

Angioedema

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KEYWORDS

- Urticaria • Angioedema • Histamine • Bradykinin • Hereditary angioedema
- Acquired angioedema • C1 esterase inhibitor • Factor XII gene mutations

KEY POINTS

- Wheals of urticaria and angioedema are due to short-lived edema in different layers of the skin, and differ in clinical and pathogenetic respects.
- The factors involved in the opening and closure of endothelial cell-cell adherens junctions, which are largely composed of vascular endothelial cadherin, are still unknown in urticaria and angioedema.
- In the spectrum urticaria/angioedema, 3 groups of diseases can be differentiated: diseases with urticaria and angioedema, diseases with angioedema alone, and diseases with urticarial lesions without angioedema.

INTRODUCTION

Urticaria and angioedema have several features in common, some of which are clinical. Both are based on a relatively short-lived edema in the skin and may be associated with edema episodes of other organs. Urticarial wheals and angioedema may be single or multiple. The individual lesion of either may persist for from a few hours to some days. Both belong to various disease entities ([Table 1](#)), and may occur in combination or in isolation. Local vasodilation and increased vascular permeability are the main changes in urticaria and angioedema.

PATHOPHYSIOLOGY

Common Pathophysiologic Features

Single urticaria and angioedema lesions have a localized fluid extravasation in common. The plasma passes through the vessel wall and, when extravascular, becomes interstitial fluid. The passage through the interstitial gaps of the endothelial cells has attracted more attention in recent years. Endothelial cells control the passage of plasma constituents from blood to underlying tissues. Endothelial permeability is mediated by transcellular and paracellular pathways ([Fig. 1](#)), which means that blood

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Table 1 Diseases with urticaria and/or angioedema		
Diseases with Urticaria Combined with Angioedema	Diseases with Angioedema and Without Urticaria	Diseases with Urticaria and Without Angioedema
Acute urticaria	Hereditary angioedema due to C1-INH deficiency (HAE-C1-INH); types I and II	Cholinergic urticaria
Chronic spontaneous urticaria	Hereditary angioedema with normal C1-INH (HAE-nCI; HAE type III), subtypes HAE-FXII and HAE-unknown	Factitial urticaria
Cold urticaria	Acquired angioedema with C1-INH deficiency (AAE-C1-INH)	Delayed-pressure urticaria
Urticarial vasculitis	Angioedema due to ACE inhibitors (AE-ACEI)	Heat contact urticaria
Exercise-induced anaphylaxis/urticaria	Angioedema with unknown cause (AE-UC) responsive to antihistamines (AE-UC-h) or unresponsive to antihistamines (AE-UC-nh)	Solar urticaria
Episodic angioedema with eosinophilia		Aquagenic urticaria
Vibration-induced urticaria/angioedema		Contact urticaria

Abbreviations: ACE, angiotensin-converting enzyme; C1-INH, C1-inhibitor.

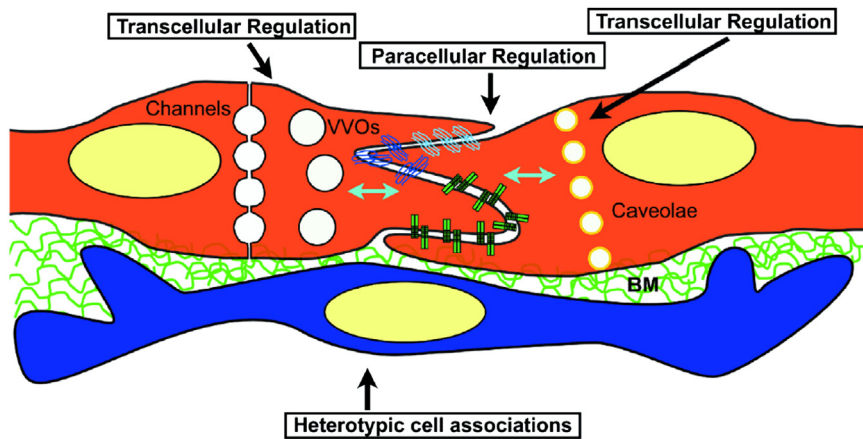


Fig. 1. Pathways that regulate barrier function in endothelial cells. The scheme shows 2 endothelial cells and the subendothelial space. Vascular permeability is regulated and maintained through 3 compartments: paracellular junctions (adherent and junctional complexes), transcellular pathways, and heterotypic cell interactions (usually pericytes). The details of this cross-talk remain largely unclear. BM, basement membrane; VVOs, vesiculovacuolar organelles. (From Goddard LM, Iruela-Arispe ML. Cellular and molecular regulation of vascular permeability. *Thromb Haemost* 2013;109:408; with permission.)

