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Angioedema: a diagnostic dilemma

Angioedema: um diagnóstico dilema

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Abstract

Introduction: Angioedema is a rare but potentially life threatening (fatal laryngeal edema) disease. It is a relapsing subcutaneous or submucosal edema caused by various factors. The episodes can vary significantly from one individual to another. Causative factors should always be sought, but a large proportion of patients have the idiopathic form of the disease. A minority of patients represent a diagnostic and treatment challenge. A comprehensive history and close monitoring of response to treatment are the most cost effective diagnostic and treatment tools. **Objective**: This paper presents a highly representative clinical case of idiopathic variety of the disease where a ten year old boy reported with a complaint of swelling over right side of the face and upper lip since 4 hours. **Conclusion**: There was no associated pain or discomfort. There was slight itching in the same area prior to the appearance of swelling. Condition showed prompt improvement following antihistamines.

Keywords: Angioedema. Idiopathic. Antihistamines.

Resumo

Introdução*: Angioedema é uma doença rara, porém, com potencial risco à vida (edema fatal de laringe). É um edema subcutâneo ou submucoso recidivante causado por vários fatores. Os episódios podem variar significativamente de um indivíduo para outro. Fatores causadores da doença sempre devem ser pesquisados, mas*

uma grande proporção dos pacientes tem a forma idiopática da doença. Uma minoria de pacientes representa um desafio no diagnóstico e tratamento. O histórico completo e o acompanhamento da resposta ao tratamento são as ferramentas de diagnóstico e tratamento de menor custo. ***Objetivo****: Este trabalho apresenta um caso clínico altamente representativo da variedade idiopática da doença: um menino de dez anos se apresentou com queixa de inchaço no lado direito da face e no lábio superior nas últimas 4 horas.* ***Conclusão****: Não havia dor associada ou desconforto, havia leve coceira na mesma área, anterior ao aparecimento de inchaço. A condição mostrou rápida melhora após medicação com anti-histamínicos.*

Palavras-chave*: Angioedema. Idiopático. Anti-histamínico.*

Introduction

L. Milton first described angioedema in 1876. Quincke (1882) was the first to assign the name angioneurotic edema to the disease. The word 'neurotic' was used as part of the name in an attempt to describe the observed effect of mental stress on exacerbation of this disease (1). In 1888, Sir William Osler provided a medical description of angioedema that distinguished an inherited form of the disease with full clinical details. Seventy-five years later, Donaldson and Evans described patients with similar clinical features and demonstrated a deficiency of C1 esterase inhibitor in the blood of these patients (2). The term angioedema refers to localized, transient swelling of the deeper layers of the skin or mucous membranes or both including respiratory and gastrointestinal tracts. It is non-pitting, erythematous or skin-colored with ill-defined margins. A burning sensation or pain may be present but pruritus is absent. The swelling can affect any part of the body, but has a predilection for the areas of more loosely attached skin e.g., periorbital areas, lips. Swelling normally responds well to antihistamines and corticosteroids; and resolves in around 24 hours or more without discoloring the skin. Occasionally, angioedema does not respond to drugs against allergies and tends to last for 5-7 days (3-5).

The degranulation of mast cells, which may be induced by immunologic or non immunologic mechanisms, and the subsequent release of histamine and various cytokines cause the edema (6). Angioedema is a consequence of a local increase in permeability of subcutaneous or submucosal capillaries and postcapillary venules causing local plasma extravasation in response to mediators such as histamine, bradykinin. Allergic angioedema (histamine-induced angioedema) is a hypersensitivity reaction to various causes such as drugs, foods, insect venoms. Kinin-induced angioedema is believed to be caused by bradykinin-induced activation of endothelial cells resulting in vasodilatation and capillary leakage. However, idiopathic forms with unknown cause and mixed forms have also been reported (3).

Although it is uncommon for a patient with this disease to report to a dental clinic, high frequency of lip involvement is a good reason to take it into consideration.

Case report

A ten year old boy reported to the Dental OPD with a complaint of swelling over right side of the face and upper lip since four hours. There was no associated pain or discomfort. There was slight itching in the same area before the appearance of swelling.

History: there was no history of a similar episode of swollen lips. He did not experience any difficulty in swallowing or breathing and any other systemic symptoms. Careful questioning was done for any insect bite, recent diet (particularly, sea foods, chocolates), any known food or drug allergy, and recent drug intake (NSAIDs) to rule out possible precipitating and aggravating factors. There was no obvious association with any physical stimuli (cold, heat, sunlight, friction), as well.

Medical history: was noncontributory; patient had no history of asthma, allergic rhinitis/conjunctivitis or atopic dermatitis.

Family history: was not significant.

Physical examination: revealed a diffuse, skin colored swelling over right cheek, extending to the

upper lip, slightly crossing the midline (Figure 1). The margins could not be defined. Swelling was non-tender, non pitting. There was no swelling of any other part of the body. He had neither skin rashes nor pruritus. Lymph nodes (submandibular – right side and submental) were non palpable. Intra oral examination revealed deep distal caries and grade I mobility with 84; grade II mobility with 74, 75; erupting 34, 44, 45. None of the deciduous tooth was tender.

