Oral medicine case book 64: Some aspects of the pathophysiology of angioedema with special reference to the upper aerodigestive tract

ABSTRACT
Angioedema refers to a localized oedematous swelling of subcutaneous or sub-mucosal tissues, caused by dilatation and increased permeability of blood vessels, usually mediated either by histamine or by bradykinin.

Deficiency or loss of functional activity of the complement component C1 esterase inhibitor (C1-INH) affects multiple systems, including the kallikrein-kinin, complement, coagulation and fibrinolytic pathways, and in the context of angioedema, the result is increased production and release of bradykinin and other vasoactive substances such as C3a. Owing to impairment of C1-INH, factors XIIa and kallikrein, by a positive feedback mechanism, bring about persistent activation of the kallikrein-kinin pathway with amplification of production of bradykinin, resulting in angioedema.

Histamine can cause histaminergic angioedema. As the name implies, this oedema is caused by degranulation of mast cells/basophils as a result of an IgE-dependant allergic reaction to extracts of food, drugs, infectious agents, or to physical stimulation; or as the result of direct degranulation of mast cells/basophils independently of IgE, caused by releasing agents such as opiates, antibiotics or radio-contrast media.

As dental, oral and maxillofacial operative procedures may trigger the development of angioedema in susceptible individuals, the dental practitioner should be familiar with its signs and symptoms, its pathophysiology and with the first-line treatment of this disorder.

Key words: hereditary angioedema, bradykinin, histamine, C1-inhibitor, factor XII

INTRODUCTION
During dental, oral or maxillofacial treatment, the patient might collapse not because of the operative or surgical procedure, but because of release of vasoactive substances resulting in angioedema with upper airway obstruction. Angioedema has been defined as “localized and self-limiting oedema of the subcutaneous or submucosal tissues, owing to a temporary increase in vascular permeability caused by the release of vasoactive mediators.” Histopathologically there is upregulation of adhesion molecules of endothelial cells with adhesion of circulating leukocytes and with a perivascular infiltrate of lymphocytes, eosinophils and neutrophils because of an increase in the endothelial intercellular spaces, and separation of perivascular collagen bundles. There are a number of variants of angioedema that may be categorized according to several possible precipitating factors and according to the nature of the specific vasoactive mediator. Angioedema may be triggered via any one of several pathogenic pathways, including firstly by histamine released from activated mast cells or basophils triggered by antigen-specific immunoglobulin E (IgE) or by mast cell degranulation precipitated by opiates, antibiotics, curare and radiocontrast media, independently of an IgE response. Secondly, angioedema may be triggered by increased levels of bradykinin as a result of either acquired or hereditary deficiency of the complement component C1 esterase inhibitor (C1 INH), or by an angiotensin-converting enzyme (ACE) inhibitor; and thirdly, in susceptible subjects, angioedema may be triggered by aspirin and other non-steroidal anti-inflammatory drugs (NSAID) against a background of altered arachidonic acid metabolism (Figure 1). Histamine, bradykinin and other bioactive mediators bind to their respective receptors on endothelial cells activating intracellular

ACRONYMS
ACE: angiotensin-converting enzyme
C1-INH: complement component C1 esterase inhibitor
IgE: immunoglobulin E
NSAID: non-steroidal anti-inflammatory drugs
PGE2: prostaglandin E2

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Histamine-mediated angioedema
- IgE-dependent mast cell/basophil degranulation
- Complement mediated: non-IgE dependent, mast cell/basophil degranulation by C3a and C5a
- Non-immunological, direct mast cell/basophil degranulation by drugs (opiates, vancomycin), food extracts or radiographic contrast media.

Bradykinin-mediated angioedema
- Hereditary, C1-INH deficiency
- Hereditary, Factor XII dysfunction
- Acquired, C1-INH deficiency
- ACE inhibitors

Idiopathic
- Unidentified underlying mechanisms

Histamine-mediated angioedema
- Histaminergic angioedema is rapid in onset, usually lasts less than 30 minutes and typically is accompanied by urticaria. Histamine release is due to the activation of mast cells, which may be caused by a variety of stimuli such as physical or chemical factors, or by certain medications. Histamine interacts with H1 and H2 receptors on endothelial cells, directly causing vasodilation and increased vascular permeability. Histamine also mediates the production of nitric oxide and the mobilization of arachidonic acid metabolites, thus further promoting the inflammatory process.

