
Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients?

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Background: Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by a deficiency of C1 esterase inhibitor (C1 INH) protein or function. Guidelines do not exist regarding diagnostic criteria or routine testing of family members of patients with HAE. Laboratory data for diagnosis include complement factor 4 level; C1 INH antigenic protein level, which is reduced in approximately 85% of patients with HAE; and C1 INH functional assay, which is considered an unreliable test in the United States secondary to inconsistent standardization of assays.

Objectives: To assess the shortcomings of diagnosing HAE and to determine whether family members of patients with HAE are being adequately screened.

Methods: The top physician prescribers of danazol in the United States were screened via an Internet questionnaire focusing on the diagnosis and current management of HAE. To assess the patient perspective on HAE, affected individuals in the United States, the United Kingdom, France, Germany, and the Netherlands participated in the Web-based International Survey of Patient Experience of Hereditary Angioedema.

Results: All 80 physicians who completed the survey were allergist or immunologists with a mean of 7 patients with C1 INH deficiency in their practices. Almost 84% of physician respondents used C1 INH level and function for diagnosis, and 63.8% used complement factor 4 levels. A total of 313 patients with HAE completed the survey. Respondents noted that only 48% of immediate family members and 26% of extended family members had been tested.

Conclusion: Guidelines could potentially alleviate delays in diagnosis and incorrect diagnoses and could lead to adequate screening of family members.

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INTRODUCTION

Hereditary angioedema (HAE) is a clinical disorder characterized by a genetically determined deficiency of C1 esterase inhibitor (C1 INH). The disorder results from mutations of the C1 INH gene located on chromosome 11.^{1,2} Traditionally, HAE has been divided into 2 subtypes. Unique among the inherited deficiencies of the complement system, HAE types I and II are inherited as an autosomal dominant disorder, with equal occurrence in men and women. Low levels of C1 INH protein and decreased function of the protein distinguish type I HAE, which accounts for approximately 80% to 85% of all HAE cases. Type II HAE, which occurs in 15% to 20% of patients, results from decreased functional activity of the C1 INH gene but with normal C1 INH levels.^{3,4} Recently, a new subtype of HAE, type III, has been described in the literature.

This type is characterized by X-linked dominant inheritance and was initially observed exclusively in women with normal levels and function of C1 INH.⁵ More recently, males have been identified who seem to have HAE but with normal complement factor 4 (C4) levels, C1 INH antigenic protein levels, and C1 INH functional assay results.

HAE is clinically manifested by recurrent episodes of localized subcutaneous or submucosal edema. The most commonly involved organs include the skin, upper respiratory tract, oropharynx, and gastrointestinal tract. Attacks usually last for 2 to 5 days before resolving spontaneously, followed by disease-free intervals of variable duration. The worldwide incidence of HAE varies from 1 in 10,000 to 1 in 150,000 persons.⁶ The disease is frequently misdiagnosed, leading to delays in diagnosis and treatment. Therapy for acute attacks is supportive, with attenuated androgens and C1 INH replacement therapy serving as common treatment options.

Multiple international guidelines have been established. Although these guidelines are continuously revised as new evidence and therapies arise, they provide useful algorithms for physicians to implement in their practice. Generally, the diagnosis of HAE is established clinically and is confirmed using laboratory testing.

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The Canadian Hungarian 2007 International Consensus Algorithm⁷ describes criteria for the diagnosis and management of HAE. This algorithm recommends screening for C1 INH deficiency by measuring C4 and C1 INH protein levels. Levels of C4 are low in patients with HAE secondary to defective control of the classical pathway of the complement cascade. In a Hungarian population,⁸ borderline normal C4 levels were detected in only 4% of newly diagnosed patients with HAE. Another study⁷ showed that C4 levels are normal between attacks in 2% of patients. Thus, a normal C4 level almost completely rules out a diagnosis of C1 INH deficiency.

