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Hereditary angioedema: 24 years of experience in a Portuguese reference center

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Key words

Hereditary angioedema; angioedema; C1-inhibitor deficiency; treatment; prophylaxis.

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Impact statement

HAE poses a high burden of disease, but there is still evidence of long diagnostic delay, especially in those without family history, emphasizing the need to raise disease awareness.

Summary

Background. *Hereditary angioedema (HAE) poses a high burden of disease, being its epidemiological and clinical data heterogeneous among countries, with no recent published studies concerning Portuguese patients. Therefore, we aimed to raise awareness of HAE and to contribute to clinical knowledge.* ***Methods.*** *An observational, descriptive, retrospective, and cross-sectional study was performed, that included a cohort of 126 patients followed in a single Portuguese center.* ***Results.*** *We observed a high prevalence of HAE-C1-INH type II (45.2% of patients). Most HAE patients (67.4%) presented the initial manifestations of the disease before adulthood, at a mean age of 12.6 ± 8.4 years. However, we found a long delay in HAE diagnosis, especially in those without family history (mean 20.7 ± 17.3 years). Stress was the most common trigger, followed by trauma and infection. Symptoms involving different systems were increasingly reported with increased disease duration. Cutaneous symptoms (95.0%) were more frequent, followed by gastrointestinal (80.7%), and respiratory symptoms (50.4%). HAE symptoms led to abdominal surgery in 22 (17.5%) patients and induced laryngeal edema requiring intubation/tracheostomy in 8 (6.3%) patients. Most patients were under long-term prophylaxis, mainly with attenuated androgens (62.7% of patients).* ***Conclusions.*** *The correct distinction between HAE and other common causes of angioedema is critical, allowing reduction of diagnostic delay, improvement of adequate management, and ultimately improving outcomes and quality of life of HAE patients.*

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant, and potentially life-threatening disease, that was first described in 1888 by Osler (1, 2).

HAE is characterized by recurrent and often unpredictable episodes of swelling, resulting from vasodilation and increased vascular permeability caused by the release of vasoactive mediators (2-4). Symptoms of HAE frequently manifest during childhood or adolescence and are lifelong persistent, but the course of the

disease is highly variable, with different clinical presentations (1, 3, 5). HAE patients typically present episodic attacks of swelling, most frequently of the skin, gastrointestinal and upper respiratory tracts (1, 5). The most severe manifestations of HAE involve the upper airways and the gastrointestinal system, with eventual asphyxia, intense abdominal pain and unnecessary abdominal surgery as a result (6, 7). HAE is thus associated with a high burden of illness, leading to anxiety and depression, impairment of daily activities, economic costs, and decreased health-related quality of life, all influenced by the frequency and severity of the attacks (8). Although HAE attacks are often unpredictable, some triggers have been described, including stress, trauma, infection, drugs, and fatigue (3).

In most patients, HAE is caused by a mutation in the SERPING1 gene, which encodes the C1-esterase inhibitor (C1-INH), leading to the quantitative or functional deficiency of this protein (4, 9). HAE with C1-INH deficiency (HAE-C1-INH) can be classified in type I, characterized by both reduced C1-INH protein levels and function, and type II, characterized by normal or high levels of C1-INH protein that is dysfunctional. C1-INH deficiency results in an uncontrolled activation of the contact system (kallikrein-kinin system), with the consequent increased production of bradykinin that, in turn, increases vascular permeability, therefore inducing swelling (3, 9, 10). In 2000, HAE with normal C1-INH (HAE-nC1-INH) was also described (11, 12). The mechanism of swelling in this type of HAE is less understood, but evidence suggests that it is also mediated by bradykinin (3, 8). HAE-nC1-INH can be further divided into HAE caused by mutations in the factor XII gene (F12), plasminogen (PLG), angiopoetin-1 (AGPT1), kininogen 1 gene (KNG1), myoferlin (MYOF), heparan sulfate (HS)-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or with an unknown genetic cause (8, 13).