constituents may pass through or between endothelial cells. The paracellular pathway is mediated by the coordinated opening and closure of endothelial cell-cell adherens junctions. These junctions are largely composed of vascular endothelial cadherin (VE-cadherin), an endothelium-specific member of the cadherin family of adhesion protein that may bind to several protein partners.¹ The barrier between the bloodstream and tissues may be influenced not only by endothelial cells but also by other mural cells. These endothelial-associated cells, pericytes, smooth muscle cells, and macrophages, might not form a permanent sheath, but instead are dynamically associated with capillaries and functional participants of the “vascular unit.”²

The exact mechanism of edema formation at the vascular level in urticaria and angioedema is still unknown, and this also holds true for the mechanism of reabsorption of the fluid after hours to days.

Different Pathophysiologic Features

Urticaria and angioedema belong to various disease entities. Both are complex reactions and occur through various pathogenetic pathways. Some types of angioedema may be hereditary and others not; this is also true for urticaria. Wheals and angioedema are clinically different lesions. The underlying process concerns superficial vessels in urticaria and deep vessels in angioedema. The structural or functional differences of the vessels leading to the different clinical signs are not known. Some of the diseases forms are described here.

Urticaria

A wheal is a single lesion of an urticaria, and is a short-living edema of the upper and mid-dermal layer of the skin, with dilation of the postcapillary venules and lymphatic vessels of the upper dermis. Urticaria is a mast-cell-driven disease, the pathogenesis of which is complex. The release of histamine from dermal mast cells plays a major role. After activation, the cutaneous mast cells release preformed mediators such as histamine, heparin, proteases, newly formed mediators such as prostaglandins and leukotrienes, and cytokines such as tumor necrosis factor α and interleukin-8. The mediators released from activated mast cells result in sensory nerve activation, vasodilation, and plasma extravasation, as well as cell recruitment to urticarial lesions. The mast-cell-activating signals in urticaria are ill defined and are likely to be heterogeneous and diverse.

Angioedema

Angioedema is a short-lived edema in the deep dermal layer of the skin and the subcutaneous tissue. Similar edema episodes may occur in the submucosal tissue of various organs. Little is known about the pathogenesis of angioedema associated with the clinical subtypes of urticaria. Histamine might play a major role. Many patients with angioedema associated with chronic spontaneous urticaria (CSU) respond to antihistamines, partially or completely. This finding confirms that histamine is involved at least in part in angioedema in patients with CSU. To date it remains unknown as to which other mediators are involved in angioedema of CSU. Bradykinin does not seem to play a major role in the pathogenesis of angioedema associated with urticaria.

In recurrent angioedema alone (ie, without urticaria), the vasoactive mediator bradykinin is clearly involved, at least in most of the diseases. Bradykinin is a vasoactive nonapeptide. High bradykinin levels in plasma may result from an overproduction of bradykinin caused by activation of the kallikrein-kinin system, or may result from an inhibited degradation of bradykinin. The role of the involvement of bradykinin and other mediators in the various angioedema diseases is discussed later in this article.

CLINICAL FEATURES

Urticaria

A wheal is a single lesion of an urticaria. The clinical manifestation of this circumscribed lesion depends, among other factors, on properties of the tissue. Swellings of thin skin with a thin dermis and a loose subcutaneous tissue may appear as larger and not well-circumscribed lesions, as seen in the regions of the eyelids and the genitals, similarly to angioedema.

Angioedema

Angioedema is a diffuse swelling of deeper skin layers. Under the heading of angioedema in a broader sense, swellings of other organs are subsumed, including self-limiting edema attacks of the gastrointestinal tract and laryngeal edema.

DISEASES WITH URTICARIA AND/OR ANGIOEDEMA

Diseases with Urticaria Combined with Angioedema

Acute spontaneous urticaria or acute urticaria

An acute urticaria is a frequent reaction, persisting for less than 6 weeks by definition, in most patients lasting only 1 day or a few days.

Usually it is a “one-off” occurrence, with recurrences only occurring on repeated exposure. The usual triggers are infections, foods, drugs including acetylsalicylic acid and other nonsteroidal anti-inflammatories, and insect stings and bites. In less than 50% the trigger remains unknown.