Currently, no guidelines specific to the United States exist for the diagnosis and management of HAE. In addition, no guidelines exist regarding routine testing of family members of patients with HAE for this autosomal dominant disorder. We sought to review data on physician screening of suspected patients and their family members to try to improve the diagnosis of HAE.

METHODS

Danazol, an attenuated androgen is commonly used for HAE prophylaxis in the United States. To assess the physician's perspective on HAE, prescribers of danazol were asked to participate in an internet questionnaire. Physicians with a positive initial response were then given a detailed retrospective questionnaire. However, this method of participant recruitment may miss some physicians who choose to withhold their prescribing practices. Questions focused on the diagnosis and current management of HAE. Physicians were not aware of the reason for the questionnaire or who was seeking data.

To assess the patient perspective on HAE, affected patients in the United States, the United Kingdom, France, Germany, and the Netherlands were invited by e-mail and postal mail to participate in the Web-based International Survey of Patient Experience of Hereditary Angioedema. The survey was conducted in the native language of the patient via an invitation from the local HAE patient organization. Each respondent completed a 30-minute anonymous online survey that sought to determine the patient's family history of HAE, to observe the flow of patients through the health care system from presentation to diagnosis, to identify differences in medical care across the various countries, and to assess the effectiveness of prevention and acute treatment of HAE. Participant confidentiality remained preserved throughout the study, and all analyses were conducted at a global level. Institutional review board approval was obtained through The Essex Institutional Review Board in Lebanon, New Jersey. All the participants provided informed consent.

RESULTS

Eighty physicians participated, with 94% identifying themselves as allergists and 6% as immunologists. Participants had a mean of 7 patients with C1 INH deficiency in their practices and a mean of 4.8 patients currently undergoing

treatment with androgens. Participating physicians had a mean of 3.3 patients with HAE that they had initially diagnosed. Almost 84% of respondents used C1 INH level and function and 63.8% used C4 levels for diagnostic criteria (Table 1). Sixty-three percent of responders retested patients, with 51% doing so during the initial visit; 12.2% of physicians retested their patients yearly, with reasons including verification and monitoring of disease state and progression.

A total of 313 patients completed the online International Survey of Patient Experience of Hereditary Angioedema (United States: n = 125, Germany: n = 64, United Kingdom: n = 52, France: n = 50, and the Netherlands: n = 22). Participants were defined as either patients with diagnosed disease or their guardians. The average age of affected patients was 37 years. Forty-three percent of participants waited longer than 1 year after experiencing their first attack before seeking medical attention. The average time to diagnosis of HAE after initial presentation of symptoms was 8.3 years. Participants visited an average of 4.4 physicians before receiving the diagnosis of HAE. In the process of visiting various physicians, 65% of participants received a misdiagnosis of their condition, with the most common misdiagnoses being allergy/allergic reaction (38%) and appendicitis (17%). Moreover, 19% of participants in the United States and 24% in Europe underwent an unnecessary surgical procedure, such as an appendectomy, secondary to a misdiagnosis or a physician's misunderstanding of their condition.

The 313 patients had an average of 2 immediate and 2 extended family members diagnosed as having HAE. However, participants responded that only 48% of their immediate family members and only 26% of their extended family members have been tested for the disorder (Figure 1). Thirty-two percent of participants stated that all their family members had been tested.

DISCUSSION

It seems that there is a need for more extensive education among allergists/immunologists and primary care physicians regarding the screening and diagnosis of HAE. A screening C4 level may be prudent to obtain in a patient with a common presenting symptom of HAE, such as angioedema or abdominal pain, when no obvious etiology is found, especially if the angioedema occurs without urticaria.^{9,10} Only 63.8% of physician respondents used C4 levels to aid in diagnosis. This may be because these physicians had a high suspicion of C1

Table 1. Tests That Physicians Currently Use to Diagnose C1 Esterase Inhibitor Deficiency

Test	Physicians, % (n = 80)
C1 esterase inhibitor level and function	83.8
Complement factor 4 level	63.8
C1 quantitative level	17.5
Complement factor 3 level	16.3
Total hemolytic complement activity	13.8