HAE has an estimated prevalence of 1:50,000 (1, 14-16). HAE-I is the most prevalent type, accounting for approximately 85% of cases, and HAE-II being responsible for approximately 15% of cases (1, 17). HAE-nC1-INH is less prevalent, but its incidence is still largely unknown (18). It is reported that approximately 25% of cases are due to *de novo* mutations (19).

Despite the crucial relevance of an early diagnosis, allowing an appropriate management of patients, HAE is still commonly misdiagnosed and considerable delays in the diagnosis of this disease still exist (15, 16, 20-22). The high variability of clinical manifestations and the frequent misdiagnosis with histamine-mediated angioedema, the absence of family history in around 25% patients, the requirement of proper interpretation of the diagnostic tests results, and the lack of diagnostic tools for the diagnosis of HA-nC1-INH, hinder timely HAE diagnosis (23).

Management of HAE patients involves three key aims: treatment of acute attacks (on-demand treatment); prevention of new attacks with long-term prophylaxis; and the prevention of attacks in periods of increased risk, such as before surgical procedures, with short-term prophylaxis (1, 8, 18, 24). HAE treatment has suffered significant improvements in the last decade (8, 18, 24, 25), but it is often suboptimal (18) and varies largely between different countries (8).

Therefore, we aimed to describe the clinical data of the largest Portuguese HAE cohort of patients. We have characterized our cohort in terms of demographics, type of disease, clinical characteristics, including age at initial manifestations and delay in diagnosis, triggers of attacks, clinical presentation, therapeutic approaches, and severity of disease.

Materials and methods

Study design, participants, and ethical considerations

This was an observational, descriptive, retrospective, and cross-sectional study, that included a sample of 126 HAE patients.

This study included all patients with confirmed diagnosis of HAE followed in Centro Hospitalar Universitário de Lisboa Norte (CHULN), Portugal, between January 1995 and July 2019. The diagnosis was based on clinical and laboratory criteria, including genetic testing when appropriate, in accordance with national (26) and international guidelines/recommendations (2, 7, 8, 18). Both symptomatic and asymptomatic HAE patients were enrolled in the study.

This study was approved by the CHULN ethics committee and was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

Demographics and clinical data collection

All data were retrieved and collected from CHULN database, between January and June 2019. For each patient, the following information was collected from medical records: gender, age, follow-up time, family clusters, patients per family, year of admission, residence area, HAE classification (HAE-C1-INH types I and II, and HAE-nC1-INH), age at initial manifestations, age at diagnosis, triggers of the disease, clinical presentation including cumulative symptoms present at the time of the initial manifestations, at the time of diagnosis and at the last clinical appointment, previous abdominal surgery, previous laryngeal attacks requiring intubation/tracheostomy and on-demand and prophylactic treatment received.

Severity of the disease was classified by attending physicians, according to the Agostoni *et al.* criteria (1), taking in consideration patients' data from the 12 months preceding the study period (**table IS**). The same period was also considered for the evaluation of treatments performed (long-term prophylaxis, short-term prophylaxis, and on-demand treatments).

All patients were included in the study, regardless of missing data.

Statistical analysis

Descriptive analysis of demographic and clinical data was performed. Categorical variables are presented as absolute (n) and relative frequencies (%), and, in general, data are presented with mean ± standard deviation (SD) (minimum and maximum) and median and 1st and 3rd quartiles (Q1-Q3), except when mentioned otherwise.

Table I *- Demographic characteristics of the cohort of HAE patients.*

Characteristics	Total (N = 126)
Gender, n (%)	
Female	70 (55.6)
Male	56 (44.4)
Age, years	
Mean ± SD (minimum-maximum)	43.6 ± 20.0 (4.0-82.0)
Median (Q1-Q3)	45.0 (28.5-57.8)
Age, n (%)	
< 18 y	16 (12.7)
≥ 18 y	110 (87.3)
Follow-up time, years	
Mean ± SD (minimum-maximum)	11.0 ± 6.4 (0.0-24.0)
Median (Q1-Q3)	10.0 (7.0-16.0)
Families, n	45
Patients per Family	
Mean ± SD (minimum-maximum)	2.8 ± 4.2 (1.0-28.0)
Median (Q1-Q3)	2.0 (1.0-3.0)
New Patients per Year	
Mean ± SD (minimum-maximum)	5.0 ± 3.6 (0.0-17.0)
Median (Q1-Q3)	4.0 (3.0-7.0)
New patients, n (%)	
≤ 2001	25 (19.8)
2002-2007	25 (19.8)
2008-2013	54 (42.9)
2014-2019 (June)	22 (17.5)
Regional distribution, n (%)	
North	1 (0.8)
Center	13 (10.3)
Lisbon and Tagus Valley	94 (74.6)
Alentejo	7 (5.6)
Algarve	9 (7.1)
Azores	2 (1.6)