In this common type of urticaria, angioedema is a frequent symptom. However, the exact incidence is unknown and is difficult to determine. Probably less than 50% of cases are associated with an angioedema. Angioedema usually occurs in the form of facial swelling, which usually responds to corticosteroids and antihistamines.

Chronic spontaneous urticaria

Angioedema is a frequent symptom of CSU. Because CSU is a frequent disease (about 1%–5% of the population are affected), angioedema associated with CSU is a considerable clinical problem.

Angioedema in CSU may occur as an angioedema of the skin or as a gastrointestinal edema (rare), a tongue edema, or an edema of the upper airways. In more than 50% of patients with CSU, recurrent angioedema of the skin or other organs occurs in addition to urticarial lesions. An urticaria without angioedema occurs in about 30% to 40% of patients with CSU. About 10% of patients have recurrent angioedema without or nearly without an urticaria. However, the precise percentages of patients with urticaria alone or with angioedema with concurrent urticaria or with angioedema alone vary within different studies.^{3–7}

Angioedema associated with CSU is most frequently localized in the eye region, lips, and tongue. Less frequently hands, feet, and genitals are affected. Associated symptoms such as fever, headache, arthralgia, gastrointestinal symptoms, and dyspnea may occur. Angioedema may occur when hives are present or at times when hives are not present.

Thus there are 2 different lesions in CSU, urticarial lesions and angioedema. Both may respond to antihistamines, which is true for a large proportion of patients. However, in other patients with CSU antihistamines do not work for either the urticaria or angioedema component.

Accordingly, the mediator for angioedema in CSU is histamine in many patients. Obviously, however, further mediators are involved (see earlier discussion), although their exact role in the development of the cutaneous edema of hives and angioedema

is unknown at present. Antihistamines may not work at low doses, but may be effective at higher doses. Omalizumab is a chimeric monoclonal antibody that works by reducing circulating free immunoglobulin (Ig)E, thereby reducing expression and function of FcεR1 on mast cells and basophils. It has shown to be effective in patients with CSU (urticarial lesions and angioedema) who exhibited IgE against thyroperoxidase.⁸

Cold urticaria

In cold urticaria, urticarial lesions and angioedema occur after exposure to cold. In more than 70% of patients the urticarial lesions are combined with angioedema.

Urticarial vasculitis

Urticarial vasculitis is a rare disease, characterized histopathologically by vessel-wall necrosis, which is a hallmark of this disease. Urticaria-like skin lesions with a faint residual pigmentation, and systemic symptoms including arthralgia and renal and lung involvement are frequent. Angioedema often occurs concurrently with urticarial vasculitis.

Exercise-induced anaphylaxis/urticaria

Exercise-induced urticaria/anaphylaxis (EIA) is a special entity. Urticarial lesions with or without angioedema may occur; more rarely, recurrent angioedema alone may also occur.

Episodic angioedema with eosinophilia (Gleich syndrome)

Episodic angioedema with eosinophilia is defined by bouts of angioedema, urticaria, fever, weight gain, eosinophilia, and an increase in IgM.⁹

Vibration-induced urticaria/angioedema

In rare cases, vibratory forces lead to urticaria or angioedema. This condition has been observed in patients after working with a pneumatic hammer, bicycling on cobbles, using massage devices, and playing musical instruments.

Diseases with Angioedema and Without Urticaria

Hereditary angioedema due to C1-inhibitor deficiency

Hereditary angioedema (HAE) due to C1-INH deficiency (HAE-C1-INH) is a rare disease with an autosomal dominant pattern of inheritance.

C1-INH controls the spontaneous autoactivation of the first complement component (C1) and activated C1. A deficiency in functional C1-INH leads to activation of the initial phase of the complement system, resulting in a permanent reduction of plasma levels of C4. It is now known, however, that it is the inhibitory effect of C1-INH not on the complement system, but on the kallikrein-kinin system, that has the essential pathogenetic role in HAE-C1-INH. C1-INH is responsible for the inhibition of the greater part of plasma kallikrein and factor XIIa, and is thus the most important regulator of activation of the kallikrein-kinin system. During acute attacks of HAE, kallikrein is insufficiently inhibited because of the deficiency in C1-INH, the kallikrein-kinin system (contact system) becomes activated, and at the end of the cascade there is an increased amount of bradykinin, the main mediator of increased vascular permeability, and hence of the edema seen in HAE-C1-INH.