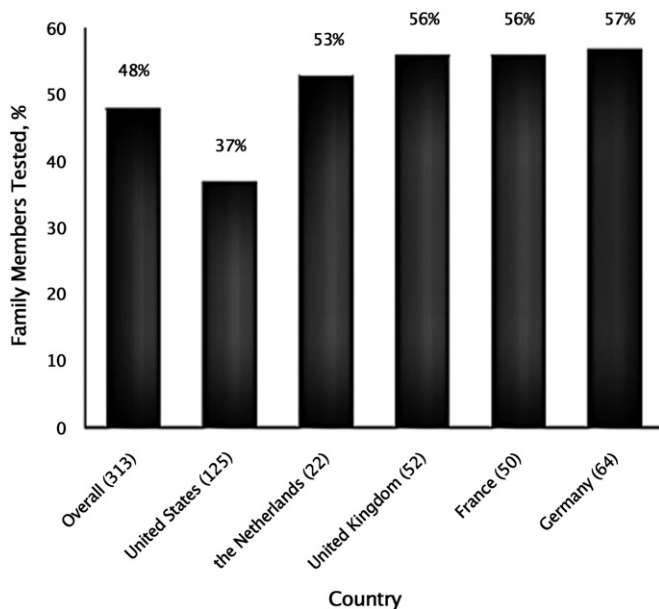


Figure 1. Mean percentages of immediate family members tested for hereditary angioedema overall and by country. Numbers in parentheses are the number of patients questioned.

INH deficiency in their patients based on clinical findings and, thus, deemed this laboratory value unnecessary. However, the general consensus is that the best screening test in the United States is a C4 level, which should be low between and especially during attacks.

In the primary care setting, a patient with swelling of unknown etiology may easily be screened via a C4 test. Because it has been shown that a normal C4 level almost rules out a diagnosis of C1 INH deficiency, obtaining this value alone may be valuable and cost-effective.¹¹ Education about the value of the C4 test should be distributed to internists and pediatricians because many patients with HAE present in the first 2 decades of life. Currently, the C4 test is not recommended for patients younger than 1 year because of its unreliability in this age group (C1 INH and C4 concentrations increase to adult levels between 2 and 3 years of age).^{12,13} In addition, physicians should be aware of the importance of obtaining a thorough family history, which may help differentiate HAE from acquired angioedema because acquired angioedema also presents with angioedema and low C4 levels. Acquired angioedema is more likely in patients who present with symptoms in middle age or above, patients without a family history, and especially if C1-quantitative level is low. If a low C4 level is obtained, confirmatory tests are needed. In the Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema,¹⁴ it was recommended that the diagnosis of any type of C1 INH deficiency or dysfunction should be confirmed with at least 2 laboratory assessments performed 1 to 3 months apart. It seems that the best screen-

ing test would be functional C1 INH level. However, this test has sensitivity and specificity concerns in the United States. That is why we stress the C4 test as the best screening test for HAE in the United States.

The lack of awareness of HAE in patients and physicians is evident from the extended length of time between patients' initial symptoms and both seeing a physician and receiving a positive diagnosis, the number of different physicians seen to make a final diagnosis, and the prevalence of misdiagnoses. An incorrect diagnosis can lead to ineffective, inappropriate, and inadequate medical care. During the approximately 8 years that patients waited to receive a diagnosis of HAE, a life-threatening attack may have occurred. Even if a patient does not exhibit HAE symptoms, a confirmed diagnosis will allow preparation for the possibility of a future attack. The diagnosis will also provide patients with the education necessary to manage HAE during daily life, including identification and avoidance of triggers, preparation for acute attacks, and how to properly react to lethal complications, such as airway obstruction.

