ORIGINAL ARTICLE

Clinical Pattern and Acute and Long-term Management of Hereditary Angioedema Due to C1-Esterase Inhibitor Deficiency

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Abstract

Background: Hereditary angioedema due to C1-esterase inhibitor deficiency (HAE-C1-INH) is a life-threatening disease.
Objectives: To describe the clinical characteristics and management of patients with HAE-C1-INH during routine clinical practice.
Methods: An observational, retrospective study was performed in patients with HAE-C1-INH. Demographic, clinical, and analytical data were collected from 2 periods: period A (October 2009-September 2010) and period B (October 2007-September 2009).
Results: We studied 112 patients with HAE-C1-INH (57.1% females). Age at onset of symptoms was 14.4 years (lower in patients who had experienced attacks in the previous year). In period B (n=87), 62.1% of patients presented at least 1 edema attack (median, 3.5 attacks/patient/2 years), and 19.1% of attacks were treated. In period A (n=77), 58.4% of patients were on maintenance therapy. Stanozolol was the most widely used drug (48.9%), with a mean weekly dose of 6.7 mg. At least 1 attack was recorded in 72.7% of patients (median, 3.0 attacks/patient/year), and 31.5% of the attacks were treated. Treatment of acute attacks increased by 12.4%.
Conclusion: Age at onset of symptoms is associated with clinical expression of disease. The higher age at onset of symptoms, the fewer number of attacks per patient and year, and the lower dose of attenuated androgens necessary to control the disease than in other series lead us to hypothesize that HAE-C1-INH could have a less severe expression in Spain. Acute attacks seem to be treated increasingly often.

Key words: Bradykinin. C1-esterase inhibitor. C1-esterase inhibitor deficiency. Hereditary angioedema. Treatment.

Resumen

Antecedentes: El angioedema hereditario por déficit del inhibidor de la C1 esterasa (AEH-C1-INH) es potencialmente mortal.
Objetivos: Describir las características clínicas y el manejo de pacientes con AEH-C1-INH durante la práctica clínica habitual.
Métodos: Estudio retrospectivo observacional de pacientes con AEH-C1-INH. Se recogieron datos demográficos, clínicos y analíticos en los periodos A (Octubre 2009-Septiembre 2010) y B (Octubre 2007-Septiembre 2009).
Resultados: Se estudiaron 112 pacientes con AEH-C1-INH (57,1% mujeres) con edad de inicio de los síntomas de 14,4 años (inferior en aquellos pacientes con ataques en el último año). En el periodo B (n=87) 62,1% tuvo al menos un ataque (mediana: 3,5 ataques/paciente /2 años) y el 19,9% de los ataques se trataron. En el periodo A (n=77) 58,4% recibieron tratamiento de mantenimiento, siendo el estanozolol el fármaco más utilizado (48,9%) (dosis media semanal 6,7mg). El 72,7% de los pacientes tuvo al menos un ataque (mediana: 3,0 ataques / paciente / año), el 31,5% se trataron. Hubo un incremento del 12,4% de tratamientos de ataques agudos.
Conclusiones: La edad de inicio de los síntomas está relacionada con la expresión clínica de la enfermedad. La edad superior del inicio de los síntomas, el menor número de ataques por paciente/año, y una dosis inferior de andrógenos atenuados para controlar la enfermedad, comparado con otros países, permite hipotetizar que el AEH-C1-INH en España tendría una expresión clínica menos grave. Existe una tendencia al alza en la frecuencia de tratamiento de ataques agudos.

Palabras clave: Bradicinina. Inhibidor de la C1-esterasa. Deficiencia del inhibidor de la C1-esterasa. Angioedema hereditario. Tratamiento.

Introduction

Hereditary angioedema due to C1-esterase inhibitor deficiency (HAE-C1-INH) is a primary immunodeficiency [1]. It is transmitted in an autosomal dominant manner, and 2 phenotypic variants have been described [2]: HAE-C1-INH type I, which is due to a quantitative decrease in levels of C1-esterase inhibitor (C1-INH) and is the more frequent (85%), and HAE-C1-INH type II (15%), which is caused by a deficit in the functioning of C1-INH [3]. HAE-C1-INH is a rare disease, with an estimated prevalence of between 1 in 10 000 and 1 in 50 000 individuals [4] and a minimal prevalence of 1.09 cases per 100 000 inhabitants in Spain [5]. Therefore, most physicians are unaware of the disease, and misdiagnosis is frequent, leading to delays in diagnosis and clinical management [1,5].