Clinically, HAE-C1-INH is characterized by recurring swelling of the skin (extremities, face, genitals), gastrointestinal attacks (painful abdominal cramps, mostly accompanied by circulatory symptoms caused by hypotension, sometimes vomiting, and diarrhea), and by edema of the larynx and other organs. Urticaria does not belong to the clinical signs of HAE-C1-INH. Among the 420 patients with HAE-C1-INH

surveyed at the Angioedema Outpatient Service in Mainz, only 2 patients have additional urticaria.

HAE-C1-INH manifests most often early in the second decade of life, also frequently in the first, and in a few patients in the third decade or even later. Recurring attacks of edema follow, the frequency of which varies greatly from patient to patient. In one study series, about 70% of patients had 12 attacks or fewer per year, and 30% more than 12 attacks.¹⁰

Attacks are triggered by trauma, pressure, situations of psychological stress, menstruation, ovulation, or infectious diseases. The tendency to edema attacks can be greatly increased by ingestion of angiotensin-converting enzyme (ACE) inhibitors; these are contraindicated in patients with HAE. Angiotensin convertase II (ATII) receptor blockers can also increase a tendency to edema attacks, albeit more rarely. In the same way, attacks may become more frequent in women receiving estrogen in contraceptives or as hormone replacement therapy.¹¹

Hereditary angioedema with normal C1-INH

In 2000, a novel type of HAE was described that was not associated with C1-INH deficiency and occurred mainly in women.¹² All patients had normal C1-INH concentration and activity with respect to C1 esterase inhibition and normal C4, ruling out both types of HAE-C1-INH (HAE-C1-INH types I and II). This hitherto unknown disease was proposed to be termed “hereditary angioedema with normal C1 inhibitor” (HAEnCI) or “hereditary angioedema type III.” HAEnCI is autosomally inherited with incomplete phenotypical penetrance.¹²

In 2006, 2 different missense mutations in a nonconservative gene region were identified in German patients, located in exon 9 of the gene coding for the coagulation factor XII (Hageman factor).¹³ In 2011 a further HAE mutation was identified, a large deletion of 72 base pairs (c.971_1018+24del72).¹⁴ To date, numerous families have been reported that include members having HAEnCI, with affected women bearing these mutations (HAE-FXII). The clinical symptoms of HAEnCI include recurrent skin swellings, abdominal pain attacks, tongue swellings, and laryngeal edema. Urticarial lesions do not belong to the clinical symptoms of HAEnCI. Oral contraceptives, pregnancy, and hormone replacement therapy often play a particular role as triggering or aggravating factors. HAEnCI has been observed predominantly in women, but male patients have been reported. Antihistamines and corticosteroids are not effective. Icatibant, a bradykinin-B2 receptor antagonist, and C1-inhibitor concentrate, as well as tranexamic acid and danazol, are effective, at least in some patients.¹⁵

Acquired angioedema with C1-INH deficiency

This form of angioedema is seen in patients whose C1-INH deficiency is due to increased C1-INH catabolism. Accordingly, C1q is usually decreased. The symptoms are the same as those of HAE-C1-INH.¹⁶ In a significant proportion of these patients there is an underlying B-cell disorder (eg, monoclonal gammopathy of unknown significance or malignant lymphoma), and it can often happen that angioedema is the presenting feature of lymphoreticular disease. In some patients autoantibodies against C1-INH are found.¹⁷

Angioedema due to ACE inhibitors

Approximately 0.1% to 2.2% of patients treated with ACE inhibitors develop recurrent angioedema, often facial or lip swelling or edema of the tongue (angioedema induced by ACE inhibitors, AE-ACEI).^{18,19} Several cases of death by asphyxiation following closure of the upper airways have been reported.²⁰ The interval between the start of

treatment with and the appearance of the first angioedema can be months or several years, so that the causal connection between the angioedema and the triggering ACE inhibitors is sometimes unrecognized or recognized late. Because of the enormously high use of ACE inhibitors, cases of AE-ACEI are not rare. ATII receptor blockers can also trigger the same forms of angioedema, though more rarely. Occasionally chronic urticaria is associated with AE-ACEI.

Angioedema with unknown cause (idiopathic angioedema)

Angioedema of unknown cause (AE-UC), or idiopathic angioedema, is the name given to cases of angioedema that cannot be identified as any of the recognized forms of angioedema. In these cases, none of the patient's relatives are affected, C1-INH deficiency is not present, and the angioedema cannot be determined to be caused by drugs or any other triggers. Knowledge about the pathogenesis and treatment of this form of angioedema is still very limited.²¹ It is one of the most frequent forms of angioedema and is therefore important in daily practice.

Some of these cases respond to antihistamines and corticosteroids, either at normal or higher doses. