Current state of hereditary angioedema management: A patient survey

Aleena Banerji, M.D.,[1] Paula Busse, M.D.,[2] Sandra C. Christiansen, M.D.,[3,4] Henry Li, M.D.,[5] William Lumry, M.D.,[6] Mark Davis-Lorton, M.D.,[7] Jonathan A. Bernstein, M.D.,[8] Michael Frank, M.D.,[9] Anthony Castaldo,[10] Janet F. Long,[10] Bruce L. Zuraw, M.D.,[3,11] and Marc Riedl, M.D., MS[3,11]

ABSTRACT

Hereditary angioedema (HAE) is a chronic disease with a high burden of disease that is poorly understood and often misdiagnosed. Availability of treatments, including C1 esterase inhibitor (C1INH) replacement, ecallantide, and icatibant, marks a significant advance for HAE patients. We aimed to better understand the current state of HAE care, from a patient perspective, after the introduction of several novel therapies. One session of the United States Hereditary Angioedema Association 2013 patient summit was devoted to data collection for this study. Patients attending the summit were self-selected, and HAE diagnosis was self-reported. Survey questions assessed patient characteristics, burden of disease, and treatment. Participant responses were captured using an audience response system. We surveyed 149 (80%) type I and II HAE (HAE-C1INH) and 37 (20%) HAE with normal C1INH (HAE-nlC1INH) patients. HAE-C1INH (72%) and HAE-nlCINH patients (76%) equally reported that HAE had a significant impact on quality of life (QOL). A third of HAE-C1INH patients were diagnosed within one year of their first HAE attack, but another third reported a delay of more than 10 years. Most HAE-C1INH (88%) and HAE-nlC1INH (76%) patients had on-demand treatment available. HAE-C1INH patients frequently had an individual treatment plan (76%) compared with 50% of HAE-nlC1INH patients. Most HAE-C1INH patients went to the emergency department (ED) or were hospitalized less than once every six months (80%). Our findings show that HAE management is improving with good access to on-demand and prophylactic treatment options. However, HAE patients still have a significant burden of disease and continued research and educational efforts are needed.

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Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by recurrent episodes of swelling that most commonly affect the extremities, gastrointestinal tract, face, or larynx. Most attacks are self-limiting, but abdominal attacks may cause severe pain, nausea, and vomiting, and those affecting the throat or larynx may be fatal due to asphyxiation. The prevalence of HAE in the literature ranges from 1:10,000 to 1:150,000.[1–3]

Three types of HAE have been defined based on the levels and activity of plasma C1 esterase inhibitor (C1INH). Type I HAE, the most prevalent form (85%), is characterized by a deficiency in plasma C1INH. In type II (15%), C1INH is secreted into the plasma but is dysfunctional. Both types are caused by mutations in the *SERPING1* gene, which codes for C1INH. In 2000, HAE with normal C1INH (HAE-nlC1INH), previously referred to as type III HAE, was initially described and remains poorly understood.[4] Clinical symptoms of HAE-nlC1INH are indistinguishable from HAE type I and II (HAE-C1INH). However, these patients have normal plasma levels of functional C1INH and complement levels.

As a chronic and debilitating disease, all three types of HAE are associated with a high burden of disease. Depression and anxiety are widely prevalent in patients with HAE.[5] Additionally, HAE remains poorly understood by the medical community and is often misdiagnosed, resulting in significant morbidity and mortality. HAE attacks are painful, potentially life threatening, and occur unpredictably

[1]*Department of Medicine, Harvard Medical School, Boston, Massachusetts,* [2]*Department of Medicine, Mount Sinai School of Medicine, New York, New York,* [3]*Department of Medicine, University of California San Diego, La Jolla, California,* [4]*Allergy Department, Southern California Kaiser Permanente, San Diego, California,* [5]*Institute for Asthma and Allergy, Chevy Chase, Maryland,* [6]*Allergy and Asthma Research Associates Research Center, Dallas, Texas,* [7]*Department of Medicine, Winthrop University Hospital, Mineola, New York,* [8]*Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio,* [9]*Department of Pediatrics, Duke University Medical Center, Durham, North Carolina,* [10]*United States Hereditary Angioedema Association, Honolulu, Hawaii, and* [11]*San Diego Veterans Administration Healthcare, San Diego, California*