Diminished C1-INH function produces uncontrolled activation of the contact system and an increase of bradykinin release [6]. Locally high transient bradykinin levels, which result from activation of the bradykinin B2 receptor (B2R), produce an increase in vascular permeability that in turn leads to massive subcutaneous and/or submucosal edema [6]. HAE-C1-INH is clinically characterized by recurrent episodes of nonpruritic, nonerythematous, and well-circumscribed submucosal or subcutaneous edema affecting various sites (extremities, face, larynx, buttocks, genitals, and gastrointestinal tract) and lasting for 2-5 days [1].

The therapeutic approach to HAE-C1-INH is based on 3 cornerstones: treatment of acute attacks, long-term prophylaxis (LTP) or maintenance treatment, and short-term prophylaxis. With respect to treatment of acute attacks, plasma-derived C1 esterase inhibitor concentrate (pdhC1INH) was available in Spain during the study period, and the bradykinin B2 receptor antagonist, icatibant acetate, only became available in March 2009. The aim of LTP is to reduce the frequency, severity, and duration of angioedema (AE) attacks [7-10]. Attenuated androgens, antifibrinolytic agents, and pdhC1INH were shown to be more effective than placebo as LTP [11].

Acute HAE-C1-INH attacks result in substantial direct medical costs and significant indirect costs associated with work absenteeism and lower productivity [12]. Furthermore, the unpredictability of acute attacks results in a significant long-term burden in the form of increased depression, reduced income potential, and missed opportunities [12,13].

This study was designed to increase awareness of HAE-C1-INH. We describe the clinical characteristics and management of patients with the disease in routine clinical practice, with a special focus on acute edema attacks.

Methods

We performed an observational, retrospective study based on data collected from the medical and laboratory records of patients with HAE-C1-INH followed up as part of routine clinical practice at the Comprehensive Angioedema Center of the Allergy Department of Hospital Universitario La Paz, Madrid, Spain.

Patient demographic, clinical and laboratory data were collected, as was all available information on attacks within 2 arbitrary periods: period A (October 2009-September 2010) and period B (October 2007-September 2009). Data were updated to September 2010.

Table 1. Patient Clinical and Demographic Characteristics

Characteristics	
Total number of patients with HAE-C1-INH	112
HAE-C1-INH, type I, No. (%)	110 (98.2)
HAE-C1-INH, type II, No. (%)	2 (1.8)
Number of families with HAE-C1-INH	53
Gender	
Female, No. (%)	64 (57.1)
Male, No. (%)	48 (42.9)
Mean (SD) age (range), y	37.5 (17.9) (4-75)
Place of birth	
Spain, No. (%)	98 (87.5)
Other countries, No. (%)	14 (12.5)
Patients with a family history of angioedema, No. (%)	98 (87.5)
Patients with family history of death by asphyxiation, No. (%)	21 (18.8)
Patients who had experienced attacks, No. (%)	96 (85.7)
Mean (SD) age at onset of symptoms, y	14.4 (10.5)
Location of first attack, No. (%)	
Peripheral	35 (36.4)
Abdominal	18 (18.7)
Facial	17 (17.7)
Genital	2 (2.1)
Upper airway	2 (2.1)
Mixed	8 (8.3)
Mean (SD) age at diagnosis, y	20.7 (15.0)
Mean (SD) delay in diagnosis, y	8.5 (11.1)
Patients diagnosed because they had an affected relative, No. (%)	67 (63.8)
Tracheotomy, No. (%)	1 (0.9)
Intubation, No. (%)	1 (0.9)
Deceased patients, No. (%)[a]	5 (4.5)
Patients who had previously received maintenance treatment, No. (%)	63 (56.3)
Drug used for maintenance treatment, No. (%)	
Attenuated androgens	54 (85.7
Antifibrinolytics	26 (41.3)
pdhC1INH	5 (7.9)
Patients who had previously received treatment for acute attacks, No. (%)	63 (56.2)
Drug used to treat acute attacks, No. (%)	
pdhC1INH	57 (50.9)
Icatibant acetate	18 (16.1)
Antifibrinolytics	15 (13.4)
Fresh frozen plasma	1 (0.9)
Complement values (most recent analysis), n=112, median (IQR)[b]	
C1-INH antigen (16.0-33.0 mg/dL)	8.4 (5.3-11.3)
C1-INH function (>50%)	18.7 (13.4-26.0)
C1q (>100 µg/mL)	140 (110.0-180.0)
C4 (14.0-60.0 mg/dL)	6.3 (4.2-9.2)

