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Review

CURRENT ASPECTS IN THE DIFFERENTIAL DIAGNOSIS OF ANGIONEUROTIC EDEMA

P. Ilkova[1*], Z. Stoyneva[2], N. Dimitrova[2]

[1]Department of Occupational Diseases and Clinical Allergy Activity, University Multiprofile Hospital for Active Treatment, "St Georgi" Plovdiv, Bulgaria
[2]Division of Occupational Diseases and Toxicology, 2nd Department of Internal Medicine, Faculty of Medicine, Medical University of Plovdiv, Bulgaria

ABSTRACT

Angioedema is a disease characterized by various triggers and an increasing prevalence.

The great Greek physician Hippocrates (377-460 BC), considered one of the most outstanding figures in the history of medicine and "Father of the Western Medicine," already used the term oídēma to describe „swelling of organs". It took many centuries later until the first description of angioedema as a distinct medical entity was minted by Quincke in 1882.

The contemporary perception, defines angioedema as a transient swelling of the skin or submucosal surface due to increased vascular permeability of small venules. The overlying skin may be normal or mildly erythematous.

Over time, many causes and factors that cause or trigger angioedema have been discussed.

There are two main types of angioedema without urticarial (histaminergic and nonhistaminergic) as the role of histamine in the pathogenesis of the disease is crucial. Angioedema is a frequent clinical condition that sometimes can be life-threatening. Different types of angioedema can be challenging to distinguish clinically. However, establishing a correct diagnosis is critical as different forms of angioedema require distinct treatment approaches.

Implementation of contemporary differential diagnostic approaches could be a prerequisite for an accurate diagnosis, which secures appropriate management strategies are possible.

Key words: angioneurotic edema, forms, differential diagnosis, diagnostic approaches

INTRODUCTION

Angioedema is a disease characterized by various triggers and an increasing prevalence (1).

The great Greek physician Hippocrates (377-460 BC), considered one of the most outstanding figures in the history of medicine and "Father of the Western Medicine," already used the term oídēma to describe swelling of organs. It took many centuries later until the first description of angioedema as Quinke minted a distinct medical entity in 1882. He suspected neurogenic factors (2).

***Correspondence to:** *Petya Ilkova, Department of Occupational Diseases and Clinical Allergy Activity, University Multiprofile Hospital for Active Treatment, "St Georgi" Plovdiv, Bulgaria, md_petja_ilkova@yahoo.com*

Was Quincke really the first who described this condition? Some authors believe that in fact the first description of angioedema was made in 1586 by Donati. (3)

In the past, so many terms had been used - such as „giant urticaria", Quincke's edema, and angioneurotic edema. (4-6)

This disease entity was first described clinically and genetically by William Osler in 1888 who originally named it "hereditary angioneurotic edema (HANE)" . It took 75 years from Osler's report until Donaldson and Evans identified the central role of C1 inhibitor (C1-INH) in the pathophysiology of HAE. (7)

Angioedema is a clinical and diagnostic problem because except for the hereditary forms there are acquired forms as well. This

fact makes it more difficult for consultants to choose the right diagnostic algorithm and adequate treatment. It is known that this disease is difficult to diagnose as well as differentiate its different forms due to the so-called "overlap" phenomenon with other pathology. A unified classification method for diagnosis and follow-up of patients with different clinical forms of the disease, accurate diagnosis and successful management of symptoms had been developed. (8)

DEFINITION

Over the last few years, EAACI (European Academy of Allergology and Clinical Immunology) and WAO (World Allergy Organization) have joined forces and published common recommendations for the diagnosis and treatment of diseases.

According to an update of the WAO and EAACI opinion published in 2018 in the World Allergy Organization Journal, Angioedema is defined as a vascular reaction of deep dermal/subcutaneous tissues or mucosal/submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling. Angioedema can be mediated by bradykinin and/or mast cell-mediators including histamine. Bradykinin-mediated angioedema can occur either on a hereditary or acquired basis, due to a deficiency/defect of C1 inhibitor (C1-INH) or other mechanisms. (9)

The definition of angioedema has been developed dynamically over time. In addition, different societies have diverse focuses on the manifestation of clinical symptoms, in particular the combination or not with urticaria.

According to the British scientific community, angioneurotic edema should be considered inseparable from chronic urticaria – so both are included in the guidelines of the British Society for Allergology and Clinical Immunology (BSACI). According to BSACI, angioedema and chronic urticaria usually occur together, but may occur separately. Angioedema is a result of a local increasing in vascular permeability, often seen in the face, oropharynx, genitals, and less commonly in the gastrointestinal tract. These swellings can be painful rather than itchy. The disease involves the submucosa, the deeper reticular dermis and the subcutaneous tissues (10).

Therefore, the summarization of currently available information and literature data is an important factor in the study of the disease and a prerequisite for its timely diagnosis and selection of the correct therapeutic approach (8).