HAE: hereditary angioedema; N: total number of patients; n: number of patients with available data; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation.

All descriptive statistical analyses were performed using R software (version 3.4.3). The Mann-Whitney test was applied for groups comparison, with P-value < .05 considered to indicate statistical significance.

Results

Demographic characteristics of study population

Table I shows the demographic characteristics of our cohort of 126 patients, from 45 families, of whom 55.6% were female. The mean age of HAE patients was 43.6 ± 20.0 years; 12.7% of patients were less than 18 years old. The mean follow-up time was 11.0 ± 6.4 years. The mean number of new patients included in our cohort per year was 5.0 ± 3.6. Almost half of the patients were included from 2008 until 2013 (42.9%). Most patients lived in Lisbon and Tagus Valley (74.6%) (**table I**).

Clinical classification and characteristics of HAE patients regarding age of initial manifestations and delay in diagnosis

The predominant type of HAE among the cohort of patients was HAE-C1-INH type I, which was found in 64 (50.8%) patients in 28 (62.2%) families. HAE-C1-INH type II was found in 57 (45.2%) patients in 13 (28.9%) families. HAE-nC1-INH was diagnosed in 5 (4%) patients in 4 (8.9%) families (**table IIS**).

Table II and **figure 1** show data regarding patients' age at the time of initial HAE manifestations and the diagnostic delay in the total cohort, in the index case (first HAE patient) of the family, and in subsequent patients in the same family.

The mean age at initial manifestations of the total population of HAE patients was 12.6 ± 8.4 years; 67.4% of patients presented initial manifestations before the age of 18 years. The mean age at diagnosis was 26.6 ± 16.7 years; 63.4% of patients were diagnosed aged 18 or older. This represented a mean delay in diagnosis of 14.4 ± 15.7 years (median delay of 10.0 [1.0-24.0] years); 29.4% of patients presented a delay in diagnosis of more than 20 years (**table II**).

As expected, index cases presented a significant higher diagnostic delay than subsequent familial cases (20.7 *vs* 9.9 years, respectively; p = 0.0001), with 39.2% of subsequent patients receiving a HAE diagnosis before adulthood *vs* only 13.5% of index cases. A diagnostic delay of ≥ 20 years occurred frequently in index cases (42.3%) whereas most subsequent HAE patients received a diagnosis in < 5 years (44.6%) (**table II**, **figure 1**).

Triggers and symptoms in the population of HAE patients

Disease triggers were not identified in 27.0% of patients. From the identified triggers, stress was the most frequently reported (47.6%), followed by trauma (33.3%), and infection (26.2%) (**table IIIS**).

Table II *- Age of initial HAE manifestations and delay in diagnosis in the first and subsequent HAE patients in family.*

