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Hereditary Angioedema Type I Triggered by Dental Treatment: A Case Report and Review of the Literature

Abstract: Type 1 hereditary angioedema (HAE) is a rare genetic condition characterized by recurrent episodes of oedema caused by a deficiency of C1-esterase inhibitor (C1-INH). A 29-year-old male presented to the oral medicine department at Guy's Hospital, London, with lip swelling following crown preparation and impressions. Haematological investigations showed reduced levels of complement C4 (0.02 g/L; reference range 0.1–0.4 g/L) and C1-INH function was <31% (reference range 85–99%). Immunology confirmed the diagnosis of type 1 HAE, with a *de novo* mutation. This case highlights how a detailed medical history and multidisciplinary teamwork ensure the correct diagnosis and management.

CPD/Clinical Relevance: To demonstrate the various dental triggers, relevant signs and symptoms, and management options for patients diagnosed with hereditary angioedema to allow for effective decision-making in a primary dental setting.

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Hereditary angioedema (HAE) is a condition presenting with recurrent episodes of severe swelling affecting the mucosa of the respiratory and gastrointestinal tracts and skin.[1] Commonly, the lips, hands, arms, gastrointestinal tract and upper airway are affected. Swelling of the respiratory tract can lead to life-threatening consequences as a result of obstruction caused by laryngeal oedema. Early diagnosis is therefore critical.[2] The aetiology is attributed to a mutation in the SERPING1 gene, which is responsible for the production of C1 esterase inhibitor (C1-INH), an acute-phase reactant and a member of the 'serpin' superfamily of serine protease inhibitors.[2] Type 1 HAE (accounting for 85% of C1INH-HAE) is associated with a reduced quantity of C1-INH, while type 2 HAE is associated with the production of dysfunctional C1-INH.[2] This results in an excessive production of bradykinin, a potent vasodilatory mediator with vascular permeability-enhancing effects. It is prevalent in approximately 1 in 50,000 people.[2] The inheritance of types I and II HAE is autosomal dominant; however, approximately 25% of cases result from *de novo* mutations, so a

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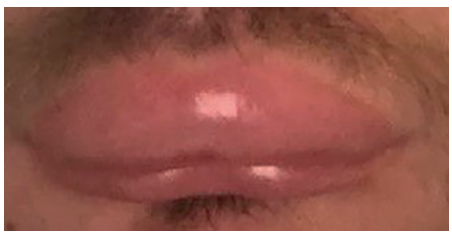

Figure 1. Diffuse upper lip swelling following dental treatment

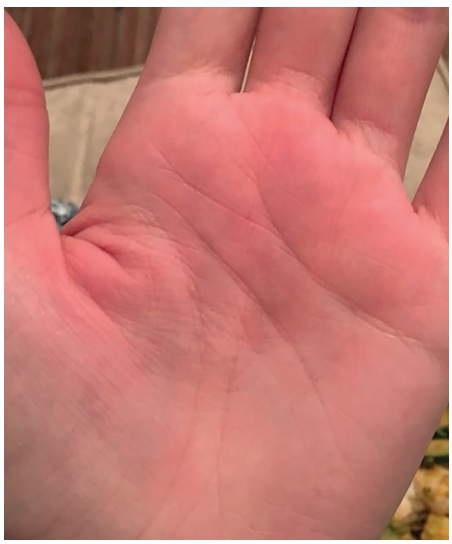

Figure 2. Rash involving palmar aspect of hands

positive family history is not required for diagnosis.[3] The risk of mortality may be as high as 30%; however, if precipitants are avoided or the emergency is effectively treated, the disease is compatible with prolonged survival.[4]

Early diagnosis can lead to the development of an individualized management plan to assist with prevention and control of angioedema attacks. The difficulty lies in healthcare professionals failing to recognize this rare condition leading to possible delays in diagnosis, or misdiagnosis due to not including hereditary angioedema in the differential diagnosis. Although the incidence of HAE in the maxillofacial region is rare, the consequences are potentially fatal, thus reinforcing the importance of appropriate patient evaluation, timely diagnosis, prevention, and treatment of future attacks. The value in distinguishing these incidences from other competing differential diagnoses allows for accurate and appropriate management. This article presents a case of HAE induced by dental treatment, as well as provides an updated literature review of HAE triggered by dental treatments in the oral cavity, advice about further investigations and reviews the available management options.

