PROMINENT FEATURES OF ALLERGIC ANGIOEDEMA ON ORAL MUCOSA

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SUMMARY – Angioedema indicates acute subcutaneous edema that characterizes improperly restricted cutaneous or mucous membrane swelling, which can occur only once or be relapsing. Edema usually occurs in the periorbital area, lips, tongue, extremities and intestinal wall. It has turned out that angioedema is usually caused by the use of angiotensin-converting enzyme inhibitors (ACE) or allergies to certain allergens (allergic or IgE-mediated angioedema), followed by C1 inhibitor deficiency (hereditary and acquired angioedema), or the cause is unknown (idiopathic angioedema). It has been shown that patients with angioedema often have urticaria, which is noted in approximately 50% of cases. Usually there is a type I allergic reaction to some food allergens or drugs or insect stings. The most common causes of allergic angioedema are bee and wasp stings, reactions to medications or injections for sensitivity testing, and certain foods (especially eggs, shellfish and nuts). In diagnostic terms, it is important to determine the potential allergen, which is commonly performed with cutaneous tests, such as prick test, etc. The main risk of angioedema is swelling of the tongue, larynx and trachea, which can lead to airway obstruction and death, therefore tracheotomy is indicated in such cases. The initial treatment of patients with most forms of angioedema included administration of antihistamines and glucocorticoids, while epinephrine is given if there is fear from laryngeal edema.

Key words: Allergy and immunology; Angioedema; Mouth; Allergens

Introduction

Angioedema is a term describing acute edema of the skin or mucosa, characterized by an irregularly shaped swelling, which usually manifests itself episodically. It affects approximately 15% of the general population and is more common in women than men. There are several different angioedema syndromes, but they all have in common a characteristic edema caused by the release of vasoactive mediators and transient permeability of subcutaneous and submucous postcapillary venules. In patients who have angioedema the observed edema is usually asymmetric and can cause discomfort as the patient’s subjective symptom. As noticed, patients who have angioedema frequently also have urticaria (about 50% of patients). Common sites of the edema are the periorbital region, lips (Fig. 1), tongue, extremities, upper respiratory

Fig. 1. Angioedema of the upper lip.

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pathways and intestinal wall. Angioedema of the intestinal wall may also occur without changes of the skin and may cause abdominal pain, nausea and less often obstruction of bowel lumina. Angioedema may also be accompanied by laryngeal edema, with a mortality rate of 25%-40%\(^4\). Episodes of swelling usually last for two to three days and are either isolated or recurrent\(^1\).

The Etiology of Angioedema

Angioedema is usually classified as type I allergic reaction (allergic or IgE mediated angioedema). In this group of angioedema, a certain allergen is triggering the hypersensitivity reaction by binding to IgE, which in turn is causing the release of histamine and other vasoactive substances in mast cells\(^5\). Symptoms usually start to develop in a minute to an hour after exposure to the allergen. Most cases of allergic angioedema are due to bee and wasp stings, drugs, food, especially eggs, mussel and nuts, injections used for allergic hypersensitivity testing, etc.

Otherwise, for hereditary and acquired angioedema, as well as for the one associated with medications, the key pathogenetic factor is an elevated level of plasma bradykinin. Nevertheless, in angioedema as well as in urticaria, the cause often remains unknown\(^6\). In case of solitary angioedema (without urticaria), the patient should be evaluated for drug intake and family medical history to identify angioedema associated with angiotensin-converting enzyme (ACE) inhibitors or hereditary angioedema\(^7\). Among medications, nonsteroidal anti-inflammatory drugs (NSAID), antibiotics and antiepileptics most frequently induce angioedema\(^8,9\).

Moreover, acquired forms of angioedema with C1 inhibitor (C1 INH) deficiency may originate as a result of autoantibodies binding to it or because of their wasting due to activation by paraproteins\(^10\). The usual findings are decreased levels of complement component C4, sometimes also decreased levels of C1 INH, as well as the presence of paraproteins\(^7\).

