ORIGINAL ARTICLE

Hereditary angioedema: first report of the Brazilian registry and challenges

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Abstract

Background Hereditary Angio-oedema (HAE) is a serious medical condition caused by a rare autosomal dominant genetic disorder, in which C1 inhibitor (C1-INH) function is reduced. There is no organized information on the HAE patient population in Brazil.

Objective The Brazilian Registry was established to disseminate diagnostic access, and to better understand the main features of the disease in our country and its clinical impact.

Methods A questionnaire was prepared and sent to specialists. The completed questionnaires were forwarded to the coordinating site and then entered into the Registry. Samples from patients with an unconfirmed diagnosis were tested for C1 inhibitor and C4 levels.

Results From 2006 to 2010, 210 patients (133 females; mean age, 30 ±17 years) were included. The median age of onset of symptoms and age at diagnosis were 6.5 and 21 years, respectively; 80.9% of the patients had subcutaneous oedema, 54% gastrointestinal and 35.7% respiratory symptoms (21% had laryngeal oedema). Laparotomy due to the disease was performed in 6.2% of the patients. The majority of patients had Type I HAE of moderate severity. Twenty-seven per cent did not receive treatment; 53% were treated with danazol alone.

Conclusion A paucity of patients with Type II HAE and a high frequency of laparotomy were observed, highlighting the need for better diagnosis in Brazil. HAE related educational activities, improved diagnosis and access to available therapy are needed in Brazil.

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Conflict of Interest

None declared.

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Introduction

Hereditary Angio-oedema (HAE) is a serious medical condition caused by a rare autosomal dominant genetic disorder, in which the C1 inhibitor (C1-INH) function is reduced either due to impaired transcription (quantitative, Type I HAE, 80–85% of patients) or production of non-functional protein (functional, Type II HAE, 15–20% of patients).[1–8]

C1-INH is the primary regulator of complement activation and of contact systems (by inhibiting certain steps, mainly C1 and C-kinins) and may play a minor role in the regulation of coagulation (factor XIIa and kallikrein) and fibrinolysis (thrombin and tissue plasminogen activator). Reduced activity of C1 esterase inhibitor results in elevated plasma levels of bradykinin.[2–6,8–13] Increased levels of vascular permeability factors may suddenly diminish local endothelial barrier function. Plasma may then leak from capillaries deep within cutaneous or mucosal tissue layers. Those who are affected experience intermittent cutaneous or mucosal swellings or 'attacks', lasting between 1 and 5 days. Oedema can affect virtually any part of the integument, but it is more common in the extremities. Swellings of the skin are typically painless but may cause disfigurement, or difficulty driving or operating machinery if hands or feet are involved. Cutaneous swelling of the genital area may occasionally lead to urinary retention. Intra-abdominal oedema, affecting bowel segments or

[§§]see Appendix

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viscera, is usually very painful, may be associated with vomiting and/or diarrhoea, is occasionally mistaken for other causes of abdominal pain and may lead to unnecessary surgical intervention. When oedema occurs in the upper airways, swelling of the tongue and laryngeal oedema with imminent respiratory obstruction is life threatening.[1,2,5–7,10,12,14] Estimated lifetime risk of death from asphyxiation is fairly high (15–33%) if the attack is left untreated.[2,4–6,15]

Exact HAE prevalence is unknown, but it has been estimated that the condition affects between 1 in 10,000 to 1 in 100,000 individuals. Although the prevalence is low, the condition can result in considerable pain, debilitation, reduced quality of life and even death of those afflicted.[1]

Today, the biochemistry of the disease is better understood, but clinicians have low awareness of HAE. Therefore, HAE is frequently undiagnosed. Approximately 50% of patients will be symptomatic by age 10. However, accurate diagnosis may be delayed for decades.[3,10,16]

As HAE is associated with significant morbidity and mortality, careful management of these patients is essential. The management of HAE requires attention to three areas: treatment of acute episodes of angio-oedema, long-term prophylaxis and short-term prophylaxis. It is important to identify and reduce potentially treatable triggers of HAE attacks.[2,12,17,18]

There was no organized information on the HAE patient population in Brazil. Therefore, we created the Brazilian Network on the Diagnosis, Management and Treatment of HAE. The first initiative of this broad programme was the development of the Brazilian HAE Registry, an essential step to improve knowledge of population characteristics and develop the next steps.

