

Assessment on hereditary angioedema burden of illness in Brazil: A patient perspective

Anderson Abdon Barbosa, M.D.,¹ Raquel de Oliveira Martins, M.D., Ph.D.,²
Renata Martins, M.D., Ph.D.,² and Anete Sevciovic Grumach, M.D., Ph.D.¹

ABSTRACT

Background: Hereditary angioedema (HAE) is an autosomal dominant disorder that affects ~1 in 50,000 individuals. The disorder is characterized by spontaneous and gradual episodes of edema in subcutaneous tissues or mucosal membrane that may endanger the patient's life. Previous studies that concern HAE treatment and burden of illness in the United States and Europe suggest an improvement in the control of HAE. However, no similar data are available in South American patients. The purpose of the present study was to evaluate the burden of disease and compliance to therapy of patients with HAE in Brazil.

Methods: We developed a structured questionnaire to assess the variables that influence the diagnosis and treatment of Brazilian patients with HAE. The questionnaire was evaluated by allergists with expertise in HAE and was reformatted before applying it. The consent form was included before survey access; approval from the ethic committee of Faculdade de Medicina do ABC (Santo André, São Paulo, Brazil) was ensured. The Brazilian association of patients with HAE distributed the survey by e-mail to associated patients all over the country, and responses were accepted within a period of 3 months after signing a consent form.

Results: Ninety patients (67 women, 23 men; average age, 36.5 years) responded; the main findings were the following: 53 of 90 (64%) had no need of visiting emergency departments in the past 6 months; 71 of 90 (79%) reported life-threatening fear due to their diagnosis; 73 of 90 (83%) had other family members affected, but 54 of 73 of these affected relatives did not look for specific HAE treatment; and 26 of 90 (29%) reported death due to asphyxia or throat swelling in family members.

Conclusion: Patients with HAE report understanding how severe their diagnosis represent, but they did not ponder how important their commitment to treatment may decrease the constant fear brought by the disease in its possible swelling crisis. Family data supported this conclusion.

(Allergy Asthma Proc 40:193–197, 2019; doi: 10.2500/aap.2019.40.4207)

Hereditary angioedema (HAE) is an autosomal dominant disorder that affects ~1 of 50,000 individuals. Involvement of several generations in the same family is commonly reported and supports a genetic predisposition.^{1,2} The disease is related to a deficit in production and/or functional activity of a plasma protein, C1 inhibitor (C1-INH). This serine protease controls the activation of the complement system, fibrinolytic system, and coagulation and contact activation pathways, as well as the C1-INH deficit results in excessive production of bradykinin.^{3,4} A patient with HAE presents with attacks of edema in subcutaneous tissue and mucosal membranes, which possibly endangers the patient's life. The most commonly affected organs are

skin, gastrointestinal tract, and upper airways, which lead to subcutaneous edema in the face, extremities, genitals; abdominal pain; vomiting and diarrhea; and laryngeal edema. This clinically perplexing condition requires a long-term approach and follow up under the care of a medical specialist.⁵ In general, patient's attitude toward his or her own health and the acceptance of the chosen therapeutic plans depend on numerous variables.⁶ These variables include demographic factors (age, sex, marital status, social class), treatment factors (duration, number of medications, cost, frequency of dosing), and disease factors (including clinical setting, therapeutic regimen, and associated features, *e.g.*, psychiatric disorders).⁷

Previous survey-based studies of HAE management and burden of illness in the United States⁸ and Europe^{9,10} showed a wide range of consequences due to patients' experience with the disease. These studies presented both a variability of frequency of attacks among study subjects as well as inclusion of patients who frequently experienced attacks despite continuous use of prophylactic medication. Moreover, the health-care delivery systems and access to therapy are different in developing countries in comparison with those more industrialized countries. The accep-

From the ¹Clinical Immunology, Faculdade de Medicina do ABC, Santo André, São Paulo, Brazil; ²Associação Brasileira de Portadores de Angioedema Hereditário A.S. Grumach has participated of educative programs developed by CSL Boehringer and Shire, and she is consultant for Shire, CSL Boehringer, and Byocrist. The remaining authors have no conflicts of interest to declare pertaining to this article. No external funding sources reported.