Characteristics	Total (N = 126)	First in family* (N = 52)	Not first in family (N = 74)
Age of initial manifestations, years			
Mean ± SD (minimum-maximum)	12.6 ± 8.4 (0.0-47.0)	13.2 ± 7.2 (0.0-30.0)	12.2 ± 9.2 (0.0-47.0)
Median (Q1-Q3)	12.0 (6.0-18.0)	13.0 (8.0-18.0)	9.0 (5.5-17.0)
Age of initial manifestations, n (%)			
< 18 y	85 (67.4)	34 (65.4)	51 (68.9)
≥ 18 y	31 (24.6)	15 (28.8)	16 (21.6)
Unknown/Not reported	10 (7.9)	3 (5.8)	7 (9.5)
Age of diagnosis, years			
Mean ± SD (minimum-maximum)	26.6 ± 16.7 (0.0-70.0)	33.2 ± 16.7 (4.0-70.0)	21.8 ± 15.0 (0.0-55.0)
Median (Q1-Q3)	25.5 (13.8-37.5)	33.0 (20.0-40.0)	21.0 (9.5-30.0)
Age of diagnosis, n (%)			
< 18 y	36 (28.6)	7 (13.5)	29 (39.2)
≥ 18 y	80 (63.4)	42 (80.8)	38 (51.4)
Unknown/Not reported	10 (7.9)	3 (5.8)	7 (9.5)
Delay in diagnosis, years			
Mean ± SD (minimum-maximum)	14.4 ± 15.7 (0.0-66.0)	20.7 ± 17.3 (0.0-66.0)	9.9 ± 12.7 (0.0-43.0)
Median (Q1-Q3)	10.0 (1.0-24.0)	15.0 (8.0-30.0)	4.0 (0.0-15.8)
Delay in diagnosis (5-year groups), n (%)			
< 5	43 (34.1)	10 (19.2)	33 (44.6)
[5 - 10[	13 (10.3)	5 (9.6)	8 (10.8)
[10 - 15[	13 (10.3)	6 (11.5)	7 (9.5)
[15 - 20[	7 (5.6)	4 (7.7)	3 (4.1)
≥ 20	37 (29.4)	22 (42.3)	15 (20.3)
Unknown/not reported	13 (10.3)	5 (9.6)	8 (10.8)

HAE: hereditary angioedema; N: total number of patients; n: number of patients with available data; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation; *first patients diagnosed in a family (if 2 or more patients are diagnosed in the same initial year: they are all considered as "First in family").

Figure 1 *- Age (years) at diagnosis* ***(a)*** *and delay (years) in diagnosis* ***(b)*** *in first and subsequent hereditary angioedema patients in family. Presented data corresponds to the percentage of patients with available data.*

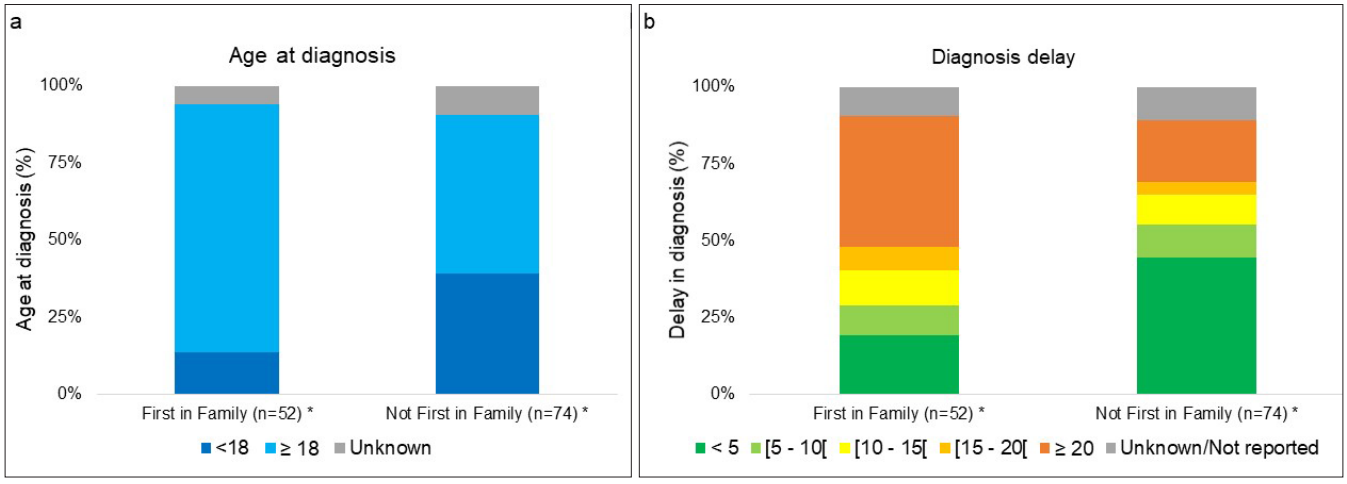

Table III - *Cumulative symptoms present at disease onset, at the time of diagnosis and at the last clinical appointment (current).*

