J Oral Maxillofac Surg
68:2307-2311, 2010

Hereditary Angioedema in Oral Surgery: Overview of the Clinical Picture and Report of a Case

Paola Sara Morcavallo, DDS, Alessandro Leonida, DDS,†*
Gabriele Rossi,‡ Massimo Mingardi, DDS,§
Manuela Martini, DDS,‖ Riccardo Monguzzi, DDS,¶
*Fabrizio Carini, MD, DMD,# and Marco Baldoni, MD, DMD***

Angioedema is a pathologic condition first described by Quincke[1] and Osler.[2] It can be genetically determined or acquired, and it is caused by a vascular reaction induced by deficiency or functional alteration of the C1 inhibitor (C1-INH), an enzyme involved in the regulation of complement, contact, fibrinolytic, and coagulation systems.[3-5]

Two forms of angioedema have been described in the literature: hereditary angioedema (HAE) and acquired or idiopathic angioedema (AAE).

HAE is characterized by dominant autosomal transmission, early onset, and a positive family history.[6,7] It is caused by a mutation of the gene for C1-INH, localized on chromosome 11.[8] Type 1 HAE is the most frequent form (85% of cases) and is associated with deficiency of functional C1-INH in plasma (10%-30% of normal values).[9] Type 2 HAE is characterized by normal or elevated plasma levels of dysfunctional C1-INH.[8] Type 3 HAE occurs mainly in women. Affected persons display the typical clinical features of C1-INH deficiency but have normal plasma levels and functionality of C1-INH. Mutations in the coagulation factor XII gene have been detected in some of these patients.[10]

AAE is characterized by late onset, usually after the fourth decade, and is not associated with a positive family history.[6] Type 1 AAE is caused by increased catabolism of C1-INH and is generally associated with a positive history of benign or malignant lymphoproliferative disorders. Type 2 AAE is associated with autoantibodies against C1-INH.[9,11,12]

Deficiency or dysfunction of C1-INH can cause a deregulation of the fibrinolytic system, of the complement pathway, of the contact system, and of the coagulation cascade, resulting in release of vasoactive substances, an increase in vessel permeability, and development of diffuse edemas.[4,9,13]

Hereditary and acquired forms of angioedema are clinically indistinguishable.[8] Edemas develop gradually over a period of 12 to 36 hours and require 2 to 5 days to subside completely.[12] The frequency and severity of edema attacks vary from patient to patient and even in the same individual.[8] This variability can change significantly over a patient's lifetime: symptoms may intensify dramatically after puberty, although some cases have been reported that had been asymptomatic until the second decade of life and later.[9]

The diagnosis of angioedema can often be suspected from a positive family history associated with the typical symptoms. Nevertheless, the diagnosis needs to be confirmed by laboratory tests to assess the quantity and function of C1-INH.[12]

The differential diagnosis of angioedema includes anaphylactic shock. Considering the potential risk of asphyxia, it is essential to obtain an accurate patient history to ensure that the most appropriate approach to emergency treatment is chosen, because cortico-

Received from the University of Milan-Bicocca, Milan, Italy.

*Postgraduate Student, School of Oral Surgery.
†Doctorate Student, School in Experimental Periodontology.
‡Postgraduate Student, Department of Periodontology.
§Doctorate Student, School in Experimental Periodontology.
‖Postgraduate Student, Department of Periodontology.
¶Doctorate Student, School in Experimental Periodontology.
#Research Professor.
**Professor.

Address correspondence and reprint requests to Dr Leonida: Clinica Odontoiatrica, Ospedale San Gerardo Nuovo, Villa Serena, Via Pergolesi, 3320052 Monza, Milan, Italy; e-mail: leo.doc73@libero.it

0278-2391/10/6809-0039$36.00/0
doi:10.1016/j.joms.2010.04.011

steroids, antihistamines, and epinephrine are ineffective in the treatment of acute attacks of angioedema.[6,8,14]

Although angioedema attacks can occur without any specific precipitating factor, in 50% of cases the precipitating cause is tissue trauma.[6,8,9] Trigger factors include dental procedures, endotracheal intubation, surgical or diagnostic interventions in the cephalic or cervical region (such as oral or maxillofacial surgery and tonsillectomy), mental or physical stress, infection, hormonal changes (menstruation, pregnancy, intake of oral contraceptives), intake of specific drugs (such as estrogens or angiotensin-converting enzyme inhibitors) or foods containing histamine or able to induce histamine release, insect bites, and strong temperature variation.[3,5,9,12,13,15]

At present, it is possible to intervene with a specific therapy according to the patient's needs.