Provisional diagnosis: idiopathic angioedema. Facial cellulitis secondary to 84 was considered as a differential diagnosis, however, unusual site of swelling (ie upper lip) as well as the absence of pain negated the possibility of an acute abscess. Other signs of acute infection such as induration, raised temperature, redness, malaise and lethargy were absent.

Laboratory investigations: complete blood count, erythrocyte sedimentation rate, urinalysis and liver function tests were advised.

Treatment: patient was started with antihistamines – pheniramine maleate (25 mg tablet twice daily). On recall, after two days, swelling over the lip completely resolved and swelling over cheek had also markedly reduced (Figure 2). All the laboratory tests reported normal values. Subsequent recall visits were scheduled but patient failed to report again.

An informed, written consent was taken from the parents for their permission regarding the publication of this clinical case.

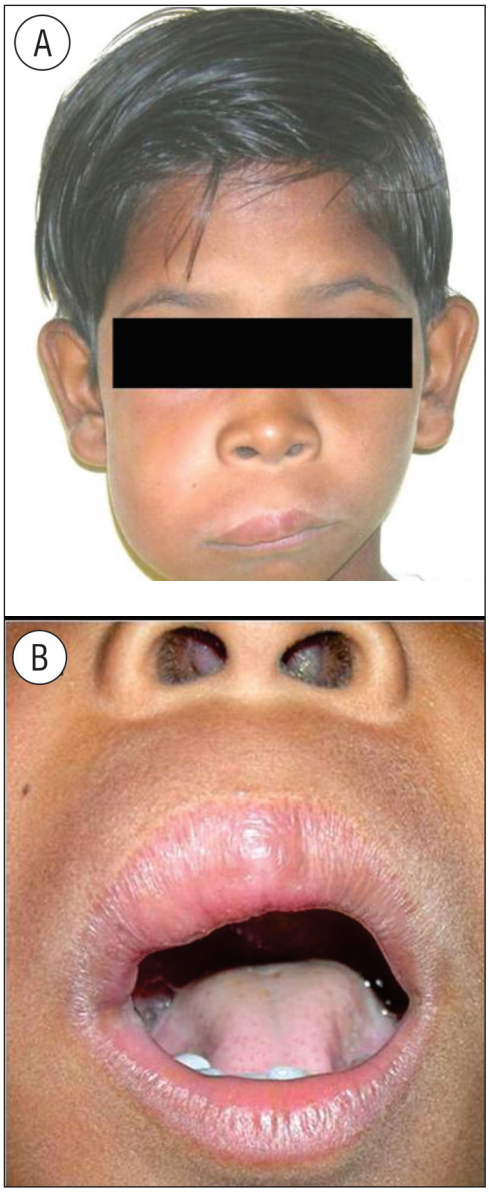

Figure 1 - (A) Marked asymmetry due to swollen right lower face in patient; (B) Swelling extended to the right side of upper lip

Discussion

The pathogenesis of idiopathic angioedema is not well understood today; also the clinicians have low awareness of this disease, thus leading to

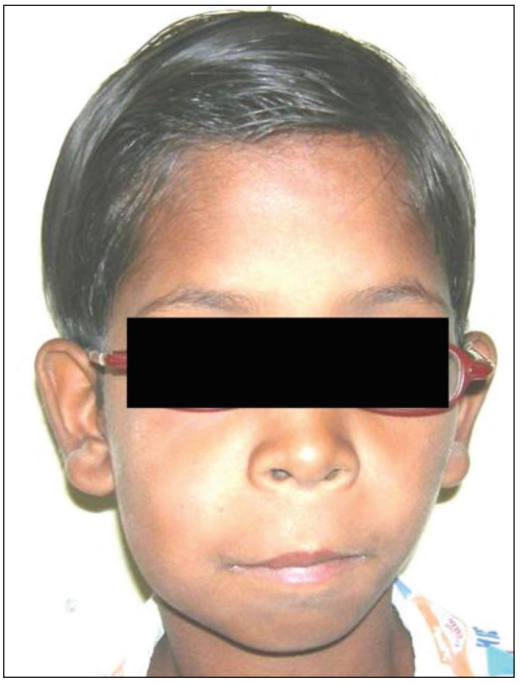

Figure 2 - Marked reduction in swelling at follow up visit (2 days later). Swelling over the upper lip had completely resolved

incorrect diagnosis. This lag in diagnosis and hence treatment certainly stems from the rarity and complexity of the presentation which can be easily mistaken for allergic and nonallergic reactions alike (2).

Most of the reported cases on angioedema were from Western countries. There were some reports of immunogenetic differences between Oriental and Caucasian populations, resulting in differences in the clinical presentation and frequency of the cases. Moreover, different dietary habits between Asian and Western countries as well as the socioeconomic status may cause different allergen sensitization (3).