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Address correspondence to Aleena Banerji, M.D., Cox 201, 55 Fruit Street, Boston, MA 02114

E-mail address: abanerji@partners.org

with varying time intervals between attacks therefore significantly impacting a patient's quality of life (QOL).[6]

Until 2008, treatments for HAE in the United States were either lacking or associated with significant side effects. Food and Drug Administration approval of several novel treatments, including C1INH replacement, ecallantide, and icatibant for on-demand treatment of attacks and CIINH replacement for routine prophylaxis marked a significant advance for patients with HAE. Although clinical trials have demonstrated the safety and efficacy of these treatments, it is also important to understand their impact on disease burden. We performed a large patient survey to understand the current state of HAE care, from a patient perspective, after the recent introduction of several novel therapies.

METHODS

Data Collection

One session of the United States Hereditary Angioedema Association patient summit, held in Orlando, FL in September 2013, was devoted to data collection for this study. Other sessions during the summit were dedicated to addressing additional patient related HAE issues. The patients that attended this summit were self-selected, and diagnosis of HAE was self-reported. The purpose of the data collection was explained to the patients in attendance by the investigators, and participant responses to questions were captured using an audience response system (Padgett Communications). Data from each individual audience response system transmitter were captured individually, allowing patterns of responses to be analyzed across the different questions. An Investigational Review Board waiver was granted because the data were de-identified.

Questionnaire

Questions were developed by collaborating HAE experts (A.B., M.R.) to characterize the current state of HAE care. Questions were categorized into several broad areas, including patient characteristics, burden of disease, and treatment options.

RESULTS

Patient Characteristics

Among 186 patients with HAE, 116 (62%) self-identified as type I, 33 (18%) as type II, and 37 (20%) as presumed HAE-nlC1INH. Patients with HAE-C1INH are analyzed and described separately from HAE-nlC1INH patients. Most HAE-C1INH patients had their first symptoms of angioedema before 18 years of age (82%), with a few reporting initial symptoms between 18–25 years of age (10%) and after they turned 25 years old (8%). HAE-nlC1INH patients presented later with 44% of patients reporting initial symptoms after 18 years of age. Although 33% of HAE-C1INH patients were accurately diagnosed within one year of their first HAE attack, there was a delay of more than 10 years in diagnosing 32% of patients. The other patients reported a lag of 1–3 years (10%), 4–7 years (13%), or 7–10 years (12%). Similarly, 60% of HAE-nlC1INH patients reported a delay in diagnosis of at least 10 years.

The majority of HAE-C1INH patients had an allergist/immunologist (78%) managing their symptoms, with a smaller number being managed by a family medicine physician (12%) or other physician (5%). Similarly, almost all HAE-nlC1INH patients were being managed by an allergist/immunologist (94%). A few HAE-C1INH (5%) and HAE-nlC1INH (3%) patients reported not having any health care professional managing their symptoms. HAE-C1INH patients lived in rural areas (24%), towns (28%), cities (31%), and large metropolitan areas with a population more than 1 million (16%) with a distribution similar to HAE-nlC1INH patients.

Burden of Disease

Most HAE-C1INH (72%) and HAE-nlCINH (76%) patients reported that HAE had a significant impact on QOL. Attack frequency was quite variable in all patients, with 28% of HAE-C1INH patients reporting at least one attack a week, another 36% reporting attacks at least once a month but less than once a week, 18% reporting attacks every 2–3 months, and 18% with attacks less than every six months. If left untreated, 86% of HAE-C1INH and 85% of HAE-nlC1INH patients reported that at least 75% of their attacks are severe enough to negatively impact their QOL.