Long-Term Prophylaxis

Long-term prophylaxis aims to reduce the frequency and severity of attacks and is indicated in patients who have significant and/or frequent episodes ($\geq$1 attack per month) of angioedema.[14] The first-choice drugs are synthetic anabolic steroids, which increase the hepatic production of C1-INH.[5,6,14,16,17] Interferon-γ or antifibrinolytic agents (such as ε-aminocaproic acid and tranexamic acid) are recommended as alternative therapy, particularly in patients who do not tolerate anabolic steroids. Interferon-γ increases the production of C1-INH, and antifibrinolytic agents inhibit the activation of plasmin and factor C1.[5,6,14]

Short-Term Prophylaxis

Short-term prophylaxis is recommended in patients undergoing invasive procedures such as dental treatment, oral or maxillofacial surgery, and endoscopic operations.[14] Therapy is based on the administration of an increased dose of anabolic steroids for 5 to 7 days before surgery and 2 to 5 days after surgery.[7,13,14,18] Alternatively, fresh-frozen plasma can be given the night preceding the operation and before the beginning of the operation.[5,6,19,20] Other options include C1-INH concentrate or antifibrinolytic agents.[5,13,18]

Therapy for Acute Attacks

Acute attacks are managed with intravenous infusion of narcotics and anti-inflammatory drugs, to maintain the patency of the respiratory tract and control pain and nausea.[5,14] In case of dehydration and hypotension caused by abdominal involvement, rehydration therapy is required.[14]

The resolution of acute episodes of angioedema can be obtained by increasing C1-INH levels in serum.[20,21] C1-INH can be given in the form of plasma concentrate or intravenous infusion of fresh-frozen plasma, which is rich in this factor.[5,8,13,14,18,20,21] Although both formulations have been used in emergency treatment, data showing proven clinical effectiveness are available only with regard to C1-INH concentrate.[21] The exhibition of these preparations allows the resolution of acute episodes in a short period of time.[5]

Anabolic steroids have limited indications in the treatment of acute attacks of angioedema because they require 1 to 2 days to be effective.[14]

Report of a Case

In March 2006, a 38-year-old woman presented to the Dental Clinic of San Gerardo Hospital in Monza, Italy, for dental consultation because of gingival inflammation and increased dental mobility (Fig 1).

Clinical examination and ortopantomography (Fig 2) confirmed the diagnosis of generalized chronic periodontitis, with evident horizontal bone resorption in both arches, as well as furcation involvement (degree 2) and mobility (degree 2) of the first and second maxillary and mandibular molars, bilaterally.

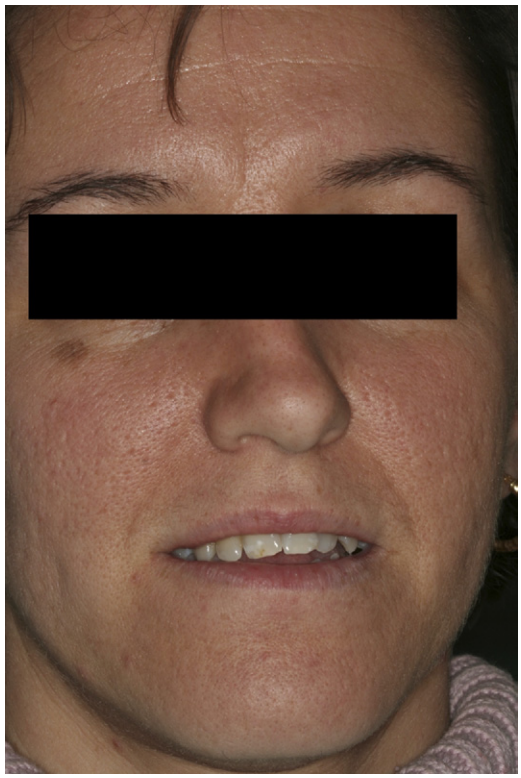

FIGURE 1. Extraoral presentation of the patient.