Supplemental data available at www.IngentaConnect.com

Address correspondence to Anete Sevciovic Grumach, M.D., Faculdade de Medicina do ABC/CEPES, Av Lauro Gomes, 2000, Santo André, 09060–870, São Paulo, Brazil. E-mail address: asgrumach@gmail.com

Copyright © 2019, OceanSide Publications, Inc., U.S.A.

tance of icatibant has had a slower uptake in countries where it was initially introduced, such as Brazil, Colombia, Mexico, and Argentina, and most countries in Latin America still use fresh-frozen plasma as rescue therapy for attacks.¹¹

At the same time, antifibrinolytic agents and attenuated androgens are still largely used as long-term prophylaxis in South American patients.¹¹ In contrast, treatment approaches such as plasma-derived C1-INH replacement, as Berinert (CSL Behring, Pennsylvania) and Cinryze (Shire Plc, now part of Takeda, Lexington, Massachusetts), recombinant C1-INH, ecallantide and icatibant, for on demand treatment are largely used in Europe and North America. When considering these previously described barriers to access to therapy in developing countries, our goal was to evaluate the burden of disease in patients with HAE and available data on treatment in Brazilian patients. To our knowledge, no similar study has been reported on patients with HAE in Latin America.

METHODS

Structuring Questions

We organized the first structured interview by using references in the literature about the disease allied with the knowledge acquired in the clinical routine treatment of HAE.^{1,2,12} In addition, questionnaires applied for other immunologically mediated diseases in the clinical immunology field such as asthma,¹³ chronic urticaria,¹⁴ and atopic dermatitis¹⁵ were also included. The structured interview consisted of 37 questions composed of two different sections: personal and epidemiologic questions about the patient, and questions about cognition and patient's behavior toward treatment. This structured questionnaire was sent to 18 HAE specialists in Brazil to evaluate and criticize its composition and efficiency. Approval and inclusion of each question was based on an acceptance rate by the experts of 75%. In addition to the initial assessment, the experts also made constructive suggestions to improve the questionnaire, which resulted in added questions and the exclusion of others. The second version was resubmitted for new assessment by the same specialists, and a 75% approval rate was reached.

In summary, the first section of structured questions focused on patient's age, gender, and social characteristics as well as information about additional occurrences of HAE in the family, the need for emergency services due to HAE attacks, the history of unnecessary procedures related to HAE, triggering factors of HAE attacks, and the need for psychological and/or psychiatric support. The second section explored points about patient satisfaction and commitment with the treatment, evaluation of the access to therapy, the relationship among patients and their physician, fear of

onset of a sudden crisis, and the hope in development of new forms of therapy. The final structured interview was composed of 46 questions: 26 questions in the first section and 20 in the second section.

Patients

Patients were invited to participate of the study by e-mail sent by the Brazilian association of patients with HAE (ABRANGHE) or by personally reaching out to diagnosed patients in the clinical immunology service at the Faculdade de Medicina do ABC (Santo André, São Paulo, Brazil). Inclusion criteria consisted of the following: a confirmed HAE diagnosis, age ≥ 18 years old, and Brazilian birth. Approval from the ethics committee of Faculdade de Medicina do ABC and informed consent from each study subject were obtained before initiation of the study (Certificado de Apresentação para Apreciação Ética (CAAE) 18357413.2.0000.0082). After explaining the aim of the survey to each study subject, a web link would direct him or her to the consent form to be completed before initiation of the survey. Confidentiality of the data and information was assured through the online survey development cloud-based company that received all responses on their online data base and then produced a spreadsheet with all of the collected data. Basic descriptive statistics were performed by using Excel 2013 (Microsoft Corporation - Redmond, Washington) to obtain simple indices, such as the mean and analysis of variation, and the ratios were converted into percentages to obtain a general and broad view of the collected responses. The same software was used to perform correlations, such as gender-related distributions and life-threatening perceptions related to a diagnosis of HAE.

RESULTS

In the period between February and June 2015, 90 patients (67 women and 23 men), with an average age of 36.5 years (range, 18–0 years; median, 35 years) answered the survey. The first HAE symptoms were reported in 40% ($n = 36$) of the patients during childhood (ages, up to 10 years old) and 29% ($n = 26$) during adolescence (ages, 11–20 years). When asked about the establishment of an HAE diagnosis, 56 (62%) answered that it happened 1 to 5 years before the day they answered the survey and 11 (12%) answered that they had their diagnosis > 15 years before the survey response. A familial history was reported in 83% ($n = 73$); 74% of these relatives (54/73) were not treating the condition. Death in the family due to upper airway obstruction was present in 29% of the respondents (26/90). Twelve of 19 respondents with ≤ 1 year of established diagnosis (67%) had at least one family member with confirmed HAE. At the same time, 94% of the patients with > 10 years of established diagnosis (15/16) had HAE diagnosed in family members.