EPIDEMIOLOGY

Data on the epidemiology of angioedema are limited, although it affects both adults and children and it is not a rare disease. There are very few publications that contain detailed epidemiological data on non-hereditary angioedema. A significant proportion of studies involve hereditary angioedema or chronic urticaria combined with angioedema.

A relatively new 2019 publication by Nedelea and Deleanu from Romania provides a detailed alignment of the prevalence of different types of angioedema. According to them, about 20% of the general population suffers from angioneurotic edema and chronic urticaria (11).

ETIOLOGY, PATHOGENESIS AND TRIGGERS

The causes of angioedema have been clarified for a long time. In the etio - pathogenetic aspect, it was found many years ago that angioedema is a consequence of local increase in permeability of subcutaneous or submucosal capillaries and postcapillary venules causing local plasma extravasation in response to mediators such as histamine, bradykinin (12).

A contemporary view should be applied in the practice in order to be more convenient. In 2016, Cicardi et al. relied on the key role of histamine in the process of occurrence of angioneurotic edema and defined 2 two main types of angioedema without urticaria (13) :

- histaminergic
- nonhistaminergic

The distinction between histamine-mediated and non-histamine-mediated angioedema is supported by other authors in more recent publications. Kanani et al. 2018, upheld the thesis that Histamine-mediated angioedema can be allergic, pseudoallergic or idiopathic.

Non-histamine mediated angioedema is largely driven by bradykinin and can be hereditary, acquired or drug-induced, such as with angiotensin-converting enzyme inhibitors. (14) Cicardi et al. disclosed new mechanisms of the pathogenetic process of angioneurotic

edema in their so popular study " Novelties in the Diagnosis and Treatment of Angioedema," published in 2016. Periodic angioedema is mediated by excessive local generation of bradykinin that stimulates B2 receptors (BK-B2R), which in turn causes edema through the intracellular NO pathway.

Bradykinin is the end product of the contact activation system and kallikrein-kinin system. The process is triggered/amplified by the presence of active coagulation factor XII.

Defining the two main phenotypes is important for diagnosis and adequate treatment. (13) Differentiation of the two main types of angioedema is crucial for the daily practice of the physicians.

Some of the most representative features of angioedema mediated by histamine and by bradykinin are reported in **Table 1.**

Table 1. *Difference between histamine-mediated and branidicin-mediated angioedema, Cicardi at al 2016*

Histamine- mediated	Bradykinini-mediated
Recognizable triggers such as insect stings, food, medications	Not accompanied by urticaria
Onset of swelling is rapid and often accompanied by urticarial and itching	History of recurrent swelling or unexplained, recurrent abdominal pain
Can affect any area of the body, although the facial area, throat and larynx are common	Family history of angioedema
Progression to anaphylaxis is possible	Progression to anaphylaxis is possible

There are several main causes and triggering factors pointed as leading in the development of angioedema. First, as one of the main causes of angioedema is ACE (angiotensin converting enzyme) inhibitor medications, due to the high frequency of AH, this kind of drugs are used by millions of people around the world. Secondly, experts from Australia for example, pointed out food and drug allergies. Swellings due to allergic reactions to foods or drugs are sometimes severe and dramatic but usually resolve within 24 hours. (15)

NSAID have been given a special plase as triggers, as per urticarial and angioedema reactions induced by them are among the most common drug hypersensitivity reactions in clinical practice. (16)

A deep diving study on infections as a trigger has found in cases no obvious cause of angioedema is defined, screening infectious focus does not always work but there is strong evidence that treatment of co-infection (dental granuloma, sinusitis, Helicobacter pylori, a urinary tract infection, significantly improves angioedema. (17)

Although rarely, metabolic disorders such as type 2 diabetes may also act as a trigger for symptoms of angioneurotic edema without urticaria. (18)

Hereditary angioedema (HAE) is defined as an autosomal dominant disease caused by low levels of the plasma C1 protease inhibitor - an important factor in the regulation of complement enzymes, coagulation, fibrinolytic and kinin systems. Deficiency of C1 INH triggers uncontrolled activation of the complement cascade, which generates symptoms of edema. The pathogenesis of HAE is complex, based on the quantitative or qualitative (functional) deficiency of the C1 esterase inhibitor. (19)

Hereditary angioedema (HAE) is classified into 3 main types:
- type 1 HAE characterized by reduced circulating levels of C1-INH - frequency of 80-85% of cases
- type 2 HAE (15-25%) - and manifested dysfunction of C1-INH
- type 3 HAE which the main haracteristics as follow - positive family history, more often affected female, symptoms could be provoked by oral contraceptives, HRT or pregnancy, normal antigenic and functional C1-INH levels were established, as well as a putative mutation in the coagulation factor XII gene transmitted autosomal dominantly: AD-FXII-HAE. Late

onset of symptoms, the presence of long asymptomatic intervals between episodes and low response to high doses of antihistamines are specific features of this type of angioedema. Authors of the publication do not recommend use the term HAE type 3 because HAE type I and II identify two specific types of C1-IH deficiency). (20)