Morcavallo et al. Hereditary Angioedema in Oral Surgery. J Oral Maxillofac Surg 2010.

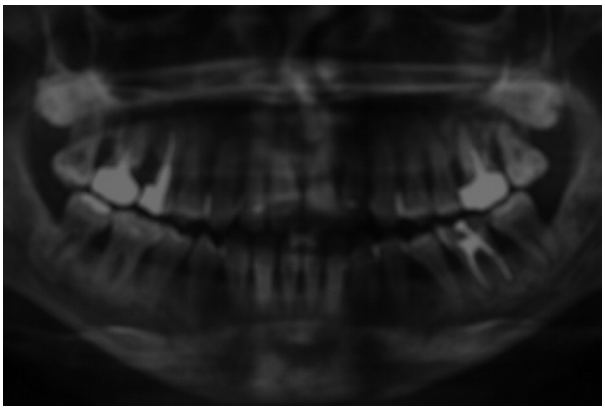

FIGURE 2. Radiographic examination of the patient.

Morcavallo et al. Hereditary Angioedema in Oral Surgery. J Oral Maxillofac Surg 2010.

During the anamnestic data collection, the patient reported that she was affected by HAE, which had been diagnosed at 13 years of age and was treated initially with C4 and C1-INH. During adolescence, frequent abdominal colic caused by stress, trauma, and menstruation had been the only symptoms of HAE. At 30 years of age, after the patient's first pregnancy, the clinical picture had been worsened by the onset of recurrent diffuse nonpruritic edemas involving the hands, feet, and face. However, she had no history of respiratory difficulties caused by the involvement of the airway mucosa.

The patient was being treated daily with antifibrinolytic agents (500 mg of tranexamic acid orally: 1 g in the morning and 1 g in the evening) as prophylactic therapy; in the case of invasive procedures, she took androgen derivatives (200 mg of danazol orally 3 times daily) from 5 days before surgery to 5 days after surgery.

The treatment plan for this patient included nonsurgical periodontal therapy and, subsequently, additional periodontal therapy with elevation of full-thickness flaps in the maxilla and mandible and extraction of compromised teeth.

Because of the necessity to carry out the specific prophylaxis before each dental procedure, we planned to perform

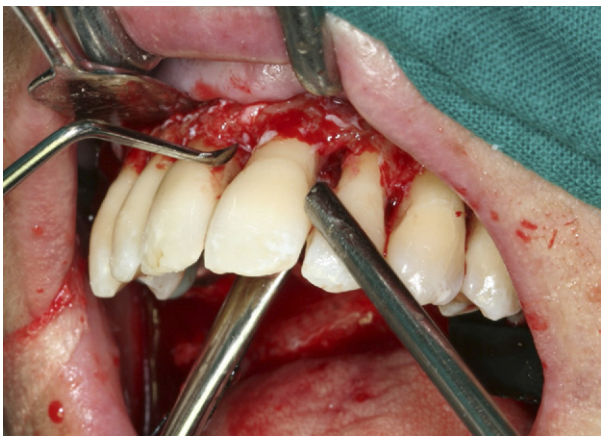

FIGURE 3. Flap elevation during periodontal surgery.

Morcavallo et al. Hereditary Angioedema in Oral Surgery. J Oral Maxillofac Surg 2010.