Abbreviations: pdhC1INH, human plasma-derived C1 esterase inhibitor concentrate.
[a]The cause of death was not angioedema.
[b]Normal complement ranges are indicated in parentheses.

The study population comprised patients of both sexes and any age with a confirmed diagnosis of HAE-C1-INH who had been seen at the allergy department. The diagnosis was confirmed by quantitative and functional measurements of C1-INH levels and/or by genetic study of the *C1INH* gene, as previously described [14].

The statistical analysis was performed using SPSS for Windows, version 9.0 (SPSS Inc). Continuous data were expressed as mean (SD) or median (IQR); categorical variables were expressed as counts and percentages. The Fisher exact test was performed to analyze the association between categorical variables. The Mann-Whitney and Kruskal-Wallis tests were applied to compare the number of attacks in different samples. The Spearman rho correlation coefficient was used to calculate correlations between quantitative variables. For patients attended in both periods, those who experienced and did not experience attacks and the number of attacks per year were compared using paired-samples tests (McNemar and Wilcoxon). All statistical analyses were 2-tailed, and a *P* value of <.05 was considered to represent a significant difference or correlation.

The study protocol was approved by the Research Ethics Committee of Hospital Universitario La Paz, Madrid, Spain (number PI-1654). As the study was retrospective and observational, the Research Ethics Committee did not request informed consent.

Results

The study population comprised 112 patients with HAE-C1-INH belonging to 53 different families. Demographic data can be seen in Table 1.

The mean age at onset of clinical symptoms was 14.4 (10.5) years, and 56.3% of patients had received LTP. Up to 55.5% of them had used a single drug as LTP, while the remaining patients had used several drugs successively. Detailed information is given in Table 1.

Seventy-seven patients were seen in the last year (Period A), and 87 were seen in period B. Seventy-two patients attended follow-up visits in both periods. Forty-five patients were undergoing LTP at the time of data collection in period A (58.4%), and stanozolol was the drug most commonly used (Table 2). Detailed information about the clinical characteristics and management of attacks in periods A and B can be seen in Table 3 and in Figures 1-3. Fifty-six out of 77 (72.7%) patients experienced a total of 447 acute attacks in period A and 54 out of 87 (62.1%) patients presented 1014 acute attacks in period B. Peripheral attacks were the most frequent in both periods, followed by abdominal attacks. It is interesting to note that the 14 upper airway attacks in period A were reported by only 5 patients. A total of 141 attacks (31.5%) were treated in period A and 194 (19.1%) in period B, and pdhC1inh was the drug most frequently used as acute treatment in both periods (Figures 1 and 3). A high percentage of attacks went untreated, although it is noteworthy that the number of attacks treated increased by 12.4 percentage points between period A and period B (Table 3). The treatment of acute attacks varied depending on the site: upper airway attacks were more frequently treated than attacks at other sites (peripheral) (Figure 2).

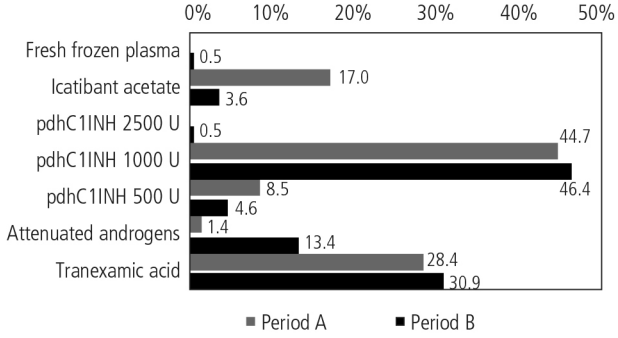
Data from patients attended in both periods reveal that 9 of 72 had attacks in period A but not in period B and that 5 of 72 had attacks in period B but not in period A; consequently, the difference was not statistically significant (*P*=.424).