Although HAE is inherited as an autosomal dominant disorder, it seems that testing family members for the disorder is not common practice. It is prudent to test family members of affected individuals to ensure proper education and treatment of HAE. This could decrease the time from initial symptoms to diagnosis. Screening family members for HAE may also be cost-effective by decreasing the number of physicians seen and the number of unnecessary tests and procedures ordered. However, although HAE is an autosomal dominant disorder, approximately 25% of disorders inherited in this manner may represent *de novo* mutations.¹⁵ HAE is a genetically heterogeneous disease, with more than 100 C1 INH gene mutations described to date spanning all the exons and exon/intron boundaries.¹⁶ However, genetic testing is rarely necessary, and, in fact, a negative test result cannot be used to exclude the diagnosis because new mutations that have not been previously identified are possible. In addition, a positive test result is consistent with the diagnosis but cannot be used to predict the natural history of the disease because the same genotypes present with various phenotypes.

This article presents data identifying the effectiveness of physicians worldwide regarding the screening and diagnosis of HAE. There is a potential bias in selecting physicians who care for many patients with HAE because they are already educated about the disease. It is anticipated that the suboptimal use of diagnostic testing and the screening of family members would be even less in the general allergist population. However, given that it is extremely rare, the time, expense, and effort to survey all physicians or all allergists would have been too burdensome. These data support that further education concerning this potentially life-threatening disorder is needed. In patients with suspected HAE, the C4 level should be determined to rule out or help diagnose HAE, to lead to more timely diagnosis, and to facilitate appropriate follow-up. In addition, family members of patients with HAE should be screened via a C4 test for the disorder. A consensus

guideline in the United States regarding the diagnosis, screening, and treatment of patients with HAE and their family members, therefore, would serve as a valuable tool and be a nidus for the education of physicians and patients about HAE, with the end result being an improvement in outcomes for patients with HAE.

REFERENCES

1. Bock SC, Skriver K, Nielsen E, et al. Human C1 inhibitor: primary structure, cDNA, cloning, and chromosomal localization. *Biochemistry*. 1986;25:4292–4301.
2. Theriault A, Whaley K, McPhaden AR, Boyd E, Connor JM. Regional assignment of the human C1-inhibitor gene to 11q11-q13.1. *Human Genet*. 1990;84:477–479.
3. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2000;105:541–546.
4. Bowen B, Hawk JJ, Sibunka S, et al. A review of the reported defects in the human C1 esterase inhibitor gene producing hereditary angioedema including four new mutations. *Clin Immunol*. 2001;98:157–163.
5. Bork K, Barnstedt S, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356:213–217.
6. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med*. 2001;161:2417–2429.
7. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol*. 2008;100(suppl 2):S30–S40.
8. Farkas H, Varga L. The Hungarian HAE experience. *Transfusion Apheresis Sci*. 2003;29:229–233.
9. Farkas H, Harmat G, Fay A, et al. Erythema marginatum preceding an acute edematous attack of hereditary angioneurotic oedema. *Acta Derm Venereol*. 2001;81:376–377.
10. Zingale LC, Beltrami L, Zanichellia A, et al. Angioedema without urticaria: a large clinical survey. *CMAJ*. 2006;175:1065–1070.
11. Zuraw BL, Sugimoto S, Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. *J Allergy Clin Immunol*. 1986;78:1115–1120.
12. Nielsen EW, Johansen HT, Holt J, Mollness TE. C1 inhibitor and diagnosis of hereditary angioedema in newborns. *Pediatr Res*. 1994;35:184–187.
13. Roach B, Kim Y, Jerome E, Michael AF. Influence of age and sex on serum complement components in children. *Am J Dis Child*. 1981;135:918–920.
14. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(suppl):S51–S131.
15. Agenda, Proceedings, Recommendations and the Power Point Presentation From Comprehensive Care for Rare Blood Disorders; February 3-5 2006; organized by the Canadian Network of Rare Blood Disorder Organizations. Program and abstracts for the Fifth C1 Inhibitor Deficiency Workshop; Budapest; May 31 to June 3, 2007.
16. Tosi M. Molecular genetics of C1 inhibitor. *Immunobiology*. 1998;199:358–365.

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