Despite the frequency of attacks, with the availability of several newer treatment options, most HAE-C1INH patients went to the emergency department (ED) or were hospitalized less than once every six months (80%), with a small minority requiring ED visits/hospitalization several times a month (4%). HAE-C1INH patients frequently reported being unsatisfied with the care they received during the ED visit (70%) but were happy with the level of care provided by the physician managing their HAE-C1INH (80%). In slight contrast, 25% of HAE-nlC1INH patients report going to the ED or were hospitalized at least once a month for an attack. Although HAE-nlC1INH patients also report being unsatisfied with ED care (85%), only half are happy with the care provided by their HAE physician.

Treatment Options

A majority of HAE-C1INH patients had an individual treatment plan (76%) developed with their HAE

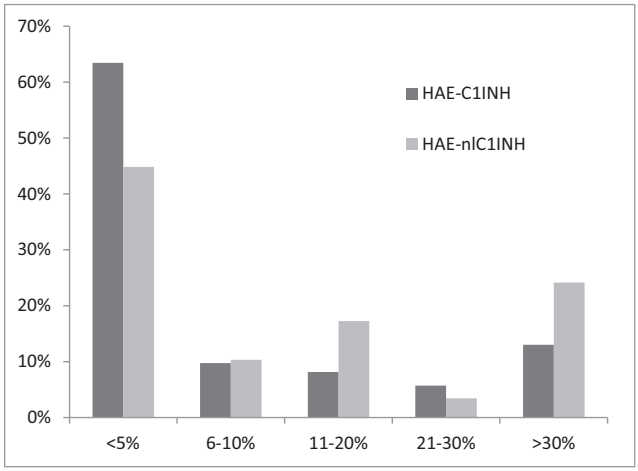

Figure 1. *Rebound or recurrence of symptoms after on-demand treatment in HAE-C1INH and HAE-nlC1INH patients.*

physician in contrast to 50% of HAE-nlC1INH patients. Most (88%) HAE-C1INH patients had on-demand treatment available and almost all of these patients (96%) had on-demand treatment available at home. Slightly fewer HAE-nlC1INH patients (76%), but still a majority, had on-demand treatment available, and all of these patients had their on-demand treatment available at home.

More than half (57%) of HAE-C1INH patients were treating at least 90%–100% of their HAE attacks on demand. However, 22% of patients were infrequently (less than 25% of the time) treating their HAE attacks. Very few HAE-C1INH patients reported rebound or recurrence of symptoms after on-demand treatment for an HAE attack in slight contrast to HAE-nlC1INH patients (Fig. 1). Half of HAE-C1INH patients repeated the same HAE drug to treat rebound symptoms, whereas 27% used a different HAE therapy, 18% do not treat recurrence at all, and 5% go to the ED. The majority (68%) of HAE-nlC1INH repeated the same HAE drug to treat rebound symptoms.

Among patients surveyed, 66% reported currently using prophylactic therapy for HAE-C1INH and most commonly receiving prophylaxis at home. In contrast, only 17% of HAE-nlC1INH patients are on prophylaxis. Despite prophylaxis, HAE-C1INH patients frequently continue to have breakthrough attacks (Fig. 2). Most HAE-C1INH patients on prophylaxis usually use a different drug to treat the breakthrough attack (68%), whereas some repeat the drug used for prophylaxis (25%).

