Hereditary angioedema: Report of the dental treatment of 12 Brazilian patients

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Objective. The aim of this study was to report on clinical experience in Brazil in the dental treatment and the oral conditions of a group of patients with hereditary angioedema (HAE).

Study Design. The study analyzed demographic data, type of HAE, intensity of attacks, long-term and short-term prophylaxis, dental procedures, and occurrence of crises after the procedures were performed. Radiographic evaluation of the number of teeth and bone loss was also performed.

Results. Data from 12 patients were collected; most were women, presenting with C1-INH-HAE type I and a history of severe attacks. All patients reported use of regular medications (long-term prophylaxis), mostly attenuated androgens, to prevent/attenuate HAE attacks. These patients had several missing teeth and alveolar bone loss. Tooth extraction was the most common procedure. In half the patients, the procedures had been performed without modification in long-term prophylaxis. The others were treated with an additional prophylaxis protocol (short-term prophylaxis), particularly those who underwent tooth extraction. None of the study patients developed HAE attacks after dental procedures.

Conclusion. The occurrence and intensity of a possible HAE attack after dental procedures are unpredictable, but with careful preliminary screening by dental and immunology teams and the use of therapeutic prophylaxis, the risk could be minimized. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:651−658)

Hereditary angioedema (HAE) is a rare autosomal dominant disease clinically characterized by sudden recurrent episodes of swelling of the skin (mainly the skin of the extremities, face, and genitals), the gastrointestinal tract, the upper airways, and other organs, resulting in high rates of morbidity and mortality.[1-3] A familial pattern of inheritance is characteristic and should be a warning of possible HAE, but in 20% to 25% of cases, spontaneous mutations can be observed. Different forms of HAE are currently recognized and genetically identifiable, the most common mutations occurring in the *SERPING1* gene, leading to quantitative (HAE type I) or qualitative (HAE type II) deficiency of C1 esterase inhibitor (C1-INH) (Table I).[1,4-7] HAE is a disease that is unfamiliar to many health care professionals and is often underdiagnosed, resulting in delay between the onset of symptoms and the diagnosis.[1] The attacks can be precipitated by local trauma, psychological stress, medical and dental procedures, estrogen levels, and infections.[1,8] Microtraumas caused by dental−oral procedures carry a high risk and increase the risk of death resulting from asphyxiation caused by swellings developing near the intervention site and in the upper airways.[4,9,10] In the past, after dental surgery and inadequate treatment, the overall mortality rate was 30% to 40%,[11] but preprocedural prophylaxis can reduce the risk of angioedema and life-threatening complications.[4]

The pathophysiologic mechanism underlying HAE is mediated by bradykinin, a potent inflammatory mediator that increases vascular permeability and is, therefore, a non−histamine-mediated process.[12] Because of this, traditional medications associated with the treatment of allergic disorders (antihistamines, corticosteroids, epinephrine) are ineffective or have limited effect in the treatment of HAE.[5] Management of HAE includes long-term and short-term prophylaxis and treatment for acute attacks.[4,8,11,13] *Long-term prophylaxis* refers to the use of regular medications to reduce the burden of the disease by preventing/attenuating attacks in patients with significant or frequent episodes.[4,14] Plasma-derived C1-INH concentrate is currently the preferred agent for long-term prophylaxis

Statement of Clinical Relevance

Hereditary angioedema (HAE) has considerable implications for dentists because dental procedures may trigger severe and life-threatening episodes. There are limited reports on the dental management of HAE, and the present study may contribute to clinicians dealing with patients with HAE.

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Table I. Different types of HAE and their pathogenesis

HAE types	*Pathogenesis*
C1-INH-HAE type I (85% of cases)	C1-INH quantitative deficiency, mutations in SERPING1 gene
C1-INH-HAE type II	C1-INH functional defect, mutations in SERPING1 gene
FXII-HAE	Normal C1-INH and mutations in factor XII gene (Hageman factor)
HAE-ANGPTI	Normal C1-INH and mutation in the angiopoietin-1 gene
HAE-PLG	Normal C1-INH and mutation in the plasminogen gene
HAE-KNG1	Normal C1-INH and mutation in kininogen 1 gene
HAE-UNK	Normal C1-INH but unknown origin