In a large study among patients with hereditary angioedema, trigger factors of various origin were found and most often they were associated with trauma or emotional stress, such as 30% of cases respondents were able to point the factor, in 23.64% edema were subcutaneous, in 38.13% abdominal and in 28.50% of the upper respiratory tract. (21)

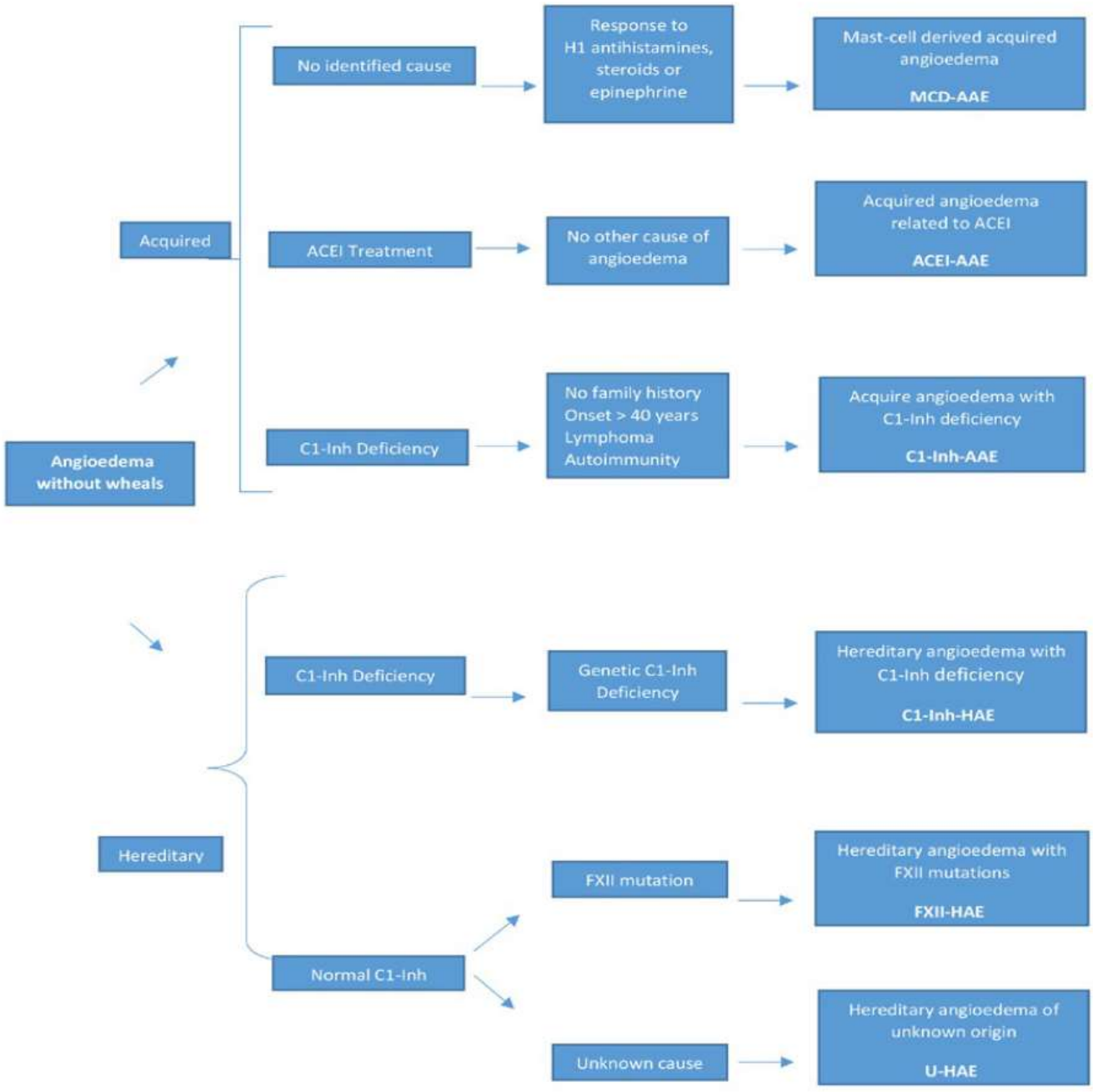

Figure 1. Schematic classification of chronic / recurrent angioedema without wheals.

Moreover, a combination of allergic and non-allergic mechanisms for the development of angioneurotic edema in the same patient could appeared - for example, opioid analgesics may cause angioedema (with or without urticaria) in

proven HAE type I in the absence of clinical and laboratory evidence of HAE activity.