Characteristics	At disease onset	At the time of diagnosis	Current
Asymptomatic patients, n (%)	14 (11.1)	14 (11.1)	7 (5.6)
Symptomatic patients, n (%)	112 (88.9)	112 (88.9)	119 (94.4)
Number of systems involved per patient			
Median (Q1-Q3)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (2.0-3.0)
Systems involved, n (%)			
Cutaneous only	48 (42.9)	29 (25.9)	14 (11.8)
Gastrointestinal only	21 (18.8)	7 (6.3)	6 (5.0)
Respiratory only	2 (1.8)	3 (2.7)	0 (0.0)
Cutaneous+Gastrointestinal only	27 (24.1)	41 (36.6)	39 (32.8)
Cutaneous+Respiratory only	3 (2.7)	9 (8.0)	9 (7.6)
Gastrointestinal+Respiratory only	1 (0.9)	2 (1.8)	0 (0.0)
Cutaneous+Gastrointestinal+Respiratory	10 (8.9)	19 (17.0)	51 (42.9)
Frequency of Cut, GI or Resp symptoms, n (%)			
Cutaneous	88 (78.6)	98 (87.5)	113 (95.0)
Gastrointestinal	59 (52.7)	69 (61.6)	96 (80.7)
Respiratory	16 (14.3)	33 (29.5)	60 (50.4)

HAE: hereditary angioedema; Cut: Cutaneous; GI: Gastrointestinal; Resp: Respiratory; n: number of patients with available data; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation.

Table III shows the cumulative reported symptoms at disease onset, at the time of diagnosis, and current (last clinical record) symptoms. Cutaneous symptoms were the most frequently reported clinical presentation, as initial (78.6%), at the time of diagnosis (87.5%) and as current manifestations (95%). Gastrointestinal and respiratory symptoms were reported as initial symptoms by 52.7% and 14.3% of patients, respectively, at the time of diagnosis by 61.6% and 29.5%, and as current manifestations by 80.7% and 50.4% of HAE patients (**table III**).

HAE symptoms led to abdominal surgery in 22 (17.5%) patients and induced laryngeal edema requiring intubation/tracheostomy in 8 (6.3%) patients.

Therapeutic approaches for the management of HAE

Figure 2 summarizes the long-term and short-term prophylaxis, and on-demand treatment, during the previous year, for the management of HAE in the total cohort of HAE patients.

Long-term prophylaxis was used by 71.4% of HAE patients: in 37.5% of HAE children and adolescents and in 76.4% of adult HAE patients. Short-term prophylaxis with plasma-derived C1-INH concentrate was administered in 20.6% of HAE patients: in 12.5% of HAE children and adolescents and in 21.8% of adult HAE patients. Seventy-six percent of HAE patients were treated with on-demand treatment, and similar frequencies were observed between pediatric and adult patients.

Table IV describes HAE patients' data regarding drugs for long-term and short-term prophylaxis, and for on-demand treatment by age group.

Attenuated androgens were used by 70.9% of adult HAE patients as long-term prophylaxis. HAE children and adolescents received long-term prophylaxis with antifibrinolytics in 31.2% of patients. Thirty-nine percent of patients aged 18 or older were medicated with on-demand attenuated androgens (increase of regular androgen dosage or pure on-demand treatment). One adolescent was also under androgens as on-demand treatment. On-demand treatment with antifibrinolytics was used by 31.7% of the patients, mainly in pediatric patients (43.8%).

On-demand plasma-derived C1-INH concentrate was administered in 25.4% of patients, predominantly in patients younger than 18 years (37.5%). Sixteen percent of adult patients received on-demand icatibant. No children or adolescents were treated with icatibant throughout one year of therapeutic (**table IV**).

Severity of the disease

The mean degree of severity of disease was 2.6 ± 1.3 (Agostoni *et al.* (1)). Eighty-three patients presented a moderate-severe form of HAE, in contrast with 24 patients classified as asymptomatic. In all patients (index or subsequent cases), clinicians most frequently reported a score of 2 (moderate), followed by a score 5 (asymptomatic) (50% and 19%, respectively) of HAE severity (**table IVS**).

Figure 2 *- Long-term prophylaxis, short-term prophylaxis, and on demand treatment used for the management of HAE in the total cohort. The values represent the number (percentage) of patients.*

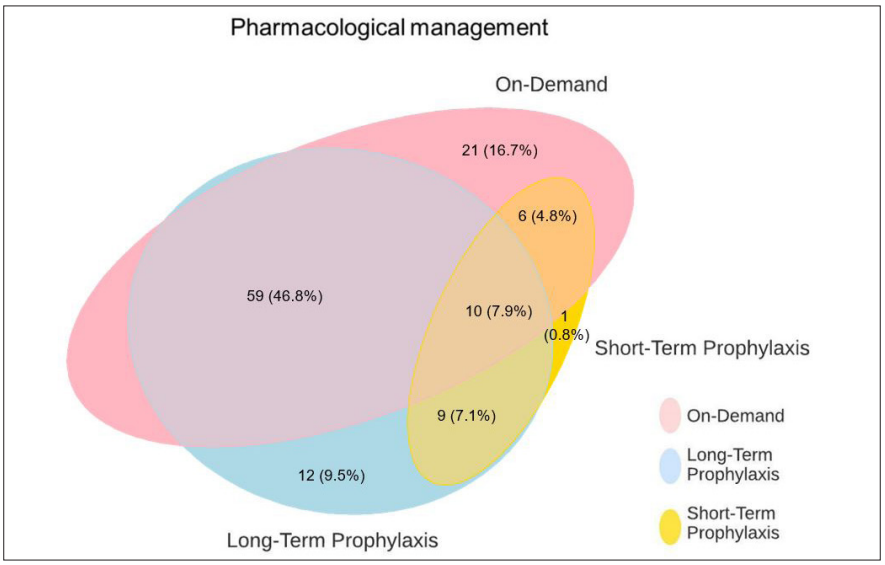

Table IV *- Long-term prophylaxis, short-term prophylaxis and on-demand treatment for the management of HAE, by age group.*

Characteristics	Total (N = 126)	< 18 y (N = 16)	≥ 18 y (N = 110)
Long-term, n (%)			
Attenuated androgens	79 (62.7)	1 (6.3)	78 (70.9)
Antifibrinolytic	10 (7.9)	5 (31.2)	5 (4.5)
Plasma-derived C1-INH	1 (0.8)	0 (0.0)	1 (0.9)
Without LTP	36 (28.6)	10 (62.5)	26 (23.6)
Short-term, n (%)			
Plasma-derived C1-INH	26 (20.6)	2 (12.5)	24 (21.8)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.0]	1.5 [1.2 - 1.8]	1.0 [1.0 - 2.0]
On-demand, n (%)			
Attenuated androgens[1]	44 (34.9)	1 (6.2)	43 (39.1)
Median of administrations [Q1-Q3]	3.0 [2.0 - 6.2]	NA	3.0 [2.0 - 5.5]
Antifibrinolytic	40 (31.7)	7 (43.8)	33 (30.0)
Median of administrations [Q1-Q3]	3.0 [2.0 - 3.2]	3.0 [2.0 - 3.5]	3.0 [2.0 - 3.0]
Plasma-derived C1-INH	32 (25.4)	6 (37.5)	26 (23.6)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.2]	1.5 [1.0 - 2.8]	1.0 [1.0 - 2.0]
Icatibant	18 (14.3)	0 (0.0)	18 (16.4)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.0]	NA	1.0 [1.0 - 2.0]
Fresh frozen plasma	0 (0.0)	0 (0.0)	0 (0.0)
Median of administrations [Q1-Q3]	NA	NA	NA

HAE: hereditary angioedema; N: total number of patients; n: number of patients with available data; NA: not applicable; Q1: 1st quartile; Q3: 3rd quartile; [1]attenuated androgens are not recommended as on-demand treatment: but the start of attenuated androgens and/or its increase of dosage were included as on-demand treatment.

Discussion and conclusions

With this study we aimed to contribute with valuable data to increase the clinical knowledge concerning Portuguese HAE patients. Since our country has approximately 10 million inhabitants, we expect an estimated 200 patients, according to the widely reported prevalence of 1:50,000 (8), meaning that our cohort represents more than half of all HAE patients living in Portugal.

We found that, although most patients presented HAE-C1-INH type I (51%), there was an overrepresentation of HAE-C1-INH type II (45%) in our cohort, which could be partially explained by the inclusion of a numerous family consisting of 28 members diagnosed with the latter type of the disease. However, even when analyzing the families included, 29% of families have HAE-C1-INH type II, which is much more than the 15% usually reported in the literature (1, 15, 16, 21, 27-32). HAE-nC1-INH was less prevalent among our cohort of HAE patients, in line with the literature (18, 30).

We observed that most HAE patients (67.4%) presented the initial manifestations of the disease before adulthood, ranging from the first year of life, until the age of forty-seven. These results are comparable with other studies (15, 21, 22, 28, 31), but slightly different results were also reported. Interestingly, a higher mean age at the initial manifestations was found in a Chinese (33) and in a Korean (29) cohort of HAE patients, and a lower median age was observed in a Brazilian cohort (34). These heterogeneous findings are certainly multifactorial, but may be partially explained by the different exposure to triggers across the world, as well as by genetic differences between these populations. Nevertheless, our findings support that HAE manifestations usually start during childhood and adolescence (20).

Despite presenting the initial HAE manifestations before 18 years, most patients (63.4%) are only diagnosed during adulthood. This significant delay in diagnosis was similar to the reported in a Swiss cohort (21) but lower compared to other studies (20, 22, 28, 31, 33). An even lower mean delay in diagnosis was reported in a Korean cohort of HAE patients, likely related to the later age of initial symptoms (29).

Our results also show that index cases present a longer delay in diagnosis compared to patients with an already identified family history of the disease. This is in accordance with the results reported by Schoffl *et al*. and Magerl *et al*. (15, 22). Moreover, a substantial reduction in the delay of diagnosis in patients born after 1980, compared with those born before 1960, was also previously reported (15), and observed in our study (data not shown). The presence of HAE family history and the increased HAE awareness by clinicians over the last decades, have likely been key in the earlier diagnosis in younger generations (5).

Stress was the most frequently reported trigger, followed by trauma, and infection. Those results are in accordance with other studies (28, 29). In a Swedish cohort, trauma and stress were also the main triggers (16). In the Swiss cohort, stress and trauma were again the most common triggers of HAE, but hormones were notably the third most common trigger (21), as has also been described by Fragnan *et al.* (31). This difference may be explained by the fact that we did not apply a category of "Hormones" or "Hormonal variations", but separate categories of "Contraception" and "Menstruation". Infection triggered the disease in 27.3% of patients from the Swiss cohort (26), a similar value to the one found in our study.

It should be noted that in our cohort almost one third of HAE patients did not identify an obvious trigger of the disease, a similar frequency when compared with the Swiss cohort (21), but lower when compared to other studies (16, 29).

As expected, with longer disease duration, symptoms from different organs/systems are increasingly reported. Cutaneous symptoms were the most frequent, followed by gastrointestinal and respiratory symptoms. These results are comparable to what has previously been reported (16, 22, 28, 31). It is well known that HAE patients often undergo unnecessary abdominal surgeries, as those attacks mimic the symptoms of acute abdominal emergencies (1-3, 5, 6). In our study, the prevalence of patients submitted to abdominal surgery was similar to the reported in the Greek cohort (20). Asphyxia occurred in 6.3% of patients, a lower value when compared to the Greek cohort in which 14% of patients were reported to undergo tracheal intubation or cricothyrotomy (20). In a study with a German cohort of 123 patients with HAE-C1-INH, the authors reported that approximately half of the individuals experienced laryngeal edema episodes (35). From those, 6 patients required intubation or cricothyrotomy (35). Although there were no registered deaths in our study, the mortality rate due to asphyxiation by laryngeal angioedema has been reported to range from 25% to 40%, in HAE patients who are not properly treated (1, 7, 35). An effective emergency treatment plan and the availability of effective self-administered on-demand treatment, like the bradykinin B2 receptor antagonist, icatibant, in most of our patients are probably key in the absence of lethality in this study. Nevertheless, the possibility of this outcome emphasizes not only the urgency of the correct and early diagnosis and management of HAE, but also the need for emergency airway management procedures, during progressive upper airway attacks in these patients. It also highlights the need for a health care provider, with HAE-specific knowledge, in close contact with the emergency department.