Angioedema Due to Angiotensin-Converting Enzyme Inhibitors

Angioedema occurs in 0.1%-2.2% of patients taking ACE inhibitors and probably develops because of elevated levels of bradykinin\(^1,11\). Manifestation is highest during the first month of drug intake (25%), although it can manifest itself even after a few years of drug usage\(^11\). Commonly, it affects the tongue, lips and face as edema, also affected may be the pharynx, larynx and internal organs. Fatal outcomes have also been recorded, therefore it is obligatory for these patients to advise them withdrawal of ACE inhibitors and administration of alternative antihypertensives\(^12-16\). Administering C1 inhibitors to such patients is of no value. Fresh plasma, however, is useful at times\(^7,17,18\). Antihistamines, corticosteroids and adrenaline are often used for therapeutic purpose in such individuals, despite their unclear effectiveness. Studies have shown an 85% reduction or complete remission rate of ACE inhibitor induced angioedema after discontinuation of medication\(^7\). The individuals whose condition is not improving even months after stopping their medication, most probably suffer from idiopathic angioedema, or they may, nonetheless, have occasionally taken an ACE inhibitor.

Angioedema due to C1 Inhibitor Deficiency

Hereditary angioedema or hereditary angioneural angioedema is a familial variant of angioedema with a C1 INH defect that often involves the intestines\(^6,8\). C1 INH is an alpha-globulin that controls the complement cascade and its deficiency leads to uncontrolled activity of the vasoactive mediators bradykinin, kallikrein and plasmin.

This is a rare disorder accounting for approximately 1% of all angioedema cases. Symptoms usually develop in childhood and adolescence. Women become ill more often than men\(^8\).

The main disorder in hereditary angioedema is a defect in C1 INH, which is inherited as an autosomal-dominant trait, with clinical disorders arising when the levels of C1 INH drop below 50%. The majority of these patients have decreased enzyme levels. The swelling usually lasts for 1-2 hours, resolving spontaneously afterwards. They are mostly recurrent\(^6,19\).

Also possible is an acquired angioedema with decreased levels of C1 INH. This occurs in adulthood and has no positive family history. Another possibility is Caldwell syndrome and the primarily acquired angioedema\(^6,20\). Caldwell syndrome is an acquired angioedema combined with hematologic disorders. This is most likely a monoclonal proliferation of B
lymphocytes, as in B-lymphocyte lymphoma, chronic lymphocytic leukemia or multiple myeloma. In the primarily acquired angioedema (acquired angioedema type 2), the patient produces IgG and IgM antibodies against C1 INH. They block the C1 to C1 INH binding, which in turn leads to elevated levels of C1, causing further a vicious cycle by inactivating the enzyme. It occurs most often after the fourth decade of life.\textsuperscript{1}

**Other Forms of Angioedema**

Sometimes the etiological factor in angioedema patients cannot be determined, which points to idiopathic angioedema. According to some studies, this type of angioedema occurs most frequently in the group of angioedemas (Table 1, Fig. 2), comprising around 38\% of cases.\textsuperscript{1,21}

Angioedema also arises from physical stimulation such as cold, heat, vibration, trauma, emotional stress and ultraviolet radiation.\textsuperscript{6,1} There is also a cytokine-associated angioedema, known as episodic angioedema with eosinophilia (Gleich syndrome), which is characterized by fever, elevated blood levels of eosinophils and IgM. Its true cause is unknown. Elevated levels of cytokines, granulocytes, macrophages, interleukins (IL-3, IL-5 and IL-6) as well as CD4+ lymphocytes are verified, which engage in the pathogenesis of the whole process.\textsuperscript{1}

**The Pathogenesis of Allergic Reactions in Angioedema**

Hypersensitivity reactions can be mediated through antibodies (reactions of immediate hypersensitivity, type I-III) or through cells (delayed hypersensitivity, type IV). Allergic angioedema is proceeded through type I hypersensitivity reaction. Such an allergic reaction is induced by the allergen binding to IgE, which is bound to the receptor, creating a signal for an intercellular cascade, which in turn results in the activation and release of mediators of inflammation. Significantly, IgE has a unique structure of its Fc fragment through which it binds itself to the mast cell and basophil receptor (FcεRI). Following this binding, the release of histamine, leukotrienes, chemotactic substances, platelet activating factors, proteases occurs, during which process degranulation of mast cells takes place.