Table 2. Acute Angioedema Attacks and Complement Values According to LTP During Period A (n=77; 45 [58.4%] on LTP)

Drug, Unit (Manufacturer)	Weekly Dose		Number of Patients on Each Drug, No. (%)	Number of Acute Attacks, Median (IQR)	Complement Values, Median (IQR)[a]			
	Mean (SD)	Range			C1-INH Antigen (16.0-33.0 mg/dL)	C1-INH Function (>50%)	C1q (>100 µg/mL)	C4 (14.0-60.0 mg/dL)
Stanozolol, mg (Winstrol, Desma, Madrid, Spain) (off-label use)	6.7 (3.7)	2-14	22.0 (48.9)	4.0 (3.0-10.0)	9.2 (6.7-13.5)	22.0 (15.4-28.7)	160.0 (140.0-200.0)	8.6 (5.1-11.4)
Danazol, mg (Danatrol, Sanofi-Aventis, Barcelona, Spain)	561.1 (427.0)	150-1400	9.0 (20.0)	2.5 (1.7-3.0)	10.6 (7.7-15.2)	28.8 (20.5-47.5)	144.0 (130.0-190.0)	10.2 (6.6-16.0)
Tranexamic acid, mg (Amchafibrin, Rottapharm SL, Barcelona, Spain)	6666.7 (3191.8)	3500-14 000	9.0 (20.0)	3.5 (2.0-6.2)	6.4 (3.9-8.9)	15.2 (11.5-21.9)	120.0 (70.0-140.0)	3.9 (1.7-5.9)
pdhC1INH, U (Berinert, CSL-Behring GmBH, Marburg, Germany) (off-label use)	3250 (957.4)	2000-4000	5.0 (11.1)	14.0 (12.0-28.5)	15.7 (5.1-19.5)	26.0 (24.4-46.5)	144.0 (107.0-147.0)	6.6 (6.2-11.2)
P Value				.003[b]	.07[c]	.01[c]	.05[c]	.02[c]

Abbreviations: LTP, long-term prophylaxis; pdhC1INH, human plasma-derived C1-esterase inhibitor concentrate.
[a]Normal complement ranges are indicated in parentheses.
[b]Statistical hypothesis testing of the differences in the number of acute attacks among patients under different LTP treatments.
[c]Statistical hypothesis testing of the differences in complement values among patients under different LTP treatments.

Furthermore, no significant difference was recorded in the total number of attacks per year, although a significant increase was recorded in the number of attacks treated (*P*=.002) in period A with respect to period B (median 0 [0-1] vs 1 [0-2]). There was also a significant increase in the number of upper airway attacks (*P*=.046) and the number of treated upper airway attacks (*P*=.039) in period A, although no significant difference in the number of attacks was observed at other sites (abdominal, genital, peripheral, and facial) or in the percentage of treated attacks at those locations.



[a]Attenuated androgens and antifibrinolytics were not prescribed in hospital

Figure 1. Drugs used to treat acute hereditary angioedema attacks.[a]

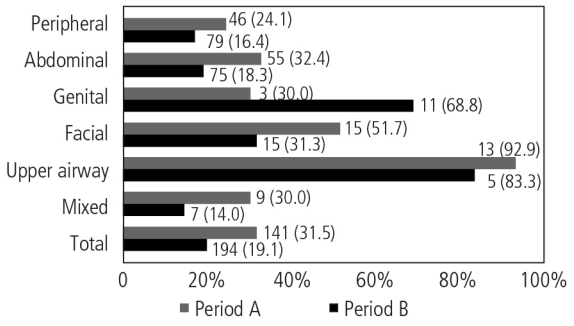


Figure 2. Treated acute hereditary angioedema attacks, No. (%).

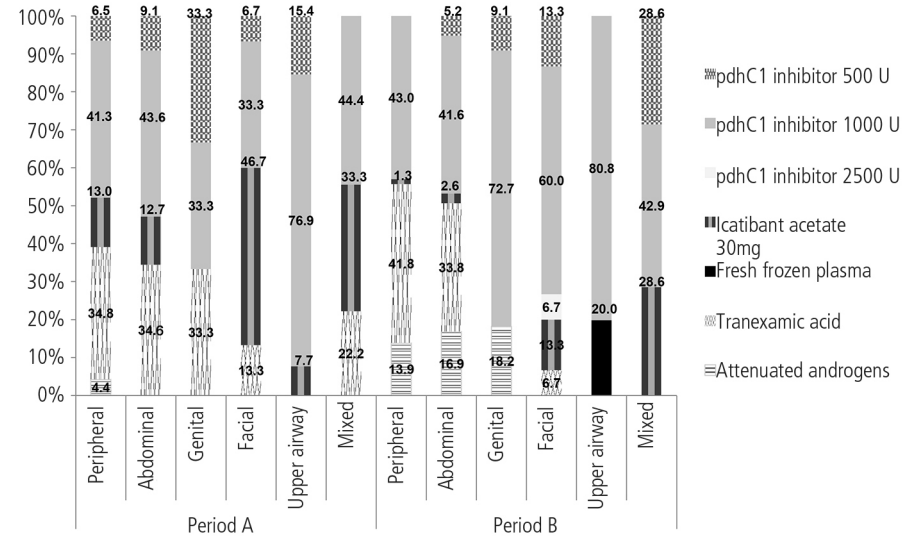


Figure 3. Drugs used to treat acute hereditary angioedema attacks by location.

The mean age at symptom onset was significantly lower in patients who had experienced attacks during the previous year (period A) than in those who did not (11.4 [7.8] vs 22.9 [10.9], *P*=.001). There was no association between having had acute attacks during the previous year and the following variables: sex, current age, family history of angioedema, family history of death by asphyxiation, and being on LTP. Similarly, in patients who experienced attacks, there was no association between these variables and the number of attacks. However, there was an association between the type of LTP and the number of attacks (patients treated with pdhC1INH had more attacks than patients receiving other types of LTP) (Table 2).

The results of the complement study are shown in Tables 1 and 2. Patients who had experienced attacks during the previous year showed lower C4 levels than those who did not (6.70 [3.98] vs 8.66 [4.40], *P*=.05). Levels of functional C1-INH and C4 were higher in patients who had received LTP during the previous year (24.5 [12.7] vs 18.4 [6.9], *P*=.015; and 8.3 [4.6] vs 5.8 [2.8], *P*=.012, respectively). Among these patients, the levels of C4 and functional C1-INH were lower in patients who received tranexamic acid than in those who received attenuated androgens or pdhC1INH. C1q levels were higher in patients receiving attenuated androgens than in those receiving tranexamic acid (Table 2).

Discussion

HAE-C1-INH is a rare disease that is poorly understood by physicians and frequently misdiagnosed, leading to delays in reaching a definitive diagnosis and prescribing appropriate treatment. The results of our study of a large sample of 112 patients add to current knowledge of HAE-C1-INH in terms of characterization of patients, attacks, and therapy.

Previous studies reported a wide range of diagnostic delay: from 21 years in an American study [15], to 13.1 years in a Spanish study [5]. In our study, the mean diagnostic delay, 8.5 years, is the lowest to date, far from the 16.3 years reported in the recent Danish study [16]. This finding has to be interpreted with caution, since relatives diagnosed before the onset of symptoms in our study have negative values for the calculation, whereas Bygum [16] assumed a value of 0 in such cases. The delay in reaching an accurate diagnosis highlights the lack of awareness of HAE-C1-INH in different countries; therefore, additional efforts to increase knowledge of this disease among specialists and primary care physicians are necessary. Diagnostic delay can be shortened by promoting testing of family members. It is

noteworthy that 63.8% of the patients in the present study were diagnosed because they had an affected relative (Table 1), thus underlining the advantage of referring patients to centers with expertise in angioedema.