Angioedema is the rapid swelling of the skin, mucosa and submucosal tissues; a potentially life threatening condition if it involves pharynx and larynx leading to respiratory embarrassment (1). Angioedema may be associated with headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, and arthralgias. In their most severe forms, they may be associated with anaphylaxis. Symptoms last for one or two days (6). The common form is mediated by allergy, which could be due to different substances like food, animal dander, extremes of temperature, emotional stress and local trauma. The well defined inherited form known as hereditary angioedema is due to deficiency and abnormal function of C1 esterase inhibitor (1).

Confirmation of clinical features and time-course are essential to the correct diagnosis, and therefore the importance of a careful history cannot be overemphasized. Some important history and clinical features in evaluation of angioedema are: speed of onset, association with urticaria/without urticaria, site of angioedema; facial/peripheral/abdominal pain, precipitating factors, natural history of attack, age of first onset, response to treatment (antihistamines/steroids/epinephrine), drug history; ACE inhibitors (AR2 antagonists/Salicylates & NSAIDs), family history, associated features suggesting rare angioedemas; connective tissue disease or lymphoproliferative disease symptoms (4). Age of onset in this case, pointed towards a possibility of hereditary angioedema but there were no gastrointestinal or urinary symptoms and abdominal colic was typically absent.

Angioedema is a common reason for attendance at the accident and emergency department. Causative factors should always be sought, but a large proportion of patients have the idiopathic form of the disease (4). It is important to correctly diagnose the condition as the treatment pathways for its management varies. A comprehensive history and close monitoring to treatment response are the key to diagnosis. Due to its non specific presentation, other cutaneous reactions can mimic angioedema, especially when symptoms are atypical. Most of these are rare, but can occasionally be confused with angioedema. They are – facial cellulitis, superior vena cava syndrome, blepharochalasis, systemic amyloidosis, dependent oedema, hypoproteinemia-related edema, Crohn's disease, burns, infections (viral, parasitic) (4, 7)

Allergic angioedema is the most common type, which may be precipitated following ingestion of common food products like seafood or chocolates. Among drugs, angiotensin converting enzyme inhibitor (ACE I) and non steroidal anti inflammatory drugs (NSAIDs) are common culprits. Increasing use of ACE I to treat hypertension in this era has led to a higher occurrence of angioedema, which has been reported in 0.1 – 6% of patients taking these drugs. This form of angioedema usually affects lips, face and tongue, for which the patients may report to the dentist (4). Thus, a carefully recorded medical history is of utmost importance. Although the risk of angioedema is higher in the first month, most cases occur after several months up to ten years of initiation of therapy. Because symptoms are not associated temporally with initiation of treatment or medication time, it often becomes difficult to consider this diagnosis (4). Second most common cause of drug induced angioedema are NSAIDs. Even the most commonly used drugs like aspirin or ibuprofen may lead to angioedema in susceptible patients (3).

The identification and elimination of the cause of angioedema represent the best therapy for a patient. However, when the underlying cause of angioedema remains unknown, the treatment must be based on symptoms. As during any treatment program, the physician should provide support and reassurance to the patient. Antihistamines are the mainstay for controlling the symptoms of the diseases; however, if any specific antihistamine is not effective, an agent from a different pharmacologic class should be used. Antihistamines are classified as H1 receptor blockers and H2 receptor blockers. H1 receptor blockers are the most commonly used drugs for the treatment of acute and chronic angioedema. These include terfenadine, astemizole, loratadine, cetrizine, fexofenadine and desloratadine (6). If antihistamines

are ineffective, antifibrinolytics often provide relief. For acute attacks, antihistamines, corticosteroids and sometimes epinephrine are usually used (4). For chronic form of the disease multidrug approach has been tried, however antihistamines play the most important role (8). However, glucocorticoids and antihistamines are most probably ineffective in nonallergic angioedema forms (9). Dapsone may be an alternative drug in extreme cases of idiopathic angioedema in patients with poor response to conventional therapy (10).Other drugs which have been tried include H2 blocker and proton pump inhibitor (3). In most patients, antihistamines are able to control symptoms but do not constitute a cure of the disease. Moreover, symptoms may recur following a variable period of time after discontinuation of drug therapy. The antihistaminic agent should initially be administered at a low dose; subsequently, the dose should be increased to a tolerable level. The drug should be taken on a regular basis and not as needed. Antihistamines cross the placenta and have a pregnancy category B classification. Thus, it is best for patients to avoid them during pregnancy, particularly during the first trimester. Also, it may be useful for some patients with angioedema to avoid aspirin, other nonsteroidal anti-inflammatory drugs, and angiotensin converting enzyme inhibitors (6).

Conclusion

From a general dentist's point of view it is important to diagnose correctly or atleast suspect the condition, and make the required referral to the specialist. It should also be borne in mind that the characteristics of these conditions are not always as evident as those described here. Depending on the severity, the appearance of these may be similar to those of other conditions and this makes the differential diagnosis difficult. We hope the present report will serve to remind us that this rare pathology should not be forgotten.

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