

## LITERATURE REVIEW

# Angioedema, a life-threatening adverse reaction to ACE-inhibitors

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## ABSTRACT

Angioedema with life-threatening site is one of the most impressive and serious reasons for presenting to the ENT doctor. Among different causes (tumors, local infections, allergy reactions), an important cause is the side-effect of the angiotensin converting enzyme (ACE) inhibitors drugs. ACE-inhibitors-induced angioedema is described to be the most frequent form of bradykinin-mediated angioedema presented in emergency and also one of the most encountered drug-induced angioedema. The edema can involve one or more areas of the head and neck region, the most affected being the face, the lips, the tongue, followed by the larynx, when it may determine respiratory distress and even death.

There are no specific diagnosis tests available and the positive diagnosis of ACE-inhibitors-induced angioedema is an exclusion diagnosis. The authors performed a review of the most important characteristics of the angioedema caused by ACE-inhibitors and present their experience emphasizing the diagnostic algorithm.

**KEYWORDS:** angioedema, ACE-inhibitors, hereditary angioedema, bradykinin, histamine.

## INTRODUCTION

Angioedema (AE) is a life-threatening condition presented as an asymmetric, localised, well-demarcated swelling<sup>1</sup>, located in the mucosal and submucosal layers of the upper respiratory airways. The edema can involve one or more areas of the head and neck region, the most affected being the face, the lips, the tongue, followed by the larynx, when it may cause respiratory distress and even death<sup>2</sup>. Less frequently, it can be located in the hands, feet or abdominal viscera.

In the literature, the first case of angioedema was presented by Milton in 1876<sup>3</sup>. Six years later, in 1882, it was described by Quincke<sup>4</sup> as angioneurotic edema.

The physiopathological mechanism of angioedema is explained by a systemic or local release of reactive mediators, such as bradykinin, histamine and other mast cell mediators, which determine an increased permeability of the vessels' walls

with secondary local extravasation of plasma and tissue swelling<sup>5,6</sup>.

Based on this pathomechanism, the classification of angioedema comprises three major types: 1). bradykinin-mediated – with either complement C1 esterase inhibitor (C1INH) deficiency or normal (or near-normal) antigenic and functional levels, 2). mast cell-mediated - with normal C1INH divided into IgE-mediated (the determinant factor being a previous sensitisation to an allergen) and non-IgE-mediated and 3). idiopathic with normal C1INH<sup>7</sup>.

The bradykinin-mediated AE can be either a hereditary (HAE) autosomal dominant disorder – a rare presentation in the emergency unit, due to a mutation in the gene encoding C1 esterase inhibitor (C1-INH) that affects between 1:10,000 and 1:150,000 people in the general population or acquired (AAE)<sup>7,8</sup>. The latest, AAE, is presented with C1INH deficiency frequently associated with lymphoproliferative diseases and/or autoantibodies against C1INH that may be responsible for C1INH

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consumption. Another form of AAE associated with normal C1INH – drug-induced AE<sup>7,9</sup> is the most frequent form of bradykinin-mediated angioedema presented in emergency, the angiotensin-converting enzyme inhibitor-induced angioedema (ACEI-AE) being the leader in this category<sup>7,10,11</sup>.

### ACE-INHIBITORS-INDUCED ANGIOEDEMA (ACEI-AE)

Angiotensin-converting enzyme inhibitors represent an important cause of drug-induced angioedema due to their very frequent use in the arterial hypertension treatment. The prevalence of ACE-inhibitors-induced angioedema in these patients was reported to be between 0.1% up to 2.5%<sup>10</sup>, and it is up to five times greater in people of African descent<sup>12,13</sup>, with higher risk in smokers and women; diabetes has been associated with lower risk<sup>7</sup>. The involvement of ACE inhibitors represents 20 – 40% of the angioedema cases presented in the emergency unit<sup>5,10,14</sup>.

The first case of ACEI-AE was described in 1980 and it was due to captopril<sup>15</sup>. Even if at the beginning it was considered a rare adverse reaction, later on, its incidence increased due to the large prescription of this antihypertensive drug class and due to the rise of life expectancy. It is not an allergic

reaction, and preformed IgE has not been observed.

The physiopathological mechanism of ACEI-AE includes the reduction of the bradykinin metabolism by preventing the conversion of angiotensin I in angiotensin II, in this way increasing the risk of angioedema. Angiotensin I, produced in the kidney by angiotensinogen conversion, is metabolised into angiotensin II in the lungs by the enzyme ACE. Angiotensin II acts as a vasoconstrictor mediator by activating angiotensin I and angiotensin II receptors and bradykinin inactivation. The ACE is involved in the degradation mechanism of bradykinin<sup>16,17</sup>. Bradykinin acts as a vasodilator.

ACE inhibitors are responsible for the decrease of angiotensin II levels and the increase of bradykinin concentration. This results in high levels of bradykinin with important vasodilation and increased vascular permeability with secondary fluid extravasation into the subcutaneous tissue and angioedema<sup>16-19</sup>. But, the exclusive role of bradykinin in producing angioedema is less likely, other possible mechanisms being an alteration of the immune responses, enhancement of substance P formation (a vasoactive peptide that increases vascular permeability by its action on neurokinin receptor 1) and bradykinin-induced histamine release<sup>20</sup>.

Angiotensin-converting enzyme inhibitors-associated angioedema is located frequently in the head and neck area, involving mostly the face, the



**Figure 1.** Angioedema associated with ACE-inhibitors involving the lips and the left side of the face.

lips, the tongue and the upper aerodigestive tract<sup>21</sup> (Figure 1). In specific cases visceral angioedema can also be present<sup>22,23</sup>.

This type of angioedema is characterised by asymmetric, non-pruritic, erythematous swelling with an insidious onset, lasting up to 24 – 72 hours and sometimes it may present spontaneous remission<sup>24</sup>. It is usually diagnosed in patients over 40 years of age due to the increased prevalence of cardiovascular pathology in this age decade<sup>25</sup>. Most reactions appear in the first week or month of initial therapy and no correlation with a specific ACE-inhibitor or dose was found. Lately, the studies revealed a higher frequency of ACEI-AE developed after multiple years of treatment<sup>5,26</sup> rather than at the initiation of the treatment.

## DIAGNOSIS OF ACEI-INDUCED ANGIOEDEMA

Considering that it is a potential life-threatening condition, it is essential to identify the causes of the angioedema. Unfortunately, there are no specific diagnosis tests available and the positive diagnosis of ACEI-AE is an exclusion diagnosis.

A detailed and carefully guided history of the patient is mandatory in order to establish the potential allergic or non-allergic type of angioedema, considering the fact that there are patients who, at the initial evaluation, only present the history of angioedema and have no signs or symptoms.

Laboratory testing can give important information about the cause in a patient presented only with a history of angioedema. Deficiency in C4 and C1 esterase inhibitor are known to relate to HAE especially in patients with family background, and with AAE in lymphoproliferative disorders or malignant tumors<sup>27,28</sup>. A low C4 should prompt a more complete laboratory evaluation, including C1 inhibitor function and protein levels and C1q levels<sup>7</sup>.

An allergological evaluation with skin prick tests performed for aeroallergen and trophallergen sensitisation is also indicated in order to identify a potential IgE-mediated reaction.

A fiberoptic evaluation of the upper respiratory tract is recommended if a laryngeal involvement is suspected. For the angioedema involving the face or the upper airways, imaging techniques are able to exclude infections, tumoral or other inflammatory swellings.

Having no specific evaluation tool, the key point in the diagnosis of an ACE-inhibitor-induced angioedema is represented mainly by the identification of this antihypertensive drug in the therapeutic background of the patient.

## TREATMENT OF ACEI-AE

The first step in the management of an angioedema is to secure the patency of the upper respiratory tract and to establish medication depending on the severity of the signs and symptoms.

In case of the angioedema caused by ACE inhibitors, as in any other drug-induced angioedema, the immediate discontinuation of the drugs is mandatory.

It is important to keep in mind that in this type of angioedema the standard treatment for allergic reactions (e.g. antihistamines, corticosteroids, epinephrine) may not have the expected effects<sup>7,29</sup> and there can be recurrent episodes of angioedema in the first few months after treatment cessation. Giving the multiple faces of the pathomechanism, other therapies were experienced, but without any proven efficacy, including: tranexamic acid, ecalantide (recombinant protein inhibits the conversion of high-molecular-weight kininogen to bradykinin by inhibiting plasma kallikrein), purified C1 inhibitor concentrate, fresh frozen plasma and Icatibant (a synthetic bradykinin B<sub>2</sub>-receptor antagonist that is approved for the acute treatment of HAE attacks)<sup>7</sup>.

## OUR EXPERIENCE

From January 2017 to October 2018, four patients (two males and two females), over the age of 50, who experienced multiple episodes of facial, pharyngeal, laryngeal or tongue edema presented to our clinic. All 4 patients were undergoing ACEI drugs treatment for arterial hypertension or other cardiac disorders for a few years. The clinical and paraclinical evaluations (nasolaryngeal fiberoptic evaluation, CT scan, chest x-Ray, allergy tests, pulmonary tests, blood tests) confirmed the ACEI-AE.

We present one of the four cases, emphasizing the diagnostic algorithm.

A 79-year-old male presented to our ENT Department with a history of five episodes of cervicofacial angioedema without hives, all episodes being manifested in the previous 4 months. Three episodes, one involving the tongue, needed adrenaline, systemic corticotherapy and antihistamine administration in the Emergency Care Unit. In the case of 2 episodes with milder severity, the patient treated himself at home with symptoms remission in almost 24 hours.

The signs and symptoms onset were usually during the night (in the second half) and there was found no correlation between the food intake and the angioedema. The patient had no history of weight loss, fever or skin rash.

From the patient pathologic background, we have retained the absence of any drug or food allergies and an arterial hypertension treated with different ACEI over the last 3 years. Four months before, he initiated the treatment with indapamide 1,5mg per day (in the morning) and enalapril 5mg per day (in the evening, before going to bed). The hereditary background gave no significant information.

At the moment of presentation, the cardiovascular status was normal, without any signs of hives or angioedema. A skin lesion was identified on the nasal pyramid, which appeared after the first episode of the angioedema.

Considering the patient's history, he was further evaluated by a mixed ENT – Allergologist team.

The initial evaluation with laboratory tests showed a differential blood count, liver function tests, urea and electrolytes, thyroid hormones and autoantibodies, as well as serum tryptase within normal limits. To evaluate the inflammatory and immune status, we assessed C-reactive protein, the serum levels of complement C3, C4 and serum immunoglobulins, which were within normal values. The serum protein electrophoresis, which is an essential parameter of homeostasis, was part of the evaluation, also within normal limits. Hepatitis serology (HBV and HCV) revealed negative results.

Also, the paraclinical investigations – abdominal ultrasound, chest x-Ray, cranio-facial CT scan – revealed no essential abnormalities related to the patient's history of angioedema.

For the skin lesion a surgical excision was performed later on, with histopathological result negative for malignancy.

An allergological evaluation a few weeks after the episode included skin prick tests for aeroallergens and food allergens and no atopic profile was identified.

Taking into consideration all tests normal results, a differential diagnosis was needed. The hereditary cause of the angioedema was ruled out in the case of our patient due to the very late onset (it usually manifests in the early years of life), the lack of familial history of angioedema and normal values of the complement factors.

The secondary determination was also considered, but there were no signs of systemic lymphoproliferative disorders, connective tissue diseases or malignant tumour.

The allergic triggers were ruled out due to the negative skin prick tests; in this case, the reaction was not IgE-mediated. Also, there was found no food ingestion causality.

Considering the drug-induced angioedema, the patient's sole medication was represented by the antihypertensive drugs. Turning our attention to the adverse effects of the two drugs, the indapam-

ide very rarely ( $<1/10000$ ) induces angioedema, while the enalapril can frequently ( $>1/100$ ,  $<1/10$ ) be responsible for angioedema involving the tongue, the lips, the larynx, the face or the epiglottis. In this case, the signs and symptoms of angioedema onset were similar to the moment when enalapril, the ACE-inhibitor, was included in the arterial hypertension therapy. A tumoral origin of the angioedema was ruled out, as the patient never presented another AE episode between the ACEI withdrawal and the skin lesion excision (a few weeks interval).

The final diagnosis was ACE-inhibitor-induced angioedema.

The patient's evolution was favourable with the definitive interruption of enalapril and its replacement with an antihypertensive drug from another medication class. It was recommended to strictly avoid ACE-inhibitors.

The prognosis in this case is favourable, subject to the possibility of a recurrence in 6 – 12 months after treatment interruption.

## CONCLUSIONS

ACEI-AE is a side effect that can occur even after many years of treatment. All patients receiving ACE inhibitors should be monitored and informed of this adverse effect with fatal outcome.

A detailed history is mandatory in all angioedema patients, considering the fact that there are patients who, at the initial evaluation, only present the history of angioedema with no other signs or symptoms.

All ACE-inhibitors should be avoided in a patient with angioedema.

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