Case report

A 29-year-old male was initially referred to the oral medicine department at Guy's Hospital, London for patch testing to exclude an allergy to dental materials. The patient described an episode of upper lip swelling (Figure 1) with extension towards the cheeks and throat, which commenced the same day following a crown preparation and impressions. The patient reported previous episodes of spontaneous swelling of the hands (precipitated by application of pressure, for example increased grip on the steering wheel) and feet, associated with features of a rash of 3 years' duration (Figure 2). He experienced four previous episodes of facial and genital swelling. Previous therapies trialled included antihistamines and oral corticosteroids, with no improvement documented.

The patient was otherwise fit and well with an allergy to penicillin noted. He did not smoke and rarely consumed alcohol. On initial examination, the hands were visibly swollen. There was no lip swelling. Intra-orally, all soft tissues were healthy.

A series of haematological investigations were undertaken including a full blood count, complement C3 and C4, C1-INH function and immunoglobulin E (IgE) level. Eosinophils and IgE levels were within normal range. Complement C4 was 0.02 g/L (reference range 0.1–0.4 g/L) and C1-INH function was <31% (reference range 85–99%). This prompted a referral to the immunology department,where a diagnosis of type 1 HAE was made, possibly due to a *de novo* mutation. All family members were subsequently screened and found to be negative for the same mutation. Treatment recommended for an acute swelling, particularly affecting the head and neck region, includes a slow intravenous injection of C1-INH 1500 units in a hospital setting. Additionally, subcutaneous icatibant 30 mg (self-administered by the patient to the abdomen) during an acute episode of angioedema was also recommended for this patient. Prophylactic use of attenuated androgen, danazol, was offered.

Discussion

HAE is a rare condition characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Type 1 HAE, an autosomal-dominant disorder, is caused by a deficiency in C1-INH due to a mutation in the SERPING1 gene. This results in low plasma levels of functional and antigenic C1-INH. This differs from type 2 HAE, where antigenic C1-INH levels are in the normal or even high range – it is the production of dysfunctional C1-INH that results in oedemic attacks due to the reduced presence of functional C1-INH.[5] C1-INH also interferes with the cleavage to C4 as part of the complement pathway, therefore a low C1-INH also results in low C4 levels in the blood, which is an effective screening tool. Patients with low functional C1-INH, C4 levels and antigenic C1-INH are most likely to have type I HAE.[5] Patients with low functional C1-INH, low C4 levels but with normal or raised antigenic C1-INH are diagnosed with type 2 HAE.[5] Type 3 is caused by a mutation in the Factor XII gene resulting in normal C1-INH levels, and is associated with women taking therapeutic oestrogen.[5]

C1-INH is responsible for regulating a number of physiological responses. It inhibits the activation and cleavage of prekallikrein to kallikrein by its action on factor XIIa and also directly inhibits activated kallikrein, which is required for the cleavage of high-molecular weight kininogen into bradykinin leading to angioedema.[5] This process may be initiated from minor tissue injury, such as from dental procedures. Therapeutic approaches target C1-INH by restoring these levels, or by inhibiting the co-products of the pathway. Danazol and stanozolol are attenuated androgens and both work by physically increasing the liver's production of C1-INH.[6] They belong to a class of anabolic steroids and involve careful tapering regimens, making them

Reference	Number of patients	Gender	Age	Dental trigger	Onset of symptoms following dental treatment	Facial swelling	Oral swelling	Airway swelling	Abdominal swelling	Management
Degroote[13]	1	F	40	Extraction	30 seconds	No	No	Yes Laryngeal oedema	No	IV epinephrine, intubation followed by aminophylline, methylprednisolone, diphenhydramine, epinephrine, danazol. Discharged on prednisolone
Atkinson[14]	5	Unknown	Unknown	Pulpectomy, hygiene treatment, minor salivary gland biopsy, root canal treatment, amalgam restorations, composite restorations and extractions	Unknown	Yes Facial swelling = 2 Upper lip swelling = 1 Lower lip swelling = 1	No	Hoarseness (1 patient)	Yes (1 patient)	Two patients received subcutaneous epinephrine
Bork[12]	4	3 F, 1 M	F= 30, 27, 32 M= 46	Extractions	30 hours	No	No	Laryngeal oedema Death	No	30 year old female treated with IV steroids, antihistamines and oxygen
					4 hours	No	Tongue swelling	Laryngeal oedema Death	No	27 year old female, intubation attempted but unsuccessful due to swelling
					9 hours	Facial swelling	No	Laryngeal oedema Death	No	32 year old female: no discussion regarding management
					7 hours	No	No	Laryngeal oedema Death	No	46 year old male – died before arrival of emergency team
Bork[26]	7	Unknown	Unknown	Dental surgery	Unknown	Unknown	Unknown	Laryngeal oedema	Unknown	Unknown
Socker[15]	2	2 M	18, 63	18 year old: dental examination, scale and polish	Unknown	Post-operative swelling: no discussion on location of swelling				Not mentioned, swelling was noted as not being severe
				63 year old: extractions	36 hours	Bilateral facial swelling	No	No	No	Prophylactic tranexamic acid and IV C1 esterase inhibitor 1000 U Admitted for 3 days, recommendation for future treatment included prophylactic IV C1 esterase inhibitor 1500 U before treatment and 1000 U 6 hours after treatment