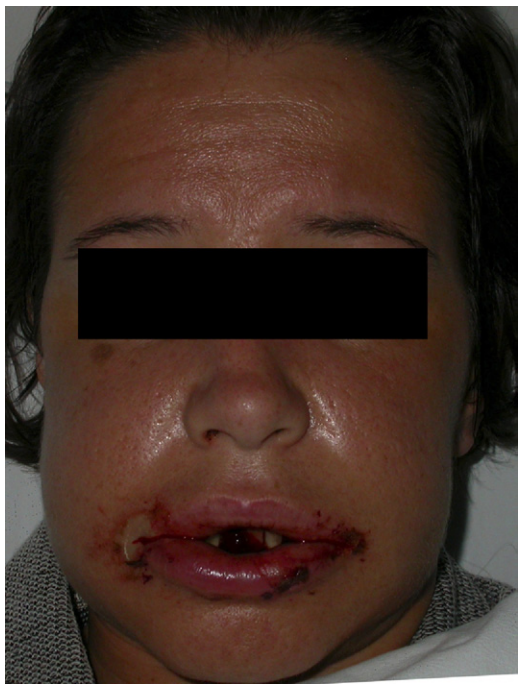

FIGURE 4. Angioedema development after surgery.

Morcavallo et al. Hereditary Angioedema in Oral Surgery. J Oral Maxillofac Surg 2010.

the nonsurgical periodontal therapy in 1 session. For the same reason, surgery was scheduled in a single operation with the patient under general anesthesia with nasotracheal intubation.

Androgen derivatives (200 mg of danazol orally 3 times daily, from 5 days before surgery to 5 days after surgery) were used as preoperative prophylaxis.

A blood sample was taken from which autologous platelet-rich plasma (PRP) was prepared at the Transfusion Centre of San Gerardo Hospital: PRP was used in postextraction sites and surgically treated periodontal defects.

After the local infiltration of 2% Carbocaine (mepivacaine hydrochloride, Scandoest 2%; Saint-Maur-Des-Fosses Cedex, France) with 1:100,000 epinephrine, mucoperiosteal flaps were elevated and the extraction of the compromised teeth was performed. Granulation tissue was removed, and PRP was placed in the bone defects (Fig 3). Finally, No. 4-0 silk stitches were applied.

In the 24 hours after surgery, the postoperative course was characterized by severe edema involving the face and the oral cavity (Fig 4). No other region of the body was involved, and the patient showed no sign of dyspnea resulting from the involvement of the respiratory tract.

A constant ooze from the surgical sites occurred, with formation of voluminous clots. Therefore the patient's hospitalization was extended 72 hours; the edema decreased gradually in the days after hospitalization (Fig 5). Periodic check-ups were scheduled 10 days, 1 month, and 2 months after surgery to monitor the state of recovery of the tissues.

Discussion

In certain cases microtrauma caused by dental treatment can trigger an angioedema attack involv-

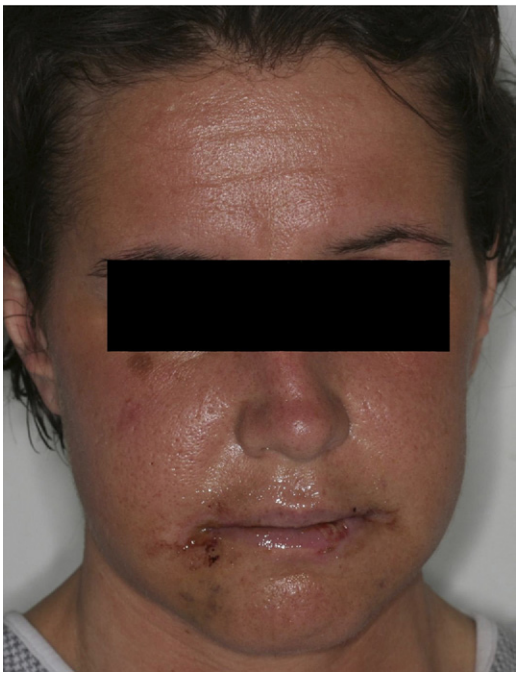

FIGURE 5. Angioedema resorption after surgery.

Morcavallo et al. Hereditary Angioedema in Oral Surgery. J Oral Maxillofac Surg 2010.

ing the respiratory tract. Four cases of death caused by asphyxia from laryngeal edema after dental extractions have been reported in the literature.[8] Moreover, in a review of the literature, the mortality rate from severe airway obstruction was reported to be 15% to 33% in patients with untreated angioedema.[22]

For these reasons, obtaining an accurate history of patients with angioedema is essential: careful preoperative, intraoperative, and postoperative treatment can reduce or prevent the occurrence of complications. As a result, dental procedures can be carried out with relative safety, and appropriate treatment can be given in case an acute attack occurs.

This case report highlights the primary role of the dentist in identifying the patient with angioedema: the careful recording of a detailed and comprehensive medical history allowed the correct identification of this clinical case and the appropriate planning of the surgical procedure, avoiding intraoperative complications.

Although preoperative prophylaxis decreases the risk of acute attacks, this risk cannot be avoided completely.[8] For this reason, it is important that both the patient and the dentist know the clinical features of acute episodes of angioedema, to identify the early signs and symptoms and permit prompt emergency intervention.

In addition, because the time interval between the occurrence of the first signs and symptoms and the onset of a clear clinical picture varies from 30 minutes to 3 days, it is important to inform the patient about the emergency procedures to be used in case an acute attack occurs.[23]

Another aspect to be considered is the importance of a careful evaluation of treatment options and indications. When possible, conservative treatment should be preferred over more invasive procedures, such as dental extraction. For this reason, it is advised that patients with angioedema should be included in a dental prevention program with periodic check-ups.

Finally, it is important to perform surgery in a hospital facility to ensure, if necessary, prompt emergency intervention and supervision of possible complications. Performing surgery in a hospital facility such as San Gerardo Hospital allowed us to control the significant postoperative sequelae through the patient's hospitalization in the days immediately after surgery.

References

1. Quincke HI: Über akutes umschriebenes Hautödem. Monatsh Prakt Dermatol 1:129, 1882
2. Osler W: Hereditary angioneurotic edema. Am J Med Sci 95: 362, 1888
3. Ogbureke KUE, Cruz C, Johnson JV, et al: Perioperative angioedema in a patient on long-term angiotensin-converting enzyme (ACE)-inhibitor therapy. J Oral Maxillofac Surg 54:917, 1996
4. Davis AE: The pathophysiology of hereditary angioedema. Clin Immunol 114:3, 2005
5. Turner MD, Oughourli A, Heaney K, et al: Use of recombinant plasma kallikrein inhibitor in hereditary angioedema: A case report and review of the management of the disorder. J Oral Maxillofac Surg 62:1553, 2004
6. Karlis V, Glickman RS, Stern R, et al: Hereditary angioedema. Case report and review management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83:462, 1997
7. Agostoni A, Cicardi M, Cugno M, et al: Clinical problems in the C1-inhibitor deficient patient. Behring Inst Mitt 93:306, 1993
8. Bork K, Barnstedt SE: Laryngeal edema and death from asphyxiation after tooth extractions in four patients with hereditary angioedema. J Am Dent Assoc 134:1088, 2003
9. Rosen FD, Davis AE: Deficiencies of C1 inhibitor. Best Pract Res Clin Gastroenterol 19:251, 2005
10. Bork K, Barnstedt S, Koch P, et al: Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 356:213, 2000
11. Cicardi M, Zingale LC, Pappalardo E, et al: Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. Medicine (Baltimore) 82:274, 2003
12. Gompels MM, Lock RJ: C1 inhibitor deficiency: Diagnosis. Clin Exp Immunol 30:460, 2005
13. Farkas H, Gyeney L, Gidófalvy E, et al: The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. J Oral Maxillofac Surg 57:404, 1999
14. Zuraw BL: Current and future therapy for hereditary angioedema. Clin Immunol 114:10, 2005
15. O'Ryan F, Poor DB, Hattori M: Intraoperative angioedema induced by angiotensin-converting enzyme inhibitors: Overview and case report. J Oral Maxillofac Surg 63:551, 2005

16. Spaulding WB: Methyltestosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). Ann Intern Med 53:739, 1960
17. Gelfand JA, Sherins RJ, Alling DW, et al: Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. N Engl J Med 295:1444, 1976
18. Leimbruger A, Jaques WA, Spaeth RJ: Hereditary angioedema uncomplicated maxillofacial surgery using short-term C1 inhibitor replacement therapy. Int Arch Allergy Immunol 101:107, 1993
19. Jaffe CJ, Atkinson JP, Gelf JA, et al: Hereditary angioedema: The use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. J Allergy Clin Immunol 55:386, 1975
20. Pickering RJ, Good RA, Kelly JR, et al: Replacement therapy in hereditary angioedema. Successful treatment of two patients with fresh frozen plasma. Lancet 1:326, 1969
21. Longhurst HJ: Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: What is the evidence? Int J Clin Pract 59:594, 2005
22. Moore GP, Hurley WT, Pace SA: Hereditary angioedema. Ann Emerg Med 17:1082, 1988
23. Chiu AG, Newkirk KA, Davidson BJ, et al: Angiotensin-converting enzyme inhibitor-induced angioedema: A multicenter review and an algorithm for airway management. Ann Otol Rhinol Laryngol 110:834, 2001