With regard to data to evaluate the social condition, 61.1% ($n = 55$) lived in high-dense urban areas ($\geq 100,000$ inhabitants), and 64% had a college degree and/or a postgraduate degree. Forty-one patients (75%) who lived in high-dense urban areas (55/90) had an imminent life-threatening perception due to the diagnosis of HAE, and the only respondent who lived in an area with $< 10,000$ inhabitants, denied having this life-threatening fear. The main triggering factors reported were the following: stress (75/90), menses (40/67), weather changes (specifically in extremes of very hot or very cold weather) (31/90), infections (27/90), mild physical traumas (mainly from pressure injuries) (23/90), physical exertion (11/90), alcoholic beverages (10/90), oral contraceptives (7/90), and dental procedures (4/90). Additional reports were related to non-specific allergic manifestations (6/90), foods (specifically those considered spicy or with coloring) (10/90), medications (5/90), clothes with synthetic fabric (1/90), and cleaning products (1/90).

Thirty-three of the 90 respondents affirmed having another chronic condition diagnosed as well as more than one at the same time: hypertension (10/33), hypothyroidism (7/33), and rheumatologic disorder (6/33). Fifty-three of the respondents (58.9%) affirmed not having the need of emergency services to control HAE attacks in the past 6 months. Thirty-two (35.6%) were submitted to abdominal surgery (exploratory laparotomy), and 30 respondents (33%) had experienced an emergency intubation procedure for airways maintenance. Fifty percent (9/18) who reported more than three visits to emergency departments in the past 6 months had already needed an intubation procedure. Unsuccessful treatments as long-standing therapeutics with antihistamines, corticosteroids, and broad-spectrum antibiotics were referred in 50% of the patients before the establishment of the diagnosis.

Sixty-two patients (69%) reported no need of psychological and/or psychiatric aid, and 30 (32%) used anxiolytic and/or antidepressants prescribed by psychiatrists due to their disease caution. Eighty percent believed that medical orientation and prescriptions were efficient and sufficient to assure a good quality of life and prevent attacks. Forty-nine percent expressed personal satisfaction with treatment as well as with their physician's attention to their condition. Commitment with their treatment was stated by 87% of respondents, regardless of social or epidemiologic differences and variables, such as income, treatment understanding, and satisfaction toward medical care. There were no differences when correlating satisfaction toward medical care with socioeconomic level as well as with an understanding of the treatment regimen. Fifty-eight of the 90 respondents considered that difficulties related with accessing their medication treatment represented the main discouraging factor about their treatment,

and 71 of 90 (78.9%) perceived a constant life-threatening fear due to the disease as well as 85 of 90 respondents (94.4%) affirmed having hope about new forms of HAE treatment. See Table 1.

DISCUSSION

HAE represents a disease with a potential fatal outcome but preventable and, fortuitously, with no sequelae if well treated. Although the availability of new medications and new knowledge about HAE improved, the present study revealed several points in treatment compliance that were not attained according to physicians and patients' view.^{7-9,11} Our study aimed to identify and understand the burden of illness carried out by Brazilian patients with HAE as a country with difficult access to therapy and restricted knowledge about HAE. Options such as long-term treatment or prophylaxis with attenuated androgens are the options for HAE control included in the government's protocol. Icatibant and plasma-derived C1-INH (Berinert) represent the only drugs approved by ANVISA (the Brazilian agency for sanitary surveillance). Although our health system offers any drug at no cost to the patient if it is indicated by official protocols, the Brazilian system neither provides reimbursement for prophylaxis nor therapy for attacks. The only way to obtain therapy for attacks is a judicial appeal for a claim to the government to finance the treatment.