DISCUSSION

We surveyed 149 HAE-C1INH and 37 HAE-nlC1INH patients, and our findings suggest that the current state of HAE management seems to be improving compared with previous patient surveys.[7,8] This is likely related to the availability of novel therapies allowing for better on-demand and prophylactic treatment options and increased satisfaction of care from their HAE physician at least for HAE-C1INH patients. Advances in patient care are clearly evident, with large numbers of HAE-C1INH and HAE-nlC1INH patients reporting access to on-demand treatment at home and using established emergency treatment plans developed by physicians familiar with HAE management. However, HAE patients still have a significant burden of disease with frequent attacks and despite progress; improvement in the care of individuals with HAE and especially HAE-nlC1INH is still needed.[7,9,10]

Early diagnosis of HAE is a critical step to improving patient management and decreasing burden of disease. On average, patients have previously reported visiting approximately four physicians over seven to eight years before receiving an HAE-C1INH diagnosis.[11] This is supported by recently published studies reporting delays of at least 8–10 years from onset of initial symptoms to diagnosis.[12,13] Unfortunately, our survey shows that significant delays in diagnosis still exist for both HAE-C1INH and HAE-nlC1INH patients. Additionally, almost half of HAE-C1INH patients reported waiting more than a year after their first attack before seeking medical attention.[11] Barriers to early diagnosis, including poor recognition of HAE symptoms and lack of understanding diagnostic labs, need to be addressed by the medical community, but also patients need to be encouraged to seek evaluation themselves. Several guidelines[14,15] addressing these barriers have recently been published. However, continued educational efforts targeting physicians and patients appear necessary to reduce this diagnostic delay.[16]

A recent study demonstrated that only 48% of immediate and 26% of extended family members were tested for HAE-C1INH and that 65% of patients reported having received a misdiagnosis with 19% in the United States (24% in Europe) undergoing unnecessary surgical procedures.[11] Such findings highlight the importance of HAE specialists discussing the risks and benefits of testing family members of HAE-C1INH patients in an effort to prevent complications in undiagnosed or misdiagnosed individuals. Improved screening for HAE-C1INH with a simple C4 level among family members of HAE-C1INH patients is an important straightforward step that can substantially increase the detection of HAE-C1INH in affected families. Additionally, reassurance that safe and effective treatments are available is an important part of this conversation.

In our survey, the introduction of several novel therapies in the United States has led to the majority of HAE-C1INH and HAE-nlC1INH not only having access to on-demand therapy but having access at home for self-administration. This is critical to treating an

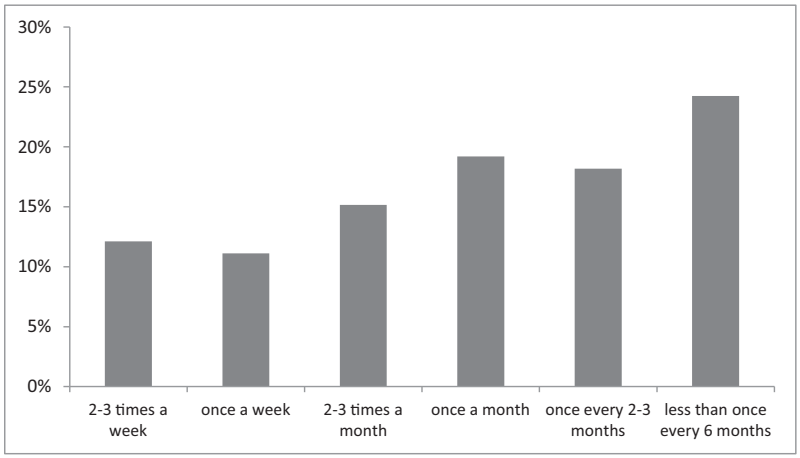

Figure 2. *Frequency of breakthrough attacks in HAE-C1INH patients using prophylactic therapy.*

attack as early as possible to prevent worsening swelling. The improved access to on-demand therapy likely explains the decreased need for emergency services and hospitalizations reported by patients in this survey. These findings show significant progress and are encouraging. However, angioedema attacks need to not only be treated as early as possible but prevented all together to continue to decrease the burden of illness in HAE patients.