The creation of cytotropic IgE antibodies and their binding to target cells takes about 14 days, while the repeated intake of allergen into the body results in reaction of the allergen to the antibodies bound to target cells, which in turn results in degranulation and the release of various mediators with a more or less apparent allergy reaction.\textsuperscript{22} Some individuals are genetically prone to local allergy reactions (atopy) accompanied by large amounts of IgE.

<table>
<thead>
<tr>
<th>Type of angioedema and its relative proportion in the group of angioedema</th>
<th>Characteristics</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary angioedema (1%-2%)</td>
<td>Autosomally dominant inherited genetic mutation affecting C1 INH protein or coagulation factor XII</td>
<td>Rare</td>
</tr>
<tr>
<td>ACE inhibitor induced angioedema (30%)</td>
<td>Delayed onset (days to months after the first use of ACE inhibitor)</td>
<td>Common</td>
</tr>
<tr>
<td>Idiopathic angioedema (38%)</td>
<td>Cause of angioedema is unknown; usually relapsing and occurring with urticaria</td>
<td>Common</td>
</tr>
<tr>
<td>Acute allergic angioedema (30%)</td>
<td>Allergen induced (e.g., food, drugs, radiologic contrast media, latex gloves)</td>
<td>Common</td>
</tr>
</tbody>
</table>
Different allergens have been defined as the cause of atopic reactions (flower pollen, house dust, animal fur and feather, sometimes milk and eggs, etc.)\textsuperscript{22-25}. If allergens become absorbed and arrive \textit{via} blood into the skin, they can induce localized erythema, swelling and pruritus (urticaria and angioedema). Reaction between allergen and IgE results in aggregation of receptors and activation of protein-tyrosine-kinase sites on their inner cellular part. Thereby, a sequence of complex processes starts, which finally leads to degranulation of target cells and the release of mediators\textsuperscript{22-25}. After IgE bridging, adenyl-cyclase is activated within the membrane, subsequently creating cAMP that engages in reactions of moving granules towards the cell membrane. A few minutes after its rise, the concentration of cAMP in cells is lowered to its initial level\textsuperscript{22}.

Mediators which are produced and stored in granules are thence released by the process of degranulation (primary mediators), as secondary mediators are being produced after the bridging of IgE. Their synthesis is carried out by calcium ions, which activate phospholipase A\textsubscript{2}, an enzyme that releases arachidonic acid from membrane phospholipids. Metabolites of arachidonic acid are chemical compounds that act as secondary mediators: lipoxygenase activity produces leukotrienes, while cyclooxygenase activity produces prostaglandins\textsuperscript{22}.

The released mediators are primarily locally effective, causing increased permeability of blood capillaries, vasodilatation, smooth muscle contraction, and secretion of mucous glands. This first, acute phase takes place within the first 15-30 minutes following allergen exposure. Tissue infiltration with inflammatory cells increases within the next 6-12 hours (eosinophils $\rightarrow$ neutrophils $\rightarrow$ mononuclears), leading to the late phase of reaction with clinical symptoms of inflammation (symptoms of rhinitis, asthma or angioedema)\textsuperscript{23}.

Secondary mediators include leukotrienes (also called slow reading substance of anaphylaxis, SRS-A)\textsuperscript{22}. The ability of attracting eosinophils is shown by histamine and a few chemotactic factors, for example eosinophil chemotactic factor of anaphylaxis (ECF-A), which is released from mast cells and basophilic leukocytes at the site of allergy reaction\textsuperscript{22}. A few hours after the onset of reaction, the late phase of reaction often occurs, its most important features being marked infiltration by eosinophils, neutrophils, basophils, macrophages and lymphocytes. The major treatment options for such reactions are antihistamines, which prevent most but not all allergy hypersensitivity reactions, considering the role of other mediators active in these events.