C1-INH, C1 inhibitor protein; *HAE,* hereditary angioedema; *SERPING1,* human C1-inhibitor *gene.*

in HAE; it replaces the deficient/dysfunctional protein, resulting in an increase in the plasma levels of C1-INH and helps regulate all of the cascade systems involved in the production of bradykinin.[4] Attenuated androgens (AAs), such as danazol, stanozolol, and oxandrolone, are the second-line options,[4,15,16] but these do not have a firmly established mechanism of action, although it has been suggested that they might influence the catabolism of kinins, thereby reducing the frequency of attacks.[17] Antifibrinolytics, such as tranexamic acid and ε-aminocaproic acid, are also used but have not been proven efficient, especially in HAE type I; however, they show superior therapeutic effects in patients with HAE with normal C1-INH.[18] Of note, only a few patients have access to C1-INH concentrate in Brazil. It is not offered by the government and is not easy to obtain, even through the court of justice. Therefore, AAs are the most frequently used drugs, with no cost for patients, as is the case with danazol.[6]

Short-term (preprocedural) prophylaxis before invasive dental procedures is indicated for patients with HAE, regardless of their type and severity score because the occurrence and intensity of a possible HAE attack are unpredictable.[4,18] Although the administration of human C1-INH concentrate (1000 units) as close as possible to the onset of the procedure is the prophylaxis of choice,[4] fresh-frozen plasma (FFP), AAs, and antifibrinolytics are the second-line agents often used in Brazil because of restricted access to C1-INH concentrate.[6] FFP is also administrated just before the procedure (2 units), and AAs are used for 5 days before and for 2 to 3 days after the procedure.[4,6] However, breakthrough attacks can occur even in patients with HAE who have received all of the preprocedural prophylactic treatments. Patients should remain under observation, and medication to treat acute attacks, such as C1-INH concentrate, icatibant (bradykinin receptor antagonist) or FFP, should be available at all times; depending on the intensity and location of the edema, treatment can be performed at home or in the emergency room.[4,8,10,11,13]

The aim of this study was to conduct a retrospective study on oral health conditions, long-term treatment and prophylaxis protocol used for dental treatment, and the occurrence of posttreatment episodes in a group of Brazilian patients affected by HAE.

MATERIALS AND METHODS

We studied reports of the clinical experience in the dental treatment of patients with HAE seen at the Clinical Dentistry Service of the Hospital Universitário Clementino Fraga Filho of the Federal University of Rio de Janeiro – Brazil (HUCFF-UFRJ). The patients had been referred from the Immunology Service of the same institution, between 2012 and 2019. This study was approved by the Ethics Committee of the HUCFF-UFRJ (protocol No. 76177317.2.0000.5257).

All patients with HAE were submitted to the protocol for dental management followed by the Clinical Dentistry Service. On the first visit, patients were questioned about the prophylactic medication proposed by the physicians before dental procedures and in cases of emergencies. Before starting treatment, the dental team had phone consultations with the physicians at the Immunology Service to explain the type of procedure that would be performed and to confirm the preprocedural prophylaxis to be used. Patients were instructed about the importance of following the correct dosage and knowing how to contact the medical staff on call within the hospital facilities. After the dental procedures, patients stayed at the Clinical Dentistry Service for 2 hours under observation; in the absence of attacks, they were discharged home, with instructions to use the prescribed medication for acute attacks at home (if available) or to seek emergency assistance, depending on the intensity and location of the edema. In the first 48 hours, the dentist kept in touch with the patients by phone and, if everything was fine, the patients returned to the Clinical Dentistry Service 7 days after the procedure.

The following data were collected from medical records: gender, age, type of HAE, intensity of attacks (mild, moderate, severe),[19] long-term prophylaxis, and short-term prophylaxis. The types of dental procedures performed and the occurrence of angioedema after the procedure were also recorded. Digital images of the initial panoramic radiographs of each patient were analyzed to describe the number of teeth, signs of horizontal and vertical alveolar bone loss, and presence of other bone alterations. The collected data were systematically transcribed into an Excel 2007 worksheet for better organization and were subjected to a descriptive analysis.

RESULTS

The demographic data and clinical findings of the 12 patients with HAE, the dental procedures performed, and the short-term prophylaxis used are presented in Table II. There were 9 (75%) females and 3 (25%) males (age range 16−70 years; mean age 42.16 years). The mean age at onset of HAE manifestations and the mean age at the time of diagnosis were 22 years and 37 years, respectively. Ten patients (83.3%) had C1-INH-HAE type I, and 2 (16.7%) had HAE with normal C1-INH and mutation on factor XII (FXII-HAE). Seven patients (58.3%) reported a family history of HAE. Cutaneous edema (100%), abdominal pain (78%), and laryngeal edema (55%) were the most common manifestations of HAE, and most patients (75%) had a history of severe attacks. Five patients (42%) had a history of HAE attacks triggered by dental treatment. All patients were on long-term prophylaxis, with 7 (58.3%) using AAs (oxandrolone or danazol), 3 (25%) using tranexamic acid, 1 (8.3%) using ε-aminocaproic acid, and 1 (8.3%) using intravenous C1-INH concentrate.

Panoramic radiographs were available for 10 patients, who had, on average, 25.1 teeth present (range 13−32). Five patients (41.7%) had 9 or more missing teeth. Nine (75%) patients exhibited radiographic signs of periodontal disease; 3 (25%) patients showed vertical alveolar bone loss, and 6 (50%) patients had horizontal alveolar bone loss. One patient had periapical lesions in 5 teeth, all of them with indication for surgical extraction, and another patient had a periapical lesion in a tooth with indication for endodontic treatment. Three impacted third molars were also detected.

Fifty-four dental procedures were performed in the 12 patients who had had prior contact with the Immunology Service staff; therefore, if necessary, these patients could receive immediate medication for acute attacks. Forty-two (77%) procedures were performed in the dental office, including 15 tooth extractions (35.7%), 9 dental restorations (21.4%), 9 supragingival biofilm and calculus removal (21.4%), 4 subgingival biofilm and calculus removal (9.5%), 4 treatments of dental prophylaxis with oral hygiene instruction (9.5%), and 1 endodontic treatment (2.3%). Twelve (23%) dental procedures were performed in the operating room, under local anesthesia and intravenous sedation, including 9 tooth extractions (75%), 1 surgical enucleation of periapical cyst (8.3%), 1 oroantral communication closure (8.3%), and 1 internal rigid fixation removal (8.3%).

Six patients (50%) were treated without changing the dose of the long-term medications already in use: oxandrolone (patients #1, #7, and #8); tranexamic acid (patients #4 and #6); and ε-aminocaproic acid (patient #3). Four patients (33%) taking danazol as long-term prophylaxis had the dose increased (600 mg/day for 5 days before and for 3 days after the procedure). One of them who had undergone 6 dental extractions (patient #2) also received 1000 IU of C1-INH concentrate 1 hour before each procedure. For patient #11, who had undergone 5 dental extractions and cystic enucleation, 2 IU of FFP was administrated before the procedures. For 2 other patients (17%), 1000 IU of C1-INH concentrate was administrated 1 hour before the procedure; for one of them (patient #10), concentrate was prescribed to be used every 3 days as long-term medication, and for the other (patient #12), tranexamic acid was prescribed. Considering all of the dental extractions, most of them (83.3%) had been performed in patients who had undergone modification in the therapeutic regimen before the procedure (short-term prophylaxis). All of them had a history of severe attacks. None of the patients in this case series developed angioedema attacks after dental procedures.

DISCUSSION

HAE has considerable implications for oral health care providers and patients because dental procedures may trigger severe and even life-threatening episodes of HAE attacks.[20] By presenting this report, we hope to contribute data on a retrospective evaluation of the clinical protocol used for 12 patients with HAE in Brazil, a developing country where access to the first-choice medication for prophylaxis is limited.

We found HAE type I (quantitative deficiency of C1-INH) to be the most common type of the disease, in agreement with the literature, with 85% of the cases.[1,20] Almost 60% of the patients reported familial history, as similarly described in the literature.[1] Two patients were affected by FXII-HAE; one of them did not have a family history, indicating possible spontaneous mutation, as also reported in the literature.[1] Although some studies of HAE report a similar male-to-female ratio,[1] in the present study, most of the patients were females, similar to 2 other case series of patients with HAE undergoing dental treatment.[10,20,21] A fact to be considered is that the individuals enrolled in this study sought dental treatment, and the literature indicates that there is a greater concern regarding oral health in females compared with that in men.[22]

The patients included in this study did not experience HAE attacks after dental procedures. This could be attributed mainly to the use of long-term prophylaxis in all of the patients, with the addition of short-term prophylaxis for some of them. Of note, in this case series, all types of dental procedures, not only surgical procedures, were included. Other points that need to be highlighted are (1) the management of stress in the patients by offering a support system with conversations and explanations about the importance of prophylactic medication; (2) the knowledge and preparation of the professionals regarding the approach to patients with HAE; and (3) the continuous

Table II. Clinical findings from 12 Brazilian patients with HAE undergoing dental treatment