Due to the similarity in the clinical symptoms of different types of angioedema, accurate identification of their etiology and pathogenesis is necessary in connection with the effectiveness of treatment. (22)

Regarding the classification of angioedema, there are many publications, however, for clinical practice it is important such a classification, which is directly related to clinical manifestations and therefore helps clinicians in making the diagnosis - **Figure 1.** (23)

CLINICAL MANIFESTATION AND DIFERRENTIAL DIAGNOSIS

Angioedema is an life-threatening condition and patients are often admitted to emergency departments. According to various data, about 1 million people per year with symptoms of angioedema visit the emergency rooms in the United States. (24)

The most characteristic clinical symptoms of different types of angioneurotic edema are presented in **Figure 2.**

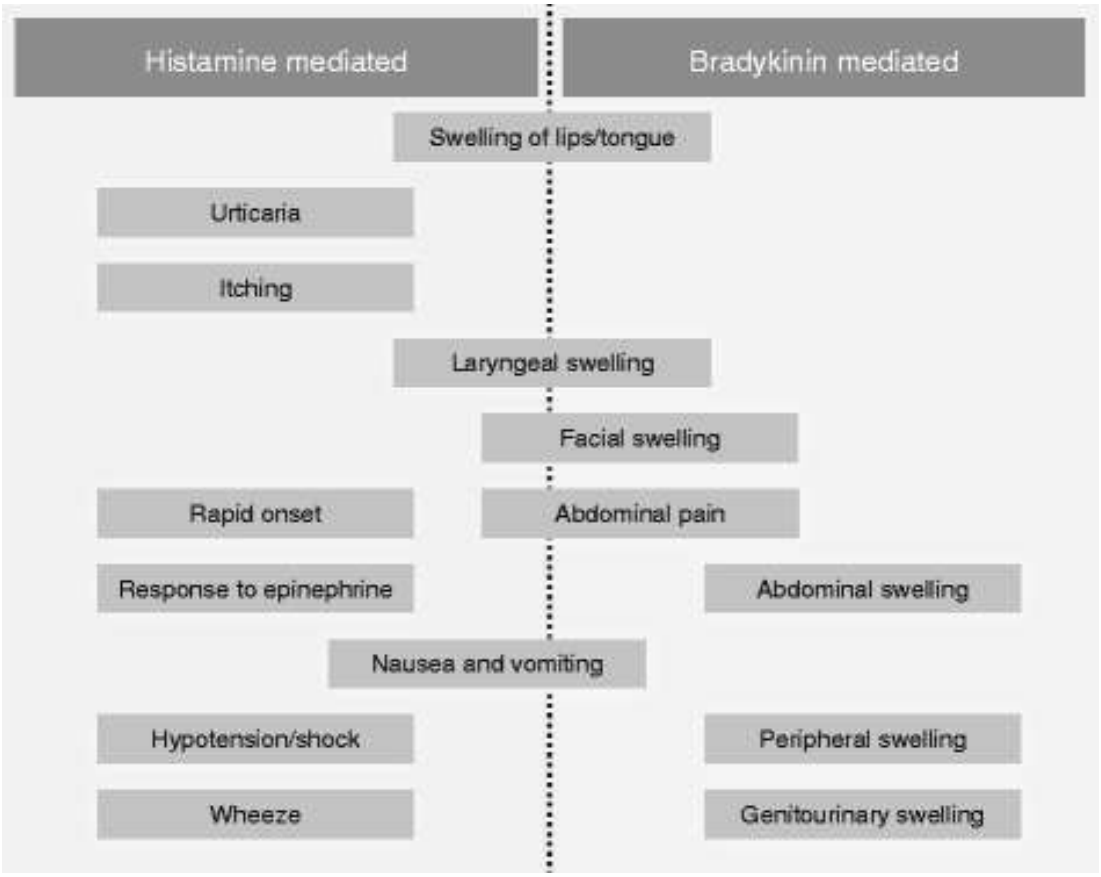

Figure 2. Distinguishing histamine- versus bradykinin-mediated angioedema, Bernstein 2017

From clinical perspectives, HAE and Acquired AE are similar and they are characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most commonly affect the skin or mucous tissues of the gastrointestinal and upper respiratory tract (25).

Depending on the onset of symptoms, angioneurotic edema may be classified as an isolated acute episode or as a chronic and recurrent form. The acute form of acquired AE may occur in combination with acute urticaria or anaphylaxis.

Chronic recurrent angioedema occurs mostly in association with chronic spontaneous urticaria, or rarely, chronic inducible urticaria and even in the setting, it can occur without evident wheals in about 10% of the cases. Chronic and relapsing angioedema without urticaria can also be a manifestation of the different forms of hereditary angioedema or of the rare acquired forms of angioedema (23).

Vision also could be affected. Bronchospasm can occur if the lining of the throat and airways are affected. Symptoms of respiratory failure develop. In severe cases, anaphylactic shock may occur and this can be life threatening (26).

Abdominal involvement in angioedema is often a challenge to diagnose. Acute onset abdominal pain is its most common presenting symptom, and misdiagnosis may lead to unnecessary surgical intervention (27).

Angioedema-related abdominal pain may present as severe acute pain or as chronic recurrent pain of moderate severity. Abdominal pain is described as spasms or colic and it is recognized as severe to excruciating in 87% of patients. Vomiting and diarrhea occur in 78% and 65%, respectively, in patients with abdominal symptoms (28).

Foods as allergens could play a significant role in the etiopathogenesis of the so-called allergic angioedema. The consumption of mussels, nuts, fruits, etc. most often leads to direct Ig E mediated degranulation of mast cells and histamine releasing which results in local swelling of tissues. From a clinical perspective, this process is manifested by abdominal pain and vomiting (29).

A few cases of a rapidly progressive toxoallergic shock after various "seafood" consumption has also been described and presents life-threatening condition for patients (30).

Clinical symptoms of angioedema are a result of increased vascular permeability - swelling of the deep dermal, subcutaneous and submucosal tissues. The swelling can be asymmetrical and affects the face, neck, arms, and genitals. No change in skin color has been observed during the development of edema and there is no itching. Pain and burning are more common accompanying symptoms of pruritus, in contrast to urticarial when pruritus is a typical complaint (31).

The combination of angioedema with wheals occurs in about 40% of patients (32,47,48).

C1 INH deficiency (hereditary and acquired) is usually presented by angioedema and it is not associated with urticaria. ACE-mediated angioedema usually presents separately, however in rare cases there may be accompanied of insignificant urticaria. Idiopathic angioedema is definitely not combined with wheals (33,40).

According to new understandings, the diagnostic approach in a patient with angioedema includes a detailed history (especially family history), possible triggers, the presence of concomitant diseases and medications patients take for their treatment. The active seeking of skin symptoms or other diagnostic signs is very important during the objective examination.

An example for diagnostic algorithm is presented on figure 3. This algorithm allows physicians to able to distinguish different types of angioneurotic edema and accordingly to undertake an adequate therapeutic strategy (23).

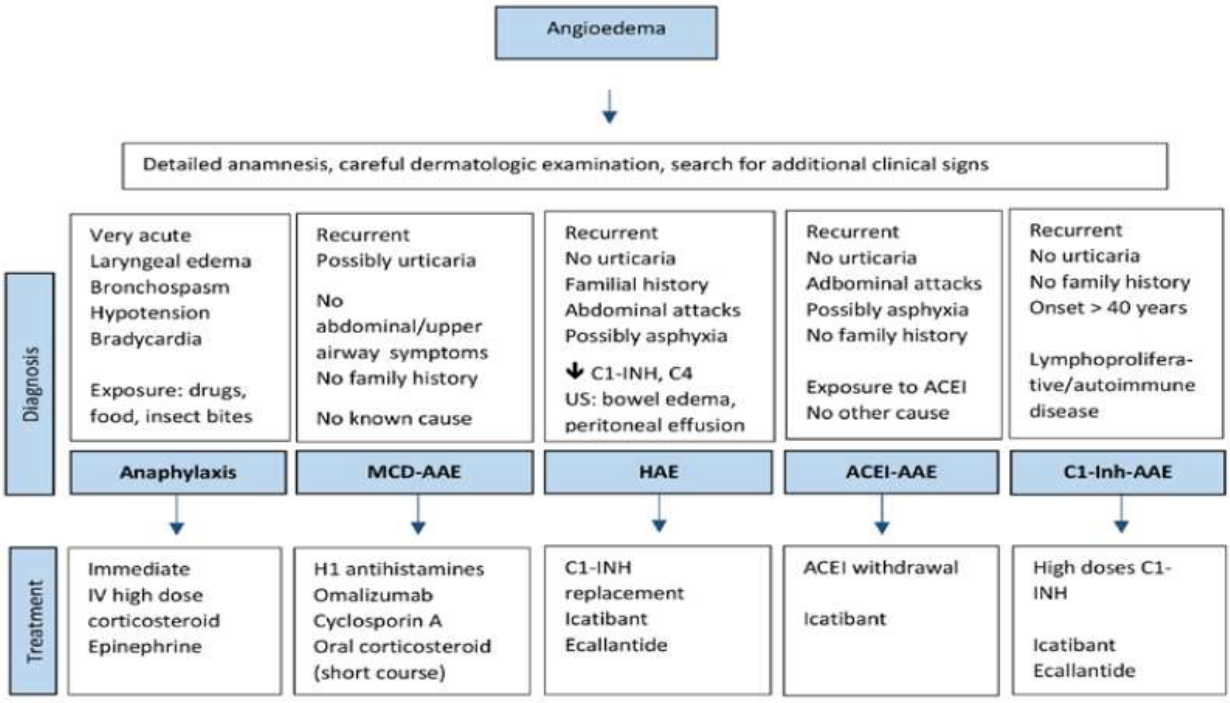

Figure 3. Algorithm for diagnosis and management of angioedema, Batista 2019
Legend: MCD – mast cell derived AAE (Histamine mediated acquired AE)

There are many diseases and syndromes could mimic angioedema as follow:

- DRESS (Drug rash with eosinophilia and systemic symptoms) - it refers to uncommon but also quite severe side effects. There is a wide list of drugs associated with this type of reaction, the most common are aromatic anticonvulsants (phenytoin, phenobarbital and carbamazepine) (34).
- Morbihan's disease - It is considered a rare complication of rosacea. It is characterized by persistent erythematous edema limited to the forehead, glabella, upper eyelids and cheeks. The swelling got worse gradually over months to years and with a typical solid consistency. The patient has no other symptomatic complaints and no specific laboratory or histopathological findings have been observed. The chronic nature of the skin condition, along with the limited location, should distinguish this from angioedema (35).
- Vena cava superior syndrome is a group of symptoms resulting from impaired blood flow to the right atrium. In most cases, the obstruction is caused by a malignant tumour within the chest. Clinical manifestations usually develop slowly and include shortness of breath, cough and hoarseness. Due to the difficult blood flow, the syndrome can be disguised as angioedema in the early stages, due to the gradual development of swelling in the face and upper limbs (29).
- Hypothyroidism - Severe hypothyroidism could be manifested by puffiness of the face and lips, strongly resembling angioedema. It is typical for him that the swellings are not transitions as in angioedema. Diagnosis is based on clinical features and low levels of thyroid hormones (36).
- Orofacial granulomatosis - is a group of chronic diseases of unknown etiology, affecting the soft tissues of the oral and maxillofacial area, clinically manifested by persistent swelling of the lips. The group includes Melkerson-Rosenthal syndrome with the classic triad of persistent swelling of the lips or face, facial nerve palsy and geographical language. Monosymptomatic cases with only labial involvement are called granulomatous cheilitis. Orofacial edema is painless and asymmetrical, most commonly affecting the upper lip. However, its chronic nature should distinguish it from typical angioedema. The diagnosis is confirmed histologically.(37)
- Clarkson's disease is a life-threatening condition characterized by recurrent episodes of sudden hypovolemic shock and massive edema due to massive plasma leakage from blood vessels near body cavities and muscles. Cutaneous edema in systemic capillary effusion syndrome is generalized and symmetrical. In addition, rapid displacement results in hypovolemia, haemoconcentration, and decreased serum albumin, a triad that is not typical for angioedema.(38)
- Gleich's syndrome – an episodic angioedema with eosinophilia, is a rare disease of unclear etiology, characterized by recurrent episodes of idiopathic angioedema, eosinophilia, and elevated serum immunoglobulin lasting up to several months. The clinical picture also shows weight gain caused by fluid retention, fever, itching and, in some cases, urticaria. The presence of specific laboratory features, together with other characteristic clinical manifestations, distinguishes it from classical angioedema (39).

Concomitant diseases complicate the diagnostic process in addition. According to more recent publications, cardiovascular diseases are a common disorder - in 33% of patients, autoimmune thyroiditis is the second most common pathology - 14.8%, followed by musculoskeletal disorders (10.2%) and diabetes (4.5%). A family history of allergic disease was observed in 8.4% of patients, with asthma being the most common allergic disorder (41).

Scientific communities all over the world present summarized diagnostic algorithms in order to facilitate physicians during the process of diagnostic and choicing of therapeutic approach. The distinction between histamine-mediated and bradykinin-mediated angioedema is essential for clinical practice, and ensures a proper therapeutic strategy.

Unfortunately, no validated, rapid, point-of-care diagnostic test is available to differentiate a bradykinin-mediated from a histaminemediated attack; however, a number of distinguishing features can guide the diagnosis (42).

American College of Allergy Asthma & Immunology (ACAAI) and Society for Academic Emergency Medicine (SAEM) have developed a diagnostic algorithm in order to support medical professionals in emergency departments - **Figure 4.**

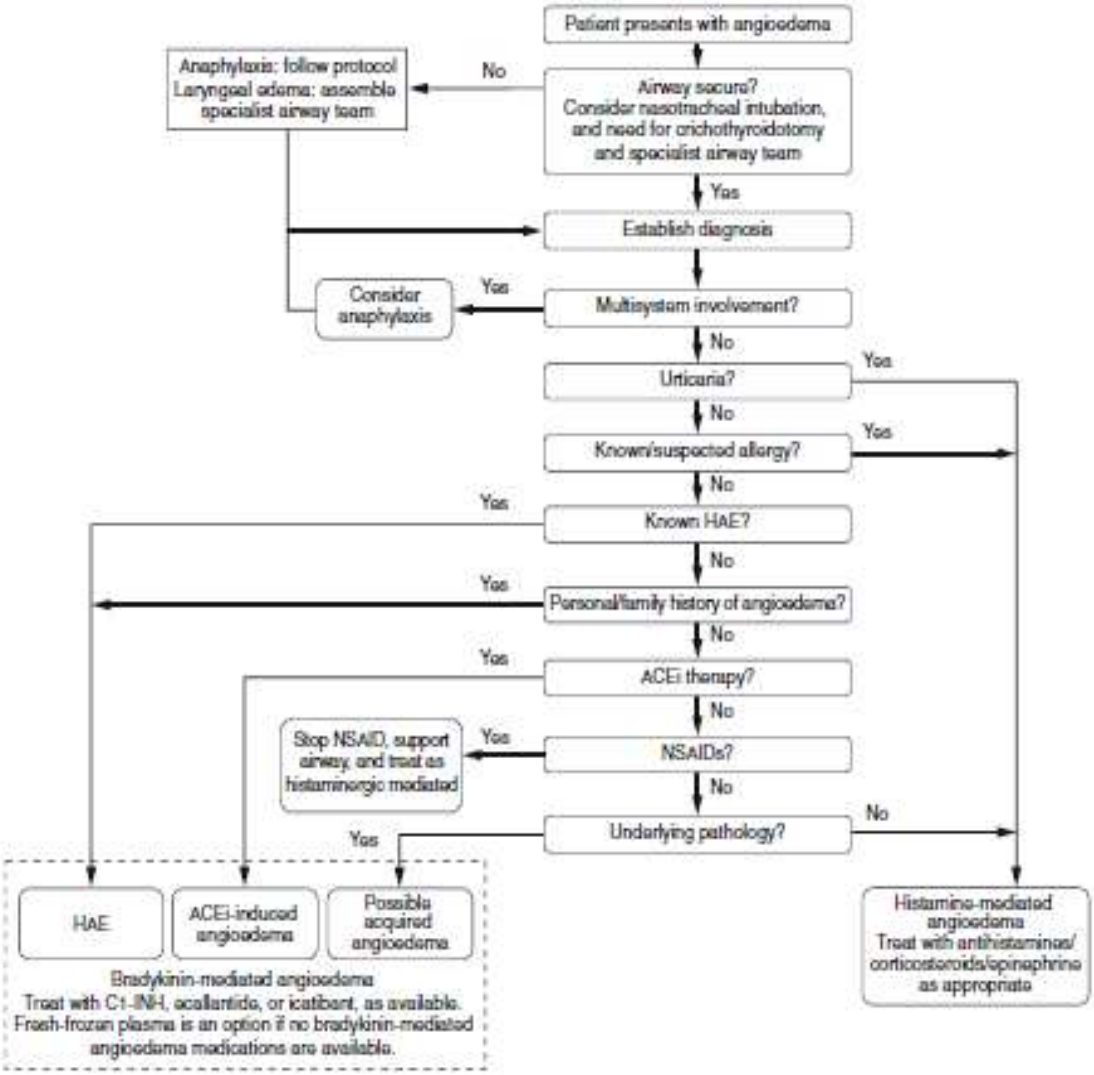

Figure 4. Diagnostic algorithm according to ACAAI & SAEM
Legend: ACAAI - American College of Allergy Asthma & Immunologyq, SAEM - Society for Academic Emergency Medicine, Moellman 2014

EAACI (European Academy of Allergy and Clinical Immunology) and WAO (World Allergy Organization) have separated in different consensus main steps in the diagnostic process in patients with NAE and AAE. The algorithm for behaviour considers the acquired forms inseparably in chronic urticaria and angioedema.

Figure 5 presents a recommended diagnostic algorithm for patients with chronic urticaria / angioedema or both, developed by EAACI, WAO and published in 2018 (43).

As can be seen, the duration of symptoms, medication uptake (ACE inhibitors, NSAIDs, etc.), concomitant diseases and family history are crucial in the diagnosis and treatment. The manifestation of each of these factors is key to the therapeutic response of the patient.
Regarding HAE there are strictly developed criteria for diagnosis in Bulgaria. The criteria are divided into two main groups (clinical and laboratory) as presence of 1 clinical and 1 laboratory criteria is mandatory.

According to recent guidelines, C1-INH deficiency or dysfunction finding is crucial for diagnosis of angioneurotic edema. Several types of tests have been approved as follow:

- Biochemical tests - measurement of C1-INH plasma levels, functionality and C4 levels. Plasma levels below 50% for C1-INH or activity <50% compared to normal are evidence of deficiency. Recurrent episodes of clinical manifestations are also important for diagnosis
- Genetic testing - in case of clear clinical and laboratory results, genetic testing for HAE-C1-INH is not required. The molecular genetic tests used today have 90-95% reliability (44).