Methods

Data collection

Physicians with expertise in the diagnosis and treatment of HAE developed a standard questionnaire to collect relevant information about the disease. The Department of Dermatology, University of São Paulo was the coordinating site and was responsible for organizing the data and also, in some situations, assisted with the diagnosis of new cases, with case discussions and even performed laboratory tests. Several groups participated voluntarily; allergists and paediatricians were consulted regarding the existence of HAE patients cared for in their outpatient groups or offices.

The protocol was approved by the Ethical Committee of Hospital das Clinicas, Faculty of Medicine of University of São Paulo, after previous evaluation by the Department of Dermatology. The data of the patients were included after obtaining their oral informed consent.

The questionnaire comprised demographic data, characteristics of the disease (age of diagnosis; location, frequency, intensity and duration of the episodes, family history and triggering factors), impact of the disease (previous hospitalization, surgeries and procedures due to HAE), treatment and laboratory results. Diagnosis of HAE was the only inclusion criterion for this study; no question was considered mandatory, hence patients with minimal information available were entered in the database.

Besides clinical symptoms, C1 inhibitor and C4 levels were measured by nephelometry with normal ranges of 21–40 mg/dL and 10–40 mg/dL, respectively. Functional C1 inhibitor evaluation was performed, when available, with the Berichrom® kit (normal range >84%) (Siemens, New York, USA). Treating physicians were instructed to obtain the patient's consent to participate in the registry, complete and forward the questionnaire to the coordinating site.

Data analysis

Due to the characteristics of the study design, no formal statistical analysis was performed. Data was summarized descriptively. Categorical data was presented as counts and percentages. For continuous data, the means, standard deviations, medians and ranges were presented.

Results

Demographics and disease characteristics

A total of 210 subjects were entered in the database from January 2006 to December 2010, with reports from 10 out of 26 Brazilian states (73% from Sao Paulo and Rio de Janeiro) (Fig. 1). Sixty-three percentage of the patients were female and the mean age was 30±17 years (median, 31.3; range, 1–89 years). The median age at onset of HAE symptoms was 6.50 years (range, 1 month–64 years) and the median age at diagnosis was 21 years (mean age, 21±14 years), Fig. 2. Family history of HAE was present in 78.1% (163/210) and 37 different families were identified out of 110 patients. Thirty-three of one hundred patients had no familial history.

Forty-four of the 210 patients (21.0%) were hospitalized due to HAE: 12/210 (5.7%) in intensive care units and 13/210 (6.2%) underwent laparotomy due to the disease.

Episodes were frequently triggered by trauma (41.9%) (Fig. 3). The majority of patients (80.9%) experienced subcutaneous oedema, 54.3% had gastrointestinal symptoms and 35.7% had respiratory symptoms (21.4% experienced laryngeal oedema) (Table 1). The episodes were reported to last 3–5 days in 59.8% of the patients, be of moderate intensity in 56% and occurred at least 4 times per year in 42.4%. Twenty-nine (13.8%) patients were asymptomatic and were identified by familial history.

Treatment

One hundred and fifty-two patients (72.3%) received treatment, of any kind, for the condition, either prophylactic or for attacks. Therapeutic approaches were diverse, with several possible combinations (Fig. 4). Danazol was widely used as a single agent (53%) or in combination with other drugs (9.2%). Epsilon aminocaproic