Demographic data (Table 1) are in line with previous knowledge, namely, HAE-C1-INH shows a slight predominance in females and its initial presentation occurs during the first or second decade of life [1,8]. The predominance of females in the present sample may be due to the more severe clinical expression of disease in women [17,18]. In our study, the frequency of type II HAE-C1-INH was much lower than the classic 15% reported by Frank et al [15] in 1976 and the 20.3% reported by Agostoni et al [19] in 1992, which is cited in most reviews of the disease [1,8,20,21,22,23]. In contrast, more recent studies with large series of patients, including the Spanish registry, also showed lower percentages of type II HAE-C1-INH [5,16,24,25], ranging from 4.9% to 6.2%. Three of these studies show a frequency of type II HAE-C1-INH of around 6% [5,16,24], which is closer to the real prevalence of type II HAE-C1-INH. The difference in prevalence of type II HAE-C1-INH between older and newer studies could be due to the use of different techniques for the measurement of C1-INH function. Nevertheless, the lower percentage in our series (1.8%) may not be representative of the real prevalence of type II HAE-C1-INH and could be due to a selection bias in the patients attending our department.

The mean age at onset of clinical symptoms (14.4 years) was higher than the 9.5 years found in a Danish study [16], the 11.2 years in a German study [24], and the 12.6 years in the Spanish registry [5]. Age at onset of symptoms was lower in patients who had experienced angioedema attacks during the previous year, potentially indicating greater disease severity in patients with earlier onset of symptoms. This observation is in line with a previous report that disease was more severe in patients with earlier onset [24]. Taking this assumption into account, the later age at onset of symptoms in our series and in the Spanish registry than in the German and Danish series leads us to hypothesize that clinical expression of HAE-C1-INH in Spain is less severe than in Denmark and Germany.

As for frequency and clinical characteristics of HAE-C1-INH attacks, up to 13 patients (17.6%) had at least 1 edema attack per month during the previous year (period A), with a median number of 3.0 (0-73) attacks/patient (Table 3), which is much lower than the data published by Bygum [16] (10.7 [0-72] attacks/patient) and Lumry et al [13] (12.0 [0-350] attacks/patient). These data also support the hypothesis that HAE-C1-INH is less severe in Spain.

Most attacks in our study were abdominal and peripheral, as described elsewhere [8,13,16,24,25].

As for LTP, a high percentage of patients had been taking attenuated androgens in the previous year (40.3%). This finding is similar to those published in the Spanish registry (43.7%) [5] and in other recent large series (39.8% in Zanichelli et al [25] and 49.5% in Lumry et al [13]). Attenuated androgens continue to be the drugs most frequently taken as LTP both in our series and in others [13,16,25]. Off-label stanozolol was the most frequently prescribed attenuated androgen in our study. This drug was chosen because it had been shown to be more effective than danazol, with a lower frequency of side effects [26]. Of note, the doses of attenuated androgens (stanozolol and danazol) prescribed in the present study were much lower than the maximum doses recommended in guidelines [1,9,22]: 200 mg daily (1400 mg weekly) for danazol and 2 mg daily (14 mg weekly) for stanozolol. The mean weekly dose of danazol in the present study (561.1 mg) was much lower than that described by Bork and Bygum [27] in a European case series (1198.4 mg weekly). The fact that patients in the present series required lower doses of attenuated androgens to control symptoms also supports the less severe expression of HAE-C1-INH in Spain. This finding could be explained by genetic factors, environmental factors, diet, or factors that are as yet undetermined. Another explanation could be a potential selection bias in the patients attending our department, although data from the Spanish Study Group on Bradykinin-