Bradykinin-mediated angioedema
- Bradykinin is a non-histaminergic angioedema, and is not responsive to antihistamines. Either as a hereditary autosomal dominant trait or as an acquired impairment, in bradykinin-mediated angioedema the complement component C1-esterase inhibitor (C1-INH) may be deficient or functionally impaired. Normally, C1-INH prevents over-activation of the complement system, and is also an inhibitor of other plasma serine proteases, including components of the kallikrein-kinin system (contact system), of factor XI (Hageman factor) and factor Xa of the coagulation system and of components of the fibrinolytic system (Figure 3). However, there is apparently no clinical effect of C1-INH deficiency on either the coagulation or the fibrinolytic systems, so the most important role of C1-INH is to control the kallikrein-kinin and the complement pathways.

About 85% of hereditary and acquired cases of C1-INH deficiency show dimunition in C1-INH levels (type 1), and the remainder show impaired functional activity of normal levels.
of C1-INH (type 2). Type 3 hereditary angioedema is associated with molecular alterations to the gene encoding the coagulation factor XII (Hageman factor), affects mainly women with normal plasma levels and functional activity of C1-INH, and is activated by oestradiol. The clinical features are identical in all the different types of hereditary angioedema.

Hereditary C1-INH deficiency types 1 and 2 are associated with molecular variations in the gene governing C1-INH, and are characterized by low levels of C2 and C4 during episodes of angioedema, but the level of the complement protein C1q is normal. On the other hand, in acquired C1-INH deficiency, there are reactive auto-antibodies towards C1-INH, or a depletion of C1-INH in association with lymphoproliferative disorders or connective tissue diseases.

Typically, acquired C1-INH is diagnosed in the fifth decade of life, and is associated with diminished levels of complement proteins C4, C2 and C1q during episodes of angioedema. Clinically, hereditary angioedema and acquired bradykinin-mediated angioedema are very similar.

The angioedema of hereditary C1-INH deficiency is episodic, non-pruritic and non-pitting. Episodes usually start in childhood or adolescence and can affect any part of the body, but particularly the extremities, the intestines, the face and the larynx, with symptoms getting worse over 24-36 hours, and if untreated, resolving within 2-5 days. The frequency and severity of the attacks are unpredictable, but unlike in histaminergic angioedema, urticaria is seldom a feature. A family history is an important factor in establishing the diagnosis of bradykinin-mediated angioedema caused by C1-INH deficiency.

In order to reduce the frequency and the severity of the episodes, subjects with hereditary angioedema should be treated with synthetic anabolic steroids that increase the production of C1-INH by the liver, or by antifibrinolytic agents that inhibit the activation of plasmin and of factor C1. Androgens are also effective in the treatment of hereditary angioedema, but for reasons unknown they are not effective in the treatment of acquired bradykinin-mediated angioedema.

For persons who are already on preventive medication for hereditary angioedema and who require dental or oral surgical treatment, it is advisable to increase the medication 5-7 days before the treatment, or alternatively to administer fresh frozen plasma or C1-INH concentrate the day before the procedure. If the patient is known to have C1-INH deficiency, than acute attacks of angioedema with severe laryngeal oedema should be treated with intravenous fresh frozen plasma or concentrate of C1-INH, together with adrenaline and perhaps with intratracheal intubation or tracheostomy. Because they only start to have an effect after some hours or even days, while anabolic steroids are necessary, they are not part of the first line of treatment.