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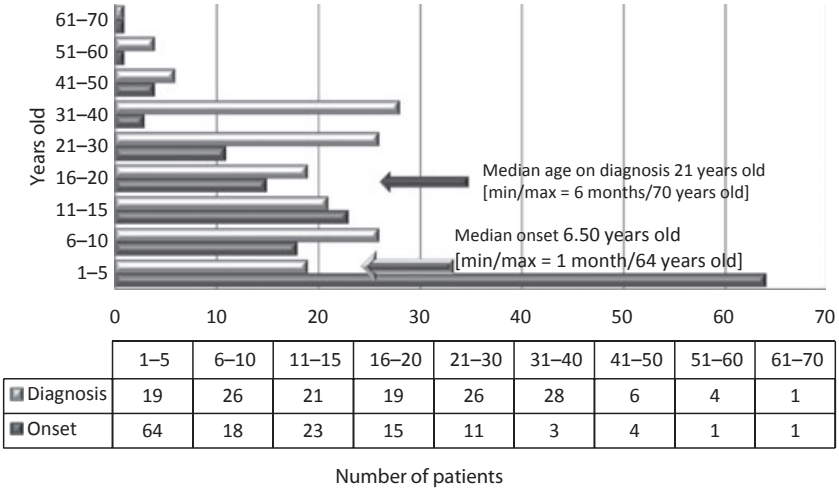
Region	Number of States	Population	% of Total Patients in Registry
North	7	15.864.454	0
Northeast	9	53.081.950	7.6
South	3	27.386.891	4.3
Southeast (includes São Paulo & Rio de Janeiro)	4	80.364.410	83.3
Center-West	3	14.058.094	0.5

Figure 1 Distribution of the cases reported according to Brazilian States and Regions.



	1–5	6–10	11–15	16–20	21–30	31–40	41–50	51–60	61–70
Diagnosis	19	26	21	19	26	28	6	4	1
Onset	64	18	23	15	11	3	4	1	1

Figure 2 Age distribution at onset of symptoms and diagnosis of condition.

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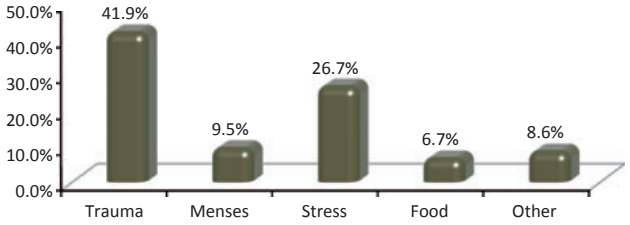

Figure 3 Triggering factors identified and reported in 111 HAE patients.

Table 1 Symptoms of HAE patients reported in the questionnaires (n=210)

	N	% (with symptoms)
Asymptomatic	**29**	**13.8%**
Subcutaneous	**170**	**80.95%**
Hands	117	55.71%
Face	108	51.43%
Feet	93	44.29%
Arms	52	24.76%
Legs	34	16.19%
Others	39	18.57%
Gastrointestinal	**114**	**54.29%**
Epigastric pain	90	42.86%
Diarrhoea	32	15.24%
Respiratory	**75**	**35.71%**
Upper airways oedema	45	21.43%
Dyspnoea	32	15.24%
Change in voice	38	18.10%
Renal	**3**	**1.43%**
Cardiac	**0**	**0.00%**
Others	**36**	**17.14%**

Bold face corresponds to the total number and percentage of the group of symptoms.

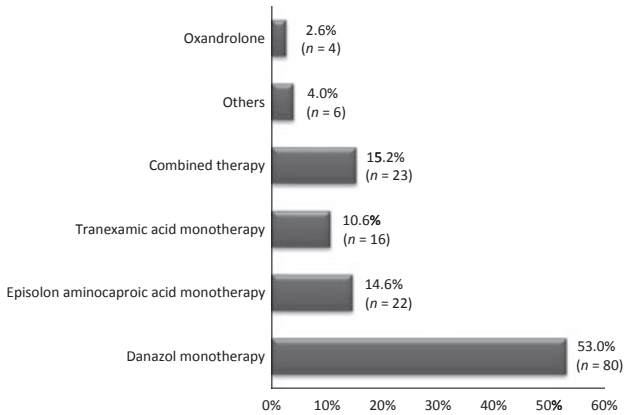

Figure 4 Approach for HAE management in the patients receiving prophylactic therapy.

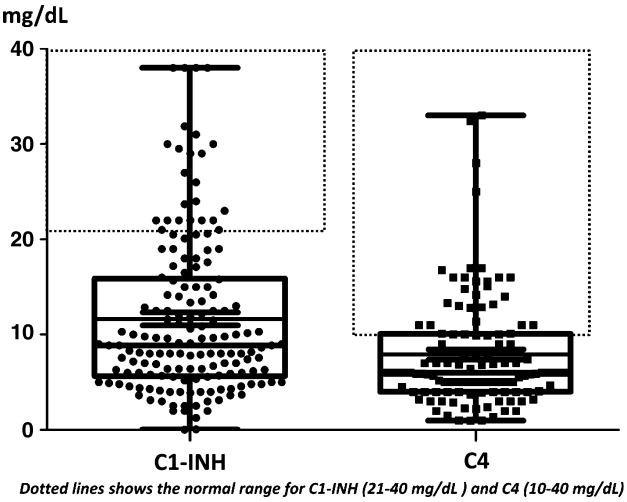

Figure 5 C1-INH and C4 levels in Brazilian HAE patients.

acid was also used as a single agent (14.6%) or in combination with other drugs (5.9%). The use of plasma for managing acute episodes was reported for 8.1% of the patients.

Laboratory results

Ten patients (4.8%) had the diagnosis of Type II HAE. C1-INH values were reported for 157 patients, with mean value of 11.67±8.43 mg/dL; median, 8.9 mg/dL and range, 0.05–38 mg/dL (normal range: 21–40 mg/dL). For C4, mean value was 7.21±5.97 mg/dL; median, 5.95 mg/dL and range, 0.02–33 mg/dL (normal range=10–40 mg/dL) (Fig. 5).

Discussion

HAE is a life threatening condition often misdiagnosed as an allergic reaction or as appendicitis.[22] Incorrect diagnosis leads to unnecessary invasive procedures or inappropriate treatment. This is a rare genetic disease that is seldom seen by clinicians;[21] therefore it is usually diagnosed by specialists several years after the onset of symptoms (on average after 10 years).

To increase awareness of HAE, we created the Brazilian Network on the Diagnosis, Management and Treatment of HAE. The results of our first initiative, the Brazilian Registry of HAE, are presented here. During the last census by the Brazilian Institute of Geography and Statistics, in 2010, the estimated Brazilian population was approximately 190 million people.[19] If we consider the disease prevalence to be 1 : 50 000, we could expect, at least, about 3800 people suffering from HAE in Brazil. We received questionnaires of 210 patients, which is a representative sample of this population. Although representative, the majority of the cases were reported from Sao Paulo and Rio de Janeiro. Increased identification of cases has been noted in other States but more national coverage and awareness are still required. It was shown that some Brazilian regions had few or no cases, reflecting under

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diagnosis, an aspect to be improved by an educational programme.

Delayed diagnosis and unnecessary invasive procedures are common in this condition. The mean age at diagnosis in our registry was 21±14 years old and 6.2% of the patients underwent laparotomy. In a web-based survey of patients in the United States and some European countries, Lunn *et al.* collected information from 313 patients. They found that it took an average of 8.3 years to diagnose HAE and that HAE was misdiagnosed in 65% of the patients as an allergic reaction or appendicitis. Around 20% of their patients underwent unnecessary surgical procedures.[22] Romero *et al.* (Argentina) reported a clinical overview of 58 patients; onset of symptoms was usually during the first decade of life, but was diagnosed 15 years later.[23] This pattern is different for members with a familial history who are screened for HAE. We found that patients diagnosed earlier (<3 years after onset of symptoms) frequently (37/40) had a positive family history. Presence of the disease in the family can lead to consultation with an expert (or with the same physician as the affected relative) and to an evaluation more focused on HAE. We have to consider that 51 patients had relatives probably affected but not previously evaluated. In contrast, 13.8% of asymptomatic cases were identified due to familial history.