We based our data on a survey with questions previously structured and critically revised by specialists. We were able to create a general perspective of the patients with HAE in Brazil based on data collected from the patients' responses. Although it helped us know that Brazilian patients with HAE have a good understanding about what HAE is, they possibly still do not have a clear idea about what the treatment means for their health and well-being. Female patients' responses were predominant as seen in other survey-based studies and could reflect a higher occurrence seen in most researches, possibly due to hormonal influence as the triggering factor.^{3,4}

The majority of the patients who lived in dense urban areas could reflect the need to be close to more health centers, mostly affiliated with educational and research centers as well. In contrast, the frequency to emergency departments needed by the Brazilian patients with HAE was not as expected. More than half of the respondents answered not having the need of hospital assistance in the past 6 months. When considering that Brazilian patients have restricted access to on-demand therapy, understanding the reason for this observation is unclear. However, most of the diagnoses were made in urban areas and populated cities because universities and other high educational centers are located there; this could explain why most respondents

Table 1 Main questions and patients' responses to the questionnaire

Question	Yes, no. (%)	No, no. (%)
Family members with HAE?	73 (83)	15 (17)
Family members treating?	36 (40)	54 (60)
Death in the family due to sudden throat swelling?	26 (28.9)	64 (71.1)
Previous abdominal surgery without definite cause?	32 (35.6)	58 (64.4)
Ever needed intubation or an emergency procedure?	30 (33.3)	60 (66.7)
Needing psychological aid due to HAE?	28 (31.1)	62 (68.9)
Any medicine for anxiety or depression?	30 (33.3)	60 (66.7)
Any treatment for HAE that did not work out?	36 (40)	54 (60)
Any adverse effects of treatment that affected quality of life?	34 (37.8)	56 (62.2)
Do you have a life-threatening fear?	71 (78.9)	29 (21.1)
Do you believe that treatment would help?	80 (88.9)	10 (11.1)
Access to HAE drugs discourages health improvement?	58 (64.4)	32 (35.6)
Hope for new therapies for HAE?	85 (94.4)	5 (5.6)

HAE = Hereditary angioedema.

were in these areas, where better care could be obtained, *e.g.*, and with better access to the Internet.

With regard to the abovementioned characteristics, the fact that a large part of the respondents lived in highly dense urban areas, the use of the Internet for applying the survey could paradoxically introduce limitations for the survey. Although the survey application distinguished patients from every region in Brazil, it reflected mostly high-dense urban areas, which meant a limitation to our survey as well as the fact that we could only reach those who had Internet access and were registered in the patients' association to answer our questions. That more than half of the respondents claimed to have a higher education degree (65% of them had a graduate or postgraduate degree) could have led to a better understanding of their health condition and, therefore, reflected a better expectation of patients' self-care.^{6,7} Although this could differentiate our study; several survey responses did not suggest (or confirm) the association of better educational degree and more adequate therapy. For example, most of the patients did not seek medical care in emergency departments during the attacks, although one-third required intubation.

Seventy-three percent of the respondents (73/90) had other family members with an HAE diagnosis and, at the same time, 74% of their relatives (54/73) had not been treated for HAE. This finding was one of the most surprising and disquieting results when considering that family screening and support should be emphasized. We envisioned a strong network among diagnosed family members with HAE because the auto-

somal dominant inheritance of the disease leads to multiple cases in a single family. In addition, 26 of 90 respondents had mortality episodes within the family due to asphyxia or to throat swelling, which are the most fatal consequences of HAE. From this perspective, we concluded that this situation among family members indicated that either the severity of the disease was underestimated or their approach to the disease and/or treatment was inappropriate. Correspondingly, this was consistent with the available international data concerning a low prevalence of diagnosis and treatment in family members of patients with an already established diagnosis of HAE.^{9,16}

In comparison with other available data about psychological burden and depression,^{12,17} only a minority of Brazilian patients seemed to need or to look for psychological aid (~31% in our responses) or psychiatric assistance (32% in our responses) to help cope with their disease. This suggested a minor prevalence of depression or anxiety in Brazilian patients with HAE in comparison with related worldwide findings.¹⁷ However, one-third of the patients used drugs to control anxiety. This finding may reflect a cultural position regarding those psychologists and psychiatrists care or the denial of the disease effects, which suggests future studies in this field. The patients' rate of satisfaction toward the availability of physicians who took care of them was positive. This conclusion was substantiated in 56% of the respondents ($n = 50$) who claimed to understand well what the disease is and were able to explain what it is to others. In addition to this matter,

access to the medicines seems to be reportedly discouraged at many levels due to their high cost, procurement difficulty, and/or the impossibility of obtaining them through the public health system.