Figure 3: Schematic diagram of the activation of the Kallikrein-kinin, complement, fibrinolytic and coagulation systems in relation to C1-INH deficiency. C1-INH regulates the Kallikrein-kinin, the complement, and the fibrinolytic pathways. (Adapted from Fitzpatrick and Johnston 2011; Huang et al., 2005; Kaplan and Joseph 2014; Chanam et al., 2013). Diminution or impaired functional activity of C1-INH will result in disregulated C1 activation with increased consumption of C2 and C4, in increased levels of kallikrein and in activation of factor XII (Heymann, 1997; Johnston, 2011; Huang et al., 2005; Webb, 2000). Kallikrein in turn, cleaves high-molecular-weight kininogen (HMWK) to produce bradykinin, directly activates factor XII, and mediates the production of C5a which is an agent causing vasodilatation and increased vascular permeability, favouring the development of oedema. Kallikrein activates the fibrinolytic system which produces plasminogen, with the capacity to stimulate the anaphylotoxin C3a, contributing to oedema, and kallikrein also directly activates factor XII which further promotes the production of bradykinin (Robbins, 2012). Factor XIIa mediates the conversion of plasma prekallikrein into kallikrein, thus amplifying and perpetuating the production of bradykinin (Robbins, 2012). Therefore, on the background of C1-INH deficiency, activated factor XII and kallikrein, by a positive feedback mechanism, bring about continuous activation of the Kallikrein-kinin system with amplification of the production of bradykinin which is the driver of the C1-INH deficiency-associated angioedema (Ghannam et al., 2013; Kaplan and Joseph, 2014; Robbins, 2012).
Since dentists and medical practitioners would not have available fresh frozen plasma or concentrate of C1-INH, subjects with a history of facial bradykinin-mediated angioedema and who need dental care should be treated in a facility with all the necessary resources.1,11

**ANGIOEDEMA ASSOCIATED WITH ACE-INHIBITORS**

Angiotensin-converting enzyme inhibitors which are frequently used for the treatment of hypertension or heart failure,13 attenuate the degradation of bradykinin, sometimes resulting in elevated levels of bradykinin that can trigger clinical manifestations of bradykinin-mediated angioedema.1,25 Angioedema associated with ACE inhibitors usually affects the laryngeal, pharyngeal and oral mucosa, particularly the tongue,1,2,10,15 resulting in compromise of the airway with the potential for respiratory obstruction.26

It is estimated that between 0.1% and 6% of all persons treated with ACE inhibitors will at some time develop angioedema.5,11 When it occurs, in about 60% of cases the onset of angioedema is within a few weeks of starting the medication, but it can also occur for the first time only after several years of medication.26

If an acute emergency occurs owing to airway obstruction, as in any bradykinin-mediated angioedema, management is as previously described. Antihistamines are not effective.1,13

**IDIOPATHIC ANGIOEDEMA**

Recurrent angioedema in the absence of urticaria is termed idiopathic as it cannot be linked to any exogenous agent or to any underlying abnormality.2 Thus, with idiopathic angioedema, there is no family history, and the patient's serum levels, and the functional activity of C1-INH and of other components of the complement system are normal, and it may or may not respond to antihistamines.6 In severe cases, idiopathic angioedema should be treated with the standard regime of adrenaline, corticosteroids and antihistamines, though the antihistamines may or may not contribute significantly to the response.

**COMMENTS**

Angioedema is the result of capillary vascular dilation and increased permeability brought about primarily by histamine-mediated allergic reactions to drugs, to extracts of food or to environmental factors; by hereditary or acquired deficiency of C1-INH (bradykinin-mediated); by ACE inhibitors (bradykinin-mediated), or by as yet unidentified factors (idiopathic).27 Most probably this classification of angioedema is an oversimplification. Although not proven, in fact, bradykinin appears to contribute to the late clinical manifestation of histaminergic angioedema.13

The problem is to clinically distinguish between the different types of acute angioedema of the upper aerodigestive tract in order to treat appropriately. Histamine-mediated anaphylactic reactions develop rapidly and must be treated promptly with adrenaline, supplemented with antihistamine and corticosteroids. Bradykinin-mediated angioedema usually develops insidiously over a few hours and should ideally be treated with C1-INH concentrate, or with fresh frozen plasma intravenously, but these agents are not readily available. Unfortunately because these reactions develop gradually, they usually occur after the patient has left the health care facility or the doctor's rooms, and are thus seldom recognized or treated appropriately.

**References**