Patient	*Age*	*Gender*	*HAE type*	*Familial history of HAE*	*Intensity of attacks**	*Long-term prophylaxis*	*Panoramic radiography findings*	*Dental procedures (N)*	*Short-term prophylaxis for dental treatment*	*Angioedema attack after dental treatment*
1	45	F	C1-INH-HAE type I	Yes	Severe	AA (oxandrolone 7.5 mg/day)	- 22 teeth - Localized horizontal bone loss	Dental prophylaxis and OHI (1)	No change in long-term prophylaxis	No
2	70	F	C1-INH-HAE type I	Yes	Severe	AA (danazol 100 mg/ every 3 days)	- 13 teeth - Horizontal and vertical generalized bone loss - 5 periapical lesions	SPGRBC (1) SBGRBC (1) Tooth extraction (6)	Danazol 600 mg/day 5 days before and 3 days after + C1-INH concentrate 1 hour before	No
3	32	F	C1-INH-HAE type I	Yes	Severe	ε-aminocaproic acid (1 g/day)	Not available	Dental prophylaxis and OHI (1)	No change in long-term prophylaxis	No
4	32	F	FXII-HAE	Yes	Moderate	Tranexamic acid (1 g/day)	- 30 teeth - 1 periapical lesion	SPGRBC (2) Endodontic treatment (1) Dental restoration (2)	No change in long-term prophylaxis	No
5	64	M	C1-INH-HAE type I	No	Severe	AA (danazol 300 mg/day)	- 22 teeth - Generalized horizontal bone loss	SPGRBC (2) SBGRBC (1) Tooth extraction (2)	Danazol 600 mg/day; 5 days before and 3 days after	No
6	64	F	C1-INH-HAE type I	Yes	Moderate	Tranexamic acid (500 mg/day)	- 23 teeth - Horizontal and vertical generalized bone loss	SPGRBC (3) SBGRBC (2)	No change in long-term prophylaxis	No
7	34	F	C1-INH-HAE type I	Yes	Moderate	AA (Oxandrolone 7.5 mg/day)	- 30 teeth	Dental restoration (6)	No change in long-term prophylaxis	No
8	43	F	C1-INH-HAE type I	Yes	Severe	AA (oxandrolone 7.5 mg/day)	- 23 teeth - Localized horizontal bone loss	Tooth extraction (4) Dental restoration (1)	No change in long-term prophylaxis	No
9	42	M	FXII-HAE	No	Severe	AA (oxandrolone 7.5 mg/day/ Danazol 400 mg/day)	Not available	Dental prophylaxis and OHI (1) SPGRBC (1)	Danazol 600 mg/day; 5 days before and 3 days after	No
10	29	F	C1-INH-HAE type I	No	Severe			Dental prophylaxis and OHI	C1-INH concentrate (1000 IU/	No

(*continued on next page*)

Table II. Continued

Patient	*Age*	*Gender*	*HAE type*	*Familial history of HAE*	*Intensity of attacks**	*Long-term prophylaxis*	*Panoramic radiography findings*	*Dental procedures (N)*	*Short-term prophylaxis for dental treatment*	*Angioedema attack after dental treatment*
						C1-INH concentrate (1000 IU/ each 3 days)	- 32 teeth - 1 periapical lesion	(1) Tooth extraction with flap (3)	1 hour before tooth extraction)	
11	35	M	C1-INH-HAE type I	No	Severe	AA (danazol 200 mg/day)	- 24 teeth - 1 periapical lesion - Palate cleft - Horizontal and vertical bone loss	Tooth extraction (5) Cystic enucleation (1) Oroantral fistula closure (1) RIF removal (1) (Procedures performed in the operating room with intravenous sedation)	Danazol 600 mg/ day; 5 days before and 3 days after + FFP 2 IU/1 hour before	No
12	16	F	C1-INH-HAE type I	No	Severe	Tranexamic acid (750 mg/day)	32 teeth	Tooth extraction with flap (4) (Procedures performed in the operating room with intravenous sedation)	C1-INH concentrate (1000 IU/ 1 hour before tooth extraction)	No

C1-INH, C1 esterase inhibitor; *FFP,* fresh-frozen plasma; *IU,* international units; *OHI,* oral hygiene instruction; *RIF,* rigid internal fixation; *SBGRBC,* subgingival removal of biofilm and calculus; *SPGRBC,* supragingival removal of biofilm and calculus.
*According to Ferraro et al.[19]

availability of the medical staff on call within the hospital facilities.

Other authors have also reported no complications after dental procedures[20] or a low prevalence[20,23] among patients who experienced HAE attacks because of lack of long-term or short-term prophylaxis.[20,21] In the past, overall mortality after dental surgery without adequate treatment was around 30% to 40%,[24] and a significant number of dental−oral procedures had been carried out even before the diagnosis of HAE.[13] Deaths of patients with HAE after dental procedures that are still being reported[10,15,16,25] are mainly related to upper airway edema in the first 24 to 48 hours after dental extractions. Thus, patients with HAE fear dental care visits and only seek assistance for emergent oral health conditions.[16] Dental extractions represent a considerable percentage of the dental procedures performed in patients with HAE, as reported by Jurado-Palomo et al.[13] and also observed in the present study.

Preparing patients with HAE for dental treatment includes long-term and short-term prophylaxis and treatment for acute attacks.[8,11,13,23] Most of the patients in this case series had a past history of severe attacks, and in fact, all of them were taking long-term prophylaxis, with most using AAs (danazol or oxandrolone). Four patients were using antifibrinolytics (ε-aminocaproic acid or tranexamic acid); one of them had been diagnosed with factor XII-HAE, with normal levels of C1-INH. Antifibrinolytics seem to have a better effect in these cases than in HAE type I.[18] Furthermore, these medications can be used by women, whereas AAs often have significant side effects. Only 1 patient was using C1-INH concentrate as first-line long-term prophylaxis, although it is not easily available from the Brazilian public health care system because of its high cost.[6]

Short-term prophylaxis for the management of invasive dental procedures is indicated for patients with HAE because attacks may occur independent of disease activity and the trauma of dental procedure.[4,9,14,21,26,27] C1-INH concentrate administrated just before the procedure is the prophylaxis of choice,[4] and its use has been reported to be successful in invasive dental procedures by previous studies.[10,14,28] Success with increased doses of danazol for short-term prophylaxis for invasive dental procedures,[8,13,23,28] alone or in association with C1-INH concentrate 1 hour before the procedure,[25] has also been previously reported. In the present study, most of the invasive procedures were performed in patients who received increased doses of danazol for 5 days before and for 3 days after the procedures, taken in conjunction with C1-INH concentrate or FFP, in 2 patients who underwent a large number of dental extractions or a complex surgical procedure. Only 2 patients had C1-INH concentrate alone as short-term prophylaxis, both of whom underwent tooth extractions with flap. All of these patients had a previous history of severe attacks. Although C1-INH concentrate and danazol have been successfully employed in previous studies and in the present one, the occurrence of attacks despite their use has been reported.[21]

In 50% of the patients in this study, dental procedures were performed successfully without the use of short-term prophylaxis and only with maintenance of the long-term medication (3 patients using oxandrolone and 3 patients using antifibrinolytics). In the case of oxandrolone, the patients were already using the maximum daily dose of the medication. An important point is that most of the procedures performed were not invasive, and most of the patients had a history of moderate attacks. However, even in the patients who underwent invasive procedures, one of whom had a history of severe attacks, there were no events of HAE after the procedures. There are infrequent reports of dental procedures performed exclusively with maintenance of long-term therapy, especially with oxandrolone. In the case series reported by Jurado-Palomo et al.,[13] some invasive dental procedures were performed only with maintenance of long-term therapy with danazol and stanozolol with no modifications.

Few studies published in the English-language literature have specifically addressed the oral health conditions of patients with HAE; some isolated reports have described precarious dental and periodontal conditions in patients with HAE.[13,20,29] Indeed, it seems that patients with HAE who have a history of attacks after medical trauma tend to visit the dentist less often, engage in oral hygiene practices more frequently, and report experiencing difficulty in obtaining dental appointments because of their condition.[30,31] Similar to previous studies, we found that a significant number of study patients (42%) who had a history of HAE attacks triggered by dental treatment had been frequently submitted to dental extractions and had a great number of missing teeth and alveolar bone loss.[13,21]

Some studies have shown that patients with HAE may also suffer from depression, anxiety, and phobias related to medical and dental complications,[32,33] necessitating careful psychophysical assessment and meticulous provision of information before dental treatment.[10] In the present study, all dental procedures were carefully explained to the patients and the physicians, which may have contributed to the reduction in stress and anxiety and possibly to the absence of HAE attacks. The study patients were monitored and treated by the Immunology Service on a permanent basis, and they had a considerable level of understanding about

the disease, prophylaxis, and drug dosages, which was reinforced by the dental team. Safe dental procedures may be achieved with careful cooperation between dental and immunology teams. However, the unpredictable nature of HAE attacks remains a clinical challenge for dentists because it may occur in any patient, regardless the type of HAE or prophylaxis.

CONCLUSIONS

This is the first study in Brazil on the dental management in a large series of patients with HAE. Many of the patients had several missing teeth and alveolar bone loss, with indications for tooth extraction. All patients received long-term prophylaxis during dental procedures, and some received additional short-term prophylaxis, particularly those who underwent tooth extractions. HAE attacks triggered by dental procedures were not observed in these Brazilian patients. Continued clinical collaboration between dental and immunology services is essential for the successful management of patients with HAE.

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