In order to achieve complete control of the disease, attenuated androgens, such as danazol, and antifibrinolytics, such as tranexamic acid, have been conventionally used as the main treatment options for long-term prophylaxis (3). In this study, two thirds of our patients presented a moderate to severe degree of disease severity, according to the Agostoni *et al.* classification (1), possibly explaining the high number of patients under long-term prophylaxis (71.4%), mainly accomplished using attenuated androgens. In a

Swiss cohort, only one third of patients were on a prophylactic treatment, mostly under danazol (21). Nevertheless, the percentage of patients undergoing long-term prophylaxis in our cohort was lower than the 87% reported in a Brazilian cohort (31). This result may be explained by the fact that these authors addressed the prophylactic treatment in symptomatic HAE patients (31), whereas our cohort included both symptomatic and asymptomatic patients. However, it is clear that scientific and clinical progress, combined with the development of novel, safer and more effective therapeutic approaches, have contributed to significant changes in the management of HAE patients in recent years (8, 24). It should be noted that several new management approaches are currently approved or under investigation, and that androgens are currently only recommended as second-line long-term prophylaxis (24, 25). Since the end of this study, four patients in our cohort, representing 20% of patients classified as severe disease, switched from androgen treatment to lanadelumab. This treatment became available in Portugal only since June 2020, after approval of the regulatory authorities and under special conditions.

The key strengths of our study included the analysis of a large group of HAE patients in Portugal, the inclusion of patients from different Portuguese regions, and the prolonged follow-up time. On the other hand, our study presents some limitations which must be acknowledged, namely the retrospective nature of the study and the absence of patient-reported outcomes measures data. These latter tools are applied to assess control and quality of life in patients with recurrent angioedema (Angioedema Activity Score (AAS), Angioedema Control Test (AECT), Angioedema Quality of Life (AE-QoL)), and include the more recently HAE-specific validated questionnaires, such as Hereditary Angioedema Activity Score (HAE-AS) and Hereditary Angioedema Quality of Life (HAE-QoL) (36, 37), which were not available and routinely applied at the time of the study. It is also not possible to generalize our data to other centers in Portugal, given that HAE-specific treatments are not available in many hospitals across the country.

In conclusion, this was the first study addressing HAE clinical data in a large group of patients from different Portuguese regions, thus contributing to a better understanding of this disease.

Overall, our data is in line with the literature regarding age of initial manifestations, age at diagnosis, delay in diagnosis, triggers and clinical presentation of the disease. However, we identified a higher-than-expected prevalence of HAE type II patients and families. More studies are required to confirm this result at a national level, and to understand the possible reasons underlying this difference.

As in other countries, our data supports that a long delay in diagnosis of HAE still exists, especially for those without family history of the disease.

Our data also shows a high use of attenuated androgens in long-term prophylaxis and even the use of these drugs as on-demand treatment. This situation emphasizes the need to implement an easy access to safer and more effective treatments, which is currently limited, frequently due to financial constraints.

Increased HAE awareness is still urgently needed in Portugal. The correct distinction between common causes of angioedema and HAE is critical to ensure minimal diagnostic delays and adequate treatment, ultimately leading to better outcomes and quality of life of HAE patients.

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Contributions

CV, MBF, ASS: conceptualization, formal analysis, visualization, writing – original draft, writing – review & editing. CV, LEC, SLdS, CC, RL, MIS, AL, JCa, JCo, EA, JM, FCD, NPF, MN, EP, MBF, ASS: data curation.

Conflict of interests

The authors declare that they have no conflict of interests.

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