Interestingly, many HAE-C1INH patients in our survey are using prophylaxis. However, HAE-C1INH patients are reporting attacks despite prophylaxis, and more concerning is patients that are not adequately managing these breakthrough attacks. The number of attacks per year averaged 26.9, with a higher incidence in women than men (mean 29.8 versus 17.9 per year), although attack duration was similar. In terms of severity, 15.5% of HAE-C1INH patients described attacks as mild (noticeable symptoms, no impact on activities of daily living), 56% as moderate (intervention desirable, activities of daily living were affected), and 28.4% as severe (intervention required, unable to perform activities of daily living).[6] Although safe and effective treatment options are increasingly available in the United States and Europe,[17] all HAE patients require an individualized treatment plan with clear education on the details of how best to use the medications to treat their attacks. As per published consensus recommendations, HAE-C1INH patients should be encouraged to treat all attacks, to treat the attack as soon as it is clearly recognized, and to always carry two doses of on-demand treatment.[14]

Our survey shows that a few patients are still presenting to the ED frequently with HAE-C1INH and more frequently HAE-nlC1INH attacks. More concerning is dissatisfaction of the care received by HAE patients in the ED. HAE-C1INH patients reported an average of 4.7 ED visits per year, with many misdiagnosed and treated for allergic reactions, including anaphylaxis (20.6%).[18] More than 40% of patients in this same survey by Huang *et al.* reported having no trust in ED physicians.[18] Physicians managing HAE patients should consider a comprehensive approach to management of the patient, including an individualized treatment plan that includes a "back-up" plan regarding emergency care when they present to the ED to guide ED physicians. This is even more critical in HAE-nlC1INH patients, where diagnostics tests are lacking. Although ideally the use of effective HAE medications will prevent angioedema emergencies and hospitalizations, airway involvement as well as severe or complex attacks may still require emergent care. Therefore, HAE physicians must work with their patients to proactively communicate with local hospitals, including written action plans, and when possible, flag medical records to indicate the rare condition and the unique specific treatment required.[19]

The limitations of our study include population bias due to the self-reported nature of HAE by all the patients but especially in patients with HAE-nlC1INH, because there are no lab tests available to confirm an HAE-nlC1INH diagnosis. The patients that attended this summit were self-selected, and we must keep in mind that they may differ significantly from the general HAE population in the United States. Data on which drug was used for long-term prophylaxis by the patient were not obtained (androgens versus C1INH). Also, data were gathered at a single time point rather than longitudinally, and not every patient answered all the questions. However, our study has several clear advantages. For example, we were able to collect data from a large number of HAE patients simultaneously and assess current state of management from the perspective of a patient with HAE.

In summary, we report descriptive data from a patient-based survey of almost 200 patients with self-reported HAE. The majority of patients had access to effective on-demand treatment options at home with an emergency plan of care in place. This represents significant progress and highlights the impact of recent

clinical advances and publications in the HAE field. Although our study was not designed to specifically assess QOL, it appears that individuals affected by HAE have better access to effective care and are more satisfied overall with the management of their condition, but improvements especially in the care of HAE-nlC1INH patients are needed. Our findings further highlight a number of continued difficulties faced by HAE patients, pointing to the need for continued research and educational efforts aimed at decreasing the burden of disease.

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Erratum

In the article *Selection of patients for sublingual immunotherapy (SLIT) versus subcutaneous immunotherapy (SCIT),* Allergy Asthma Proc 36, 100–104, 2015; doi: 10.2500/aap.2015.36.3830, there is an error in the Figure 2 legend. The correct legend is: Figure 2. The long-effects of Oralair 300 IR over the treatment period of three years with two year follow-up compared to placebo. Patients, ages 18–50, were randomized to placebo or verum for 2 (A) or 4 (B) months preseasonally and coseasonally. The primary end point was the daily combined score. A and B both demonstrate statically significant differences in the least square means of the daily combined score in the SLIT treatment groups compared to placebo. Posttreatment efficacy of Oralair was observed in years 4 and 5.

The authors regret the error.

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