Clinical Findings in Angioedema

Angioedema affects more often women than men. Considering age, it is most common in young adults. Sometimes there is a short prodromal period, still the patient usually experiences sudden swelling of the skin and mucosa, accompanied by little or no itch\textsuperscript{6}. Typical sites of edema are eyelids, lips, genitals and distal parts of extremities. The affected skin is usually pale, sometimes slightly red. Normally, there is one or only a few lesions. The swelling reaches its maximum in several hours and starts to dwindle afterwards. The whole process typically lasts between 8 and 72 hours\textsuperscript{6}. Angioedema is often associated with urticaria\textsuperscript{26}.

In angioedema, there is a risk of edema of the tongue, the larynx and the trachea, which can lead to airway obstruction and death, therefore tracheotomy is indicated. In frequent recurrences, the same site is usually affected as in previous cases.

Diagnosis of Angioedema

Diagnostic criteria in angioedema are similar to those in urticaria\textsuperscript{6,27}. For determining allergy as the etiology of angioedema, taking patient medical history is important to define the potential triggering factors. Family history has to be taken in order to exclude any hereditary components\textsuperscript{1}. Medical history is the key factor to diagnosis. Skin testing is most important (primarily prick test), and if it is not available, then \textit{in vitro} tests can be performed, for example the radioalergosorbent test (RAST). In that case, by determining the IgE specific for certain allergens, an allergy to potential allergens can be demonstrated \textit{via} blood. In patients with positive family history of hereditary angioedema or with an assumption for decreased levels of C1 INH, serum markers for complement activity are evaluated\textsuperscript{1}.

In allergy disease diagnostics, it is important to examine family records of allergy diseases, as well as the patient medical history from his/her youngest age on.
The allergy basis for disease is often verified through evaluation of total IgE and the result of skin testing is complemented by findings of IgE specific to a certain allergen. The sort of testing essential to perform is determined by a detailed medical history and clinical examination of the patient. Allergy testing is mostly performed on the skin, whereby very small amounts of a standardized solution of purified allergens are applied either into the skin or on its surface, observing and measuring any local allergy reaction of the skin.

Skin testing for verification of type I reaction may be performed by various methods, e.g., by puncture (prick test), application of allergen by scratching the skin (scratch test) and rarely by an intradermal test, i.e. applying the allergen into the skin using a needle. Prick testing is the commonest method used to identify hypersensitivity to inhalation and nutritive allergens. This test is performed on the skin of the forearm by placing a small amount of potential allergen extract, which is then pierced by a lancet. Within 20-30 minutes, a positive outcome will exhibit a wheal or swelling at the site of piercing. The size of the wheal may correlate with the intensity of allergic reaction. The test is performed for exhibiting early allergic reactions, such as urticaria and angioedema, drug allergies, allergic rhinitis and conjunctivitis, prurigo, strophulus infantum, atopic dermatitis and allergic vasculitis.

Prick test is the most often performed testing because of its simplicity, safety and fewer false-positive results. Prick testing is considered to be a simple and harmless method. Severe reactions in prick testing are extremely rare. Still, on very rare occasions systemic anaphylactic reaction and a life threatening condition may occur during the testing, therefore a physician with a ready to use anti-shock equipment should be present at the testing. A disadvantage of prick testing is lower sensitivity as compared with other allergy tests, therefore more sensitive tests may be needed after a negative prick test, if an assumption of allergy is made by the physician.

Scarification test (test by scratching) is performed on the volar side of the forearm previously cleansed with alcohol or petrol. A lancet is used to scratch a linear furrow on the surface of the skin (must not bleed), at a length of about 3 cm, onto which a buffer solution (negative control) and later on allergens, separately in test concentrations, are applied. The test is used to demonstrate hypersensitivity to preservatives, additives, drugs and fresh nutritive allergens. Reaction is observed 20 minutes afterwards. A wheal with a transverse diameter greater than 3 mm (+) is considered as a positive reaction.

### Differential Diagnosis in Angioedema

In angioedema there are, unlike urticaria, many potential diagnoses that are significant for differential diagnosis. Firstly, assessment of hereditary angioedema and cognate acquired C1 INH deficiency should be made. Hereditary angioedema is almost never accompanied by urticaria which, on the contrary, may be present besides the acquired form of angioedema. The hereditary variant has also more often intestinal symptoms. In all cases, the level of C1 INH should be measured. Episodic angioedema with urticaria and eosinophilia is very rare. Having been considered part of the hypereosinophilic syndrome, it is nevertheless most likely a separate, benign disorder. Thereby, urticaria and swelling frequently affect the head, the neck and the upper part of the torso, with a relatively durable angioedema, persisting even for a few days. Such an edema is caused by degranulation of eosinophils and the release of a main protein, which then causes degranulation of mast cells.

Acute allergic dermatitis, which can exhibit localized edema, should also be considered on differential diagnosis, supposing a visible erythema, pruritus and often vesicles. Early manifestations of herpes zoster, especially on the face, can sometimes be accompanied by a more intensive swelling, although there is a characteristic one-sided erythema, therefore making it possible to distinguish from angioedema. The beginning of erysipelas is also marked by swelling, often around the lips, however, the skin is erythematous, the lesions are gradually progressing peripherally and the patient has fever with leukocytosis.

With the lips being affected, it could be a case of Melkerson-Rosenthal syndrome, yet the swelling is much more massive. Oral allergy syndrome is also possible as the most common manifestation of allergy to food, significantly more common in individuals who are also allergic to pollen. In this phenomenon, proteins similar to those in pollen are found in apple, pear, peach, nectarine, carrot, celery, sour cherry, ki-
wifruit, tomato, banana and melon, so that, whilst consuming these viands, the oral cavity and the perioral region react with swelling, erythema and pruritus.

**Treatment for Angioedema**

The crucial factor for successful treatment is detection and avoidance of triggers, early recognition of an attack and prompt aid offering when airways are affected\(^1\). Certainly, the list of medications that the patient is taking should be investigated, which may point to the usage of ACE inhibitors or angiotensin receptor blockers. The initial treatment for the patient in the majority of forms of angioedema is taking antihistamines which, by blocking histamine cell receptors, are disabling the activity of histamine and glucocorticoids, while epinephrine is given if there is fear from laryngeal edema.

There are multiple treatment principles for allergic angioedema. Firstly, it is essential to identify the allergen and to try to avoid it. If this is not possible, desensitization therapy could be carried out. Corticosteroids are also useful to stabilize the lysosomal membrane hence complicating degranulation as well as agents that hinder the conversion of histidine into histamine by inhibition of histidine decarboxylase enzyme\(^2\). The amount of mediators released from target cells can also be decreased using substances that hinder the entering of calcium ions into cells (cromolyn sodium), beta-receptor stimulants that increase the cell concentration of cAMP (adrenaline, isoproterenol) or by giving teofilin that hinders the inactivation of cAMP by inhibiting phosphodiesterase\(^2\).

**Angioedema in Clinical Practice**

Angioedema as sudden swelling of the skin, the mucosa or both, including digestive tract, is sometimes causing practical problems in determining its etiology\(^2\). Allergic angioedema (caused by IgE mediated reaction) most often appears as a hypersensitivity reaction to various causative agents such as drugs, food, insect poison, and others\(^2\).\(^3\)\(^9\).

Research has been done stating immunogenetic differences between Caucasians and people of Asian origin, manifesting in clinical presentation of allergic diseases\(^1\)\(^-\)\(^3\). Furthermore, differences in dietary habits and socioeconomic status between the Western and Asian countries may create differences in allergen hypersensitivity\(^10\).

Kulthanan *et al.* conducted a study that included 100 angioedema patients\(^9\). Results showed the angioedema to manifest mostly on the periorbital skin and the lips, with 49% of patients having general symptoms. The most common cause of angioedema was allergic reaction to various substances. As it is affirmed, around half of these patients had urticaria at the same time. Allergic angioedema was mostly food induced (41.7 %), especially by seafood, followed by medication (39.6%). Among foods, angioedema was mostly caused by seafood (70%). Out of medications, angioedema was mostly caused by antibiotics (63.2%), especially amoxicillin (25%). Recurrences of angioedema were frequently observed (in 39% of cases)\(^10\).

Idiopathic recurrent angioedema is characterized by 3 or more episodes of angioedema occurring with no identifiable cause within 6 to 12 months. Patients with severe or recurrent episodes of angioedema as well as patients with C1 INH deficiency should be referred to a specialist in allergy-immunology\(^1\).

Acute allergic angioedema is often accompanied by urticaria, which has the same etiopathogenesis\(^2\)\(^9\)\(^3\). Allergy reactions to food, drugs, environmental contacts, insect stings and other substances may cause instantaneous IgE-mediated hypersensitivity reaction. Systemic release of histamine and other mediators from mast cells can cause angioedema, or even a more comprehensive alteration, all the way to a systemic anaphylactic reaction. Allergic angioedema occurs more frequently in patients who also have allergic rhinitis, asthma and atopic dermatitis\(^10\).

Common triggers in mast cell-mediated angioedema are medications (aspirin, NSAIDs, antihypertensives, narcotics and oral contraceptives), food (nuts, eggs, shellfish, soy, wheat, milk) and other substances (venom, latex)\(^1\).

Reactions to food and drugs, however, may emerge even without correlation to allergy. In this way, some medications like radiocontrast media and opiates can cause a non-immune degranulation of mast cells (pseudoallergic reactions), which do not include an immune mechanism.

As in acute urticaria, medical history is crucial to identify the cause of angioedema. Most patients are
generally aware of the relation of allergens and drugs with the development of acute angioedema. It is most important to perform skin tests with occasional conduction of RAST of single allergens, especially in case of dermographism, extended skin changes, very young children, persisting skin changes, etc. Evidence for specific hypersensitivity to allergens is crucial for future treatment\(^{29,30}\). Detection of the responsible allergen indicates avoidance of the allergen as to evade the occurrence of future allergic reactions.

References

Sažetak

IZRAŽENA OBILJEŽJA ALERGIJSKOG ANGIOEDEMA NA SLUZNICI USNE ŠUPLJINE

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Angioedem označava akutni potkožni edem koji obilježava nepravilno ograničeno oticanje kože ili sluznice koje se javlja jednokratno ili opetovano. Edem se obično javlja u predjelu periorbite, usnica, jezika, udova i crijevne stijenke. Pokazalo se da je angioedem često izazvan uzimanjem inhibitora angiotenzin-konvertirajućeg enzima (ACE) ili alergijom na neke alergene (alergijski ili angioedem posredovan IgE-om), zatim deficijencijom C1 inhibitora (nasljedni i stečeni angioedem) ili je uzrok nepoznat (idiopatski angioedem). Pokazalo se da bolesnici s angioedemom često imaju i urtikariju, što se zapaža u oko 50% slučajeva. Najčešće se radi o alergijskoj reakciji tipa I. na neke alergene hrane ili lijekova ili na ubod insekata. Utvrđeno je da su najčešći uzroci alergijskog angioedema ubod pčela i osa, reakcije na lijekove ili injekcije za testiranje preosjetljivosti te određena hrana (osobito jaja, školjke i orašasti plodovi). U dijagnostičkom pogledu važno je utvrditi potencijalni alergen, što se najčešće izvodi kožnim testovima, kao što je ubodni test i dr. Rizično kod angioedema je oticanje jezika, grkljana i dušnika, što može dovesti do začepljenja dišnih putova i smrti, pa je tada indicirana i traheotomija. Početno liječenje bolesnika u većini oblika alergijskog angioedema je uzimanje antihistaminika i glukokortikoida, dok se epinefrin daje ako postoji bojazan od edema grkljana.

Ključne riječi: Alergija i imunologija; Angioedem; Usta; Alergeni