In terms of type of HAE, only 10 patients out of 210 (4.8%) had type II. Fabiani *et al.* (Argentina) found that 5.7% (5/88) of their patients had this functional defect.[9] According to published reports, it is expected that 15–20% of patients should have type II HAE.[20] Consequently, we believe that in our group, the low frequency of type II HAE was primarily due to the limited access to the functional C1-INH assay. To fulfil this need, reference laboratories, which will perform assays free of charge for the Brazilian population, were established.

In a 6-month prospective study, the majority of the episodes involved subcutaneous (93%), abdominal (86%) and laryngeal (41%) symptoms.[23] We have begun a prospective study using another, more extensive questionnaire, which is currently in progress. Nevertheless, the results of this study concur with published evaluations of similar populations, regarding onset of symptoms during the first decade of life, family history and episode duration, frequency, location and intensity.[3,10,16,20,22,23]

The proportion of patients reporting food as triggering factor (6.7%) was remarkable. The revision of the 2010 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angio-oedema[15] and other literature about HAE[1,12] reported that the most common triggering factors included puberty, oestrogen-containing contraceptives, hormone replacement therapy, menstruation, pregnancy, stress, infections, ACE-inhibitors and minor trauma; the implication of food as a triggering factor for HAE episodes provides new insight into this disease.

In addition to the limited clinical description of HAE, the treatment of HAE has been a challenge in our country as well as in all Latin American countries. The availability of drugs for acute attacks was almost non-existent except for in Argentina, which has long had access to plasma derived C1 inhibitor. Our patients are usually treated with danazol for prophylaxis; plasma is still administered during acute episodes. We observed increased C1 inhibitor and C4 concentrations in 15/210 (7.1%) in patients under therapy with danazol. The indications for long-term preventive therapy vary widely and may be very broadly defined[24]: more than one attack per month, rapid progression of attacks, limited access to prompt treatment (which is our case), history of laryngeal involvement, more than three emergency treatments per year, intubation for an HAE attack, more than 10 missed days of school or work per year, severe anxiety or impaired quality of life, effect on lifestyle (vacation, family or sports) and dependency on pain medication.[15,24,25]

We found geographical differences in clinical management of the disease; in Sao Paulo prophylactic therapy was mainly based on the use of danazol, however in Rio de Janeiro it was balanced between danazol (29.9%) and epsilon aminocaproic acid (25.4%). The use of high doses of androgens was reported (600 mg/day) by other centres, with side effects.[26,27] According to our data, most patients received a median dose, 200 mg/day, which has acceptable long term adverse effects, according to recent data.[28] The absence of specific therapy for HAE attacks probably contributed to the higher doses of danazol reported in our study. However, even in countries with access to therapy for acute attacks, long-term therapy with androgen derivatives was used in 25–50% of the patients.[25]

Tranexamic acid has been reported as the antifibrinolytic agent preferentially used in other countries. Its availability is limited in our country because it is not supported by the Government. No definitive clinical response related to antifibrinolytics has been established and their efficacy is based on observational studies.[28] At the time the data was collected, no report of patients treated with the newer HAE therapeutic options had been published. In Brazil, icatibant was launched at the end of 2010 and other drugs, even plasma derived C1 inhibitor, are not yet widely available.

The Brazilian Network on the Diagnosis, Management and Treatment of HAE aims to create educational programmes for physicians of several specialties (paediatricians, allergists, dermatologists, gastroenterologists and general practitioners) and for patients; to develop laboratories for diagnosis; to assist Patients' Advocacy Groups and to provide patients with the best treatment options for the disease. It is remarkable how the diagnosis of patients has improved after this first registry was established. A network was created to spread the registry to all Latin American countries. In order to maintain the initial efforts and widen the coverage of the Brazilian Registry, the Brazilian Society of Allergy and Immunopathology included an official registry on their website and educational programmes have been supported.

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*Sequence of names organized according to the number of cases registered.

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