- Prenatal diagnostic test is possible through genetic testing of chorionic villi or amniotic fluid, and this is done only by strict criteria and indications. Postnatal diagnostic test in children is recommended after the first year, as the results are not reliable below this age (45).
- There are no specific diagnostic tests for the ACE-mediated AAE inhibitor. The diagnosis is based on the presence of angioedema, without wheals, lack of family history, of ACE inhibitor up taking. In some patients, episodes of recurrent angioedema may occur even after discontinuation of treatment should be taken into consideration (46).

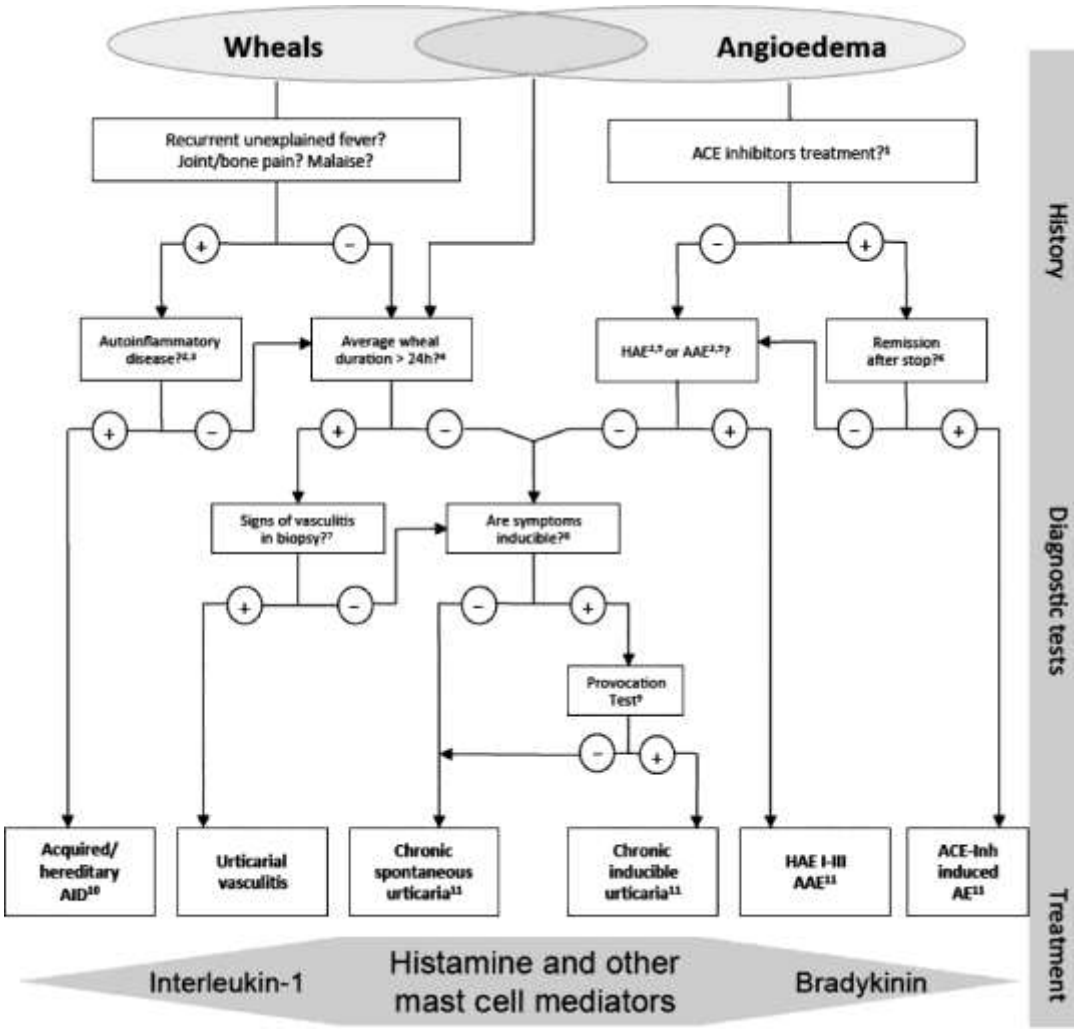

Figure 5. EAACI and WAO diagnostic algorithm for urticaria and angioedema, Zuberbier 2018

CONCLUSIONS:

Angioneurotic edema is a localized and self-limiting edema of subcutaneous or submucosal tissue due to a temporary increase in vascular permeability caused by the release of vasoactive substances. It is often accompanied by urticaria.

Despite of its growing clinical influence, many aspects of the etiology and pathogenesis remain under low level of understanding so far. The frequency, demographic characteristics, diagnostic algorithms and therapy of angioedema need further exploring.

Knowledge on the clinical manifestation of the disease in its various forms allows rapid orientation in the diagnosis and choosing the most appropriate therapeutic approach.

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