J Oral Maxillofac Surg
68:2311-2319, 2010

Control of Life-Threatening Head and Neck Hemorrhage After Dental Extractions: A Case Report

Benn Larkin Lieberman, DMD, Michelle K. Kennedy, DMD,†*
Dorothy R. Lorenzo, DMD,‡ Louis J. Reed, MD,§
Arthur K. Adamo, DDS,‖ Vito A. Cardo, Jr, DDS,¶ and
*Victor M. Badner, DMD, MPH***

Report of a Case

A 54-year-old man presented to the North Central Bronx Hospital Dental Clinic (Bronx, NY) on October 30, 2007, with a complaint of pain in his right mandible. The patient's vital signs were unremarkable on presentation with a blood pressure of 140/75 mm Hg and a pulse rate of 85 beats/min. The patient reported having a stroke 10 years previously that was managed with aspirin therapy for 7 years. The patient denied taking any medications. He had no known drug allergies but admitted to occasional alcohol use. He denied any drug or tobacco use on the medical intake questionnaire and during the initial consultation. He noted a history of bruising easily but reported having previous dental extractions without incident. A panoramic radiograph (Fig 1) showed multiple nonrestorable teeth (maxillary right third molar, maxillary right first premolar, maxillary right canine, maxillary left second premolar, maxillary left first molar, mandibular left first premolar, mandibular right second molar, and mandibular right third molar) with bone loss consistent with generalized periodontal disease. Clinical examination showed gross caries and gross mobility of the maxillary right third molar, maxillary right first premolar, maxillary right canine, maxillary left second premolar, maxillary left first molar, mandibular right second molar and mandibular right third molar, as well as a fractured crown and an exposed endodontic metal post in the

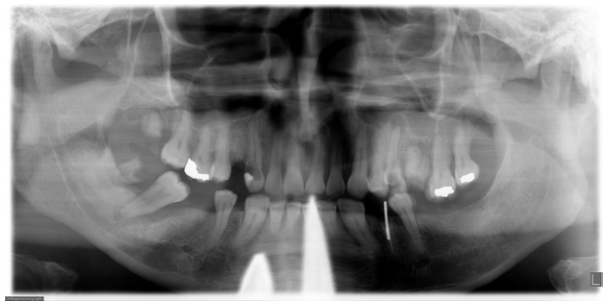

FIGURE 1. Preoperative panoramic radiograph (October 30, 2007).

Lieberman et al. Hemorrhage After Dental Extraction. J Oral Maxillofac Surg 2010.

Received from North Bronx Healthcare Network, Bronx, NY.

*Director of Oral and Maxillofacial Surgery, North Central Bronx Hospital.

†Former Resident; Currently, Attending, Oral and Maxillofacial Surgery, Brookdale University Hospital.

‡Chief Resident, Oral and Maxillofacial Surgery, Brookdale University Hospital.

§Associate Visiting Physician, Division of Hematology/Oncology, Department of Medicine.

‖Director, Oral and Maxillofacial Surgery.

¶Director, Oral and Maxillofacial Surgery, Brookdale Universtiy Hospital; Former Chairman, Caritas Hospital.

**Chairman, Department of Dentistry/Oral and Maxillofacial Surgery.

Address correspondence and reprint requests to Dr Lieberman: North Bronx Healthcare Network, 1400 Pelham Pkwy S, Bldg 1, Room 3N34, Bronx, NY 10461; e-mail: benn.lieberman@nbhn.net

0278-2391/10/6809-0040$36.00/0
doi:10.1016/j.joms.2010.02.020