Table 1. Literature review of cases of angioedema triggered by dental interventions (continued on page 60).

Reference	Number of patients	Gender	Age	Dental trigger	Onset of symptoms following dental treatment	Facial swelling	Oral swelling	Airway swelling	Abdominal swelling	Management
Rice[16]	1	F	28	Extraction	Few hours	Orofacial swelling	Orofacial swelling	Stridor	No	C1 esterase inhibitor given
Morcavallo[17]	1	F	38	Periodontal surgery and extractions	Within 24 hours	Facial oedema	Oral oedema	No	No	Prophylactic tranexamic acid 1 g morning and evening and danazol TDS for 5 days Danazol TDS 5 days post surgery
Bork[18]	140 cases of HAE attacks from 705 extraction sessions	M, F	Mean age: 43.6 years	Extractions	Mean: 8.4–14.3 hours	Isolated facial oedema = 97 cases	No	Isolated laryngeal oedema = 12 cases	No	Before 128 of these extraction session,s prophylaxis with C1 inhibitor 500 or 1000 units was given, of the 140 cases which developed HAE attack, 16 had received prophylactic treatment
						Both facial and laryngeal oedema = 31 cases				
Baliga[19]	1	F	42	Pulp extirpation lower left premolar	Not known-swelling arose after patient returned home	Lower and upper lip, infraorbital rim, lower border of Mandible, submandibular, submental	Upper and lower labial and buccal vestibule obliteration	No	No	Hydrocortisone sodium succinate, methyl-prednisolone acetate, ranitidine, and pheniramine maleate
Bork[4]	6	Unknown	Unknown	Extractions	4–30 hours	Unknown	Unknown	Laryngeal swelling Death	No	Unknown
Jurado-Palomo[20]	4	Unknown	Unknown	Two extractions, one bridge	Unknown	No	No	Mild upper airway angioedema	No	Spontaneous resolution
				Placement of braces	A few months later	No	Palatal oedema	No	No	Unknown
Cifuentes[21]	1	M	18	Orthognathic surgery	30 hours	Facial oedema	No	Pharyngeal, and glottic oedema	No	Methyl-prednisolone, emergency tracheal incubation, fresh-frozen plasma
Kumar[22]	1	M	47	Extraction UL7	3 hours	Bilateral facial swelling, lip swelling	Soft palate swelling	Pharyngeal wall swelling, neck swelling	No	Steroids and antihistamines
Forrest[11]	1	F	50	Extraction LR6, LR7	48 hours	Facial swelling	Tongue, soft palate, uvula swelling	Pharynx, larynx Death	No	

Table 1. Literature review of cases of angioedema triggered by dental interventions (continued from page 59). TDS: three times daily.

more appropriate for administration prophylactically in the long term, but not for acute attacks. Anti-fibrinolytics such as ε-aminocaproic acid and tranexamic acid work by inhibiting plasmin activity, which directly regulates the complement pathway but also prevents the release of further vasoactive proteins, which in turn decreases further tissue inflammation.[7] Fresh frozen plasma (FFP) transfusions have been used historically to aid increasing the volume of complement components in human plasma. However, due to their associated safety risks including anaphylaxis, viral transmission and transfusion-related lung injury, it appears safer to use C1-INH concentrates.[8] Advances have also been made in the development of new treatments for HAE. Icatibant is a synthetic protein used to inhibit bradykinin B2 receptors and thus decrease the activity of bradykinin.[9] It can be self-administered subcutaneously, unlike alternatives such as ecallantide. Ecallantide acts on a different pathway by inhibiting kallikrein; however, due to its potent response and risk of anaphylaxis, it can only be administered subcutaneously by a medical professional.[10]