Table 3. Characteristics of Attacks

Characteristic	Period A (October 2009-September 2010)	Period B (October 2007-September 2009)
Patients with available data	77	87
Patients experiencing acute attacks (symptomatic), No. (%)	56 (72.7)	54 (62.1)
Total number of attacks	447	1014
Median number of attacks per patient, No. (range)	3.0 (0-73)	3.5 (0-144)
Median (IQR) number of attacks per symptomatic patient	4.0 (3.0-11.0)	9.0 (3.7-25.0)
Mean (SD) number of attacks per symptomatic patient	7.9 (0.9)	18.7 (26.9)
Attacks by site, No. (%), patients affected, No.		
Peripheral	191 (42.7), 34	482 (47.5), 41
Abdominal	170 (38.0), 30	411 (40.5), 30
Facial	29 (6.5), 15	48 (4.7), 14
Genital	10 (2.2), 8	16 (1.6), 8
Upper airway	14 (3.1), 5	6 (0.6), 5
Thoracic	3 (0.7), 2	1 (0.1), 1
Mixed	30 (6.7), 11	50 (4.9), 10
Treated acute attacks, No. (%), patients treated, No.	141 (31.5), 41	194 (19.1), 33

induced Angioedema (SGBA) support our findings. It is well known that the goal of LTP is to reach the lowest effective dose that reduces the number and severity of HAE-C1-INH attacks without the need to normalize C1-INH levels [1,9,22,28]. This goal implies the possibility of using dosing regimens other than the daily dose, such as those based on alternate days or rotating schedules. In our series, some patients were taking stanozolol 2 mg 1 day a week and others 2 mg/day, thus making it difficult to compare doses between patients and between studies. In the present study, we propose that the weekly dose rather than the daily dose be used to facilitate comparisons between series.

The higher number of acute attacks in the previous year in patients undergoing LTP with pdhC1INH in our series could be related to more severe expression of HAE-C1-INH in patients who were offered LTP with off-label pdhC1INH (Berinert).

The increase in the percentage of acute angioedema attacks treated in the previous year indicates a tendency to expand the indication to treat acute attacks, irrespective of localization and severity, as recently recommended by the Hereditary Angioedema International Working Group [9]. It is worth noting the negligible use of fresh frozen plasma, which was prescribed to only 1 patient who experienced an upper airway attack while on vacation in a country where no other drug was available. In addition, attenuated androgens and tranexamic acid are widely used to treat acute attacks at home, even though we had never recommended it to our patients (Figure 1). Upper airway and facial attacks were more frequently treated with appropriate specific treatments than attacks at other sites, probably owing to the risk of asphyxia because of edema (Figure 3).

Concerning analytical parameters, the higher levels of functional C1-INH and C4 in patients who received LTP with attenuated androgens and pdhC1INH may be associated with the mechanism of action of these 2 drugs: replacement of C1-INH by pdhC1INH and increased hepatic synthesis of C1INH in the case of attenuated androgens [7], with a subsequent increase in C4 levels secondary to reduced consumption because of increased C1INH function. The higher C1q levels in patients receiving LTP with attenuated androgens could be related to an increase in their synthesis or to lower consumption due to the increase in C1INH.

We present the features of HAE-C1-INH in a large series of patients managed in a center with expertise in angioedema in Spain. Our data show a decrease in diagnostic delay, a relationship between age at onset of symptoms and clinical expression of disease, milder severity of disease in Spain than in other European countries (Denmark, Germany) and the USA, and a trend towards increased frequency of treatment of acute attacks, with a higher frequency of adequate treatment for attacks at sites with a higher risk of asphyxia (upper airway and face).

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Conflicts of Interest

Carmen Gómez-Traseira has received sponsorship for educational purposes from Shire. She also received support from Shire for the preparation of this manuscript.

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Elia Pérez and Carmen García-Ara declare that they have no conflicts of interest.

Previous Presentation

An abstract based on this study was presented at the Seventh C1 Inhibitor Deficiency Workshop, May 2011: "Clinical management of patients with hereditary angioedema due to C1 INH deficiency". A second abstract was presented at the European Academy of Allergy and Clinical Immunology Congress, June 2012: "Retrospective Epidemiological Study of Angio-oedema Attacks in Patients with Hereditary Angio-oedema due to C1-Esterase Inhibitor Deficiency". A third abstract was presented at the Sociedad Española de Alergología e Inmunología Clínica Congress, November 2012: "Estudio epidemiológico de ataques de angioedema en pacientes con angioedema hereditario por deficiencia del inhibidor de la C1-esterasa".

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