CONCLUSION

In the present study, compliance to treatment in patients with HAE seemed not to be proportional to the burden of disease. This conclusion was confirmed by responses that showed that 60% of the patients ($n = 53$) did not seek emergency services in the past 6 months and, in contrast, ~79% ($n = 71$) had a constant life-threatening fear for their lives due to the diagnosis of HAE. We concluded that patients with HAE comprehended the severity of their diagnosis, but they did not ponder how the importance of their commitment to treatment may decrease their fear. Although the majority of the patients answered that they were satisfied with their treatment and their physician's attention, a familial history of HAE without medical care is still hard to understand when considering that almost one-third of the respondents also claimed to have had death cases in their family due to an airway obstruction. At the same time, patient concerns about the difficulty of accessing medication sadly reflect a poor health program regarding attention to a rare disease in Brazil. Some of these patients related the need to travel from their own state or territory to obtain proper medical care or to finally establish their diagnosis.

These data portrayed a different perspective compared with patients with HAE in the United States or Europe who already have easier access to on-demand medications.^{8,9,18} This survey added an important view about how behavior of patients with HAE, exemplified in the face of a new diagnosis, was related to their acknowledgment of HAE and limited access to therapy. Treatment compliance in patients with HAE was reflected in the spectrum of factors that ranged from patients' behavior and how much the burden of illness weighs on them. In other words, it indicated a balanced relation between coping with the disease and accepting it as part of them. Therefore, we expect that, enabled by a new perspective of treatment and diagnosis, patients with HAE would transform their fear into care and use their disease knowledge to ensure safety for themselves and their relatives with HAE.

ACKNOWLEDGMENTS

We thank the specialists who kindly evaluated the questionnaire and to Conselho Nacional de Desenvolvimento Tecnológico e Científico (CNPq) (105345/2015–6) for supporting the research and to a grant from the Shire Research Program for Investigators issued to A.S. Grumach.

REFERENCES

1. Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet*. 2012; 379:474–481.
2. Giavina-Bianchi P, Arruda LK, Aun MV, Campos RA, Chong-Neto HJ, Constantino-Silva, RN. et al. Brazilian Guidelines for Hereditary Angioedema Management - 2017 Update Part 1: Definition, Classification and Diagnosis. *Clinics* (Sao Paulo). 2018; 73: e310.
3. Bouillet L. Hereditary angioedema in women. *Allergy Asthma Clin Immunol*. 2010; 6:17–20.
4. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006; 119:267–274.
5. Valle SOR, França AT, Campo RA, Grumach AS. Angioedema hereditário (Hereditary Angioedema). *Rev Bras Alerg Imunopatol*. 2010;33:80–87. Available at http://www.sbai.org.br/revistas/Vol333/angioedema_33_3.pdf.
6. World Health Organization. Adherence to long term therapies: evidence for action. Geneva: World Health Organization, WHO, 2003.
7. Vermeire E, Hearnshaw H, Van Royen P, and Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001; 26:331–342.
8. Banerji A, Busse P, Christiansen SC, et al. Current state of hereditary angioedema management: a patient survey. *Allergy Asthma Proc*. 2015; 36:213–217.
9. Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. *Acta Derm Venereol*. 2015; 95:706–710.
10. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014; 9:99.
11. Fabiani J, Valle SO, Olivares M, Nieto S, Landeros EH et al. Improving Care of Hereditary Angioedema With C1 Inhibitor Deficiency (Type 1 and Type 2 Hereditary Angioedema) in Latin America. *J Investig Allergol Clin Immunol* 2014; 24:445–447.
12. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, and Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010; 31:407–414.
13. Baiardini I, Braidò F, Giardini A, et al. Adherence to treatment: assessment of an unmet need in asthma. *J Invest Allergol Clin Immunol*. 2006; 16:218–223.
14. Ferreira EAP, Mendonça MB, Lobão AC. Adesão ao tratamento da urticária crônica (Treatment adherence of Chronic Urticaria). *Estudos de Psicologia* (Campinas) 2007; 24:539–549.
15. Ohya Y, Williams H, Steptoe A, et al. Psychosocial factors and adherence to treatment advice in childhood atopic dermatitis. *J Invest Dermatol*. 2001; 117:852–857.
16. Lunn ML, Santos CB, Craig TJ. 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? *Ann Allergy Asthma Immunol*. 2010; 104:211–214.
17. Fouche AS, Saunders EF, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2014; 112:371–375.
18. Kalaria S, and Craig T. Assessment of hereditary angioedema treatment risks. *Allergy Asthma Proc*. 2013; 34:519–522. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.