinforce the importance of testing family members of patients with a diagnosis of HAE to detect this hereditary disease and ensure that patients who are at risk of an angioedema attack have access to effective treatment.

Importantly, 64% of newly diagnosed relatives had reported symptoms that were consistent with HAE. However, the questions about symptoms in our questionnaire were general, and the symptoms may not have been related to HAE. Indeed, 40% of subjects in whom HAE was ruled out also reported symptoms. This result highlights the challenges of clinically recognizing HAE given that symptoms may be relatively common and attributable to other causes. Even in individuals with a known family history of HAE, suggestive clinical symptoms did not lead to subsequent diagnostic testing before study enrollment, although the reasons for this were not discernable from collected study data.

Of the 14 subjects who were newly diagnosed with HAE, 11 were children with HAE who may have exhibited few or mild symptoms of the condition at the time of the study. Because of this early diagnosis, these individuals may gain access to treatment and be better prepared to effectively treat future angioedema symptoms, thereby preventing morbidity associated with undiagnosed and untreated HAE. However, two subjects were young adults between the ages of 18 and 30 years, and one subject was older than age 50 years, demonstrating the potential benefit of testing adult relatives of patients with known HAE.

Two subjects had laboratory results that were equivocal for HAE, and these results could not be used to rule out a diagnosis. In this study, laboratory tests used to diagnose HAE were C4, C1 inhibitor antigen, and functional C1 inhibitor.¹⁵ We used two methods to measure functional C1 inhibitor, an ELISA (LabCorp, Burlington, NC) and a chromogenic assay (National Jewish Medical and Research Center, Denver, CO). The

two subjects for whom HAE could not be ruled out had equivocal functional C1 INH according to the ELISA method and normal functional C1 INH according to the chromogenic method. In one subject, ELISA results were confirmed to be normal upon repeated testing after the study, and the subject was confirmed not to have HAE. HAE is suspected in the other subject, who will continue to be closely followed and will undergo additional complement testing at a later age. In clinical practice, equivocal ELISA laboratory tests should be repeated or a chromogenic test should be ordered to determine the level of functional C1 INH and definitively confirm or exclude the diagnosis of HAE. In addition, the patients should be followed closely for clinical signs and symptoms of angioedema, recognizing that complement testing during a symptomatic period may provide additional relevant data.

Several limitations of this study should be considered when interpreting the data. HAE is a rare disease, and the study was conducted at four centers in the United States, therefore the numbers of HAE patients and first-degree relatives evaluated were relatively small. Most of the first-degree relatives who were newly diagnosed were the children of patients. It is possible that sampling bias occurred due to the convenience of adult patients enrolling children in the study versus enrollment of other adult first-degree relatives. However, it is also possible that adult first-degree relatives may have been previously tested and therefore the untested population in families with HAE is predominantly young individuals. Only about one-third of identified family members participated in the research protocol. This response rate is not unexpected in clinical research, particularly when procedures such as a blood draw are required. Finally, the symptom questionnaire was not a validated tool and was not specific to HAE. However, this was purposeful as a means to collect descriptive information on all symptoms that could plausibly be related to HAE and, thereby, compare clinical history with diagnostic test results.

In conclusion, HAE is a rare inherited disease, in which patients often experience a delay between the onset of symptoms and diagnosis. First-degree relatives of patients with HAE are at risk for having the condition, and testing should be strongly considered to ensure that individuals who are at risk for an angioedema attack have access to effective treatment as a means to prevent morbidity and mortality. Our study supports such HAE family screening efforts by demonstrating a 30% rate of confirmed C1 INH deficiency in previously untested family members of individuals with HAE. In addition, the results highlight the relative insensitivity of clinical symptoms in distinguishing between affected and unaffected family members.

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