Dental interventions have the ability to trigger an acute episode of angioedema (Table 1). In some situations, these can be fatal with the possibility of death being a conceivable consequence.[4,11,12] The various interventions include: extractions, orthognathic surgery, pulp extirpations, bridge placement, crown preparations, restorations, scaling and intra-oral biopsies.[4,11–22] Time of onset of angioedema following a dental procedure varies between patients, from as quickly as 30 seconds to up to 2 days following treatment; therefore all patients must be informed of the signs and symptoms, and the need to seek urgent care. The gender was often undocumented in the cases described in Table 1, and therefore it was difficult to ascertain whether HAE was more predominant in a particular gender. The age of the patients was also often not documented, but from those where it was included, it ranged from 18 to 63 years. Management strategies used varied widely between studies and included corticosteroids, danazol, subcutaneous epinephrine, antihistamines, intravenous C1-INH and FFP (Table 1).

If a patient is identified as being at risk of angioedema, liaising with the patient's general medical practitioner as well as their immunologist will ensure the best pathway of care. Treatment in a hospital setting with close clinical observation may be necessary. The immunologist will be able to advise on prophylactic management prior to dental interventions to reduce the risk of significant angioedema. Prophylactic regimens quoted in the literature include C1-INH 500 units, 1000 units or 1500 units given before dental treatment.[15,18,21] Bork *et al* compared patients who received prophylactic C1-INH to patients who did not, and concluded that prophylactic treatment significantly reduces the risk of symptoms following an extraction.[18] Other preventive treatment methods mentioned include the use of FFP, anti-fibrinolytic drugs, such as tranexamic acid, androgen derivatives and anabolic steroids.[17] Jaffe *et al* showcased that if FFP is transfused one day before surgery it has the potential to raise the levels of C4 and C1-INH.[23]

Hormonal influences are also thought to trigger an attack, therefore the use of contraceptives containing oestrogen and hormone replacement therapy is not advised.[24] ACE inhibitors have the ability to induce angioedema by blocking the degradation of bradykinin.[25]

As this case demonstrates, because patients may present undiagnosed, it is important to undertake a complete and thorough medical history enquiring about a history of repeated swellings affecting the face and extremities. Furthermore, oral hygiene instruction, dietary advice and regular visits to a general dental practitioner should be encouraged in patients with a known diagnosis of HAE to prevent the need for future operative dental interventions, which have the potential to trigger an acute attack.

Angioedema *versus* anaphylaxis

Some signs and symptoms of angioedema and anaphylaxis can overlap; however, it is important to differentiate between the two conditions.

- Angioedema is defined by NICE as 'swelling of deep dermis, subcutaneous, or submucosal tissue, often affecting the face, genitalia, hands, or feet. Less commonly, submucosal swelling affects the bowel and airway'.[27]
- Anaphylaxis is defined by NICE as 'a severe, life-threatening, generalized or systemic hypersensitivity reaction that is characterized by rapidly developing airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes.'[27]

NICE guidelines have outlined three criteria that make a diagnosis of anaphylaxis more likely:[27]

- Sudden onset and rapid progression of symptoms;
- Life threatening airway and/or breathing and/or circulation problems;
- Skin and/or mucosal problems.

The diagnosis of anaphylaxis is further strengthened by a known exposure to an allergen including food, medication or venom.

Typically, anaphylaxis is a systemic process whereas angioedema occurs in a localized site. Anaphylaxis can occur with or without angioedema. A sense of impending doom along with urticaria may be present during an anaphylactic attack, while the swellings associated with angioedema tend to be non-pruritic.

However, as we have shown in our literature review, HAE also has the potential to cause an airway swelling leading to airway compromise and death, thus urgent care for either angioedema or anaphylaxis is advised.

Although HAE is a rare phenomenon, it should be included in the differential diagnosis of patients presenting with recurrent episodes of facial swelling. Prompt recognition and effective treatment is critical due to the risk of fatal laryngeal attacks. While dental extractions tend to be the most common dental precipitant, our literature review showed a wide variety of other interventions, including pulp extirpations, bridge placement, crown preparations, restorations, scaling and intra-oral biopsies that have the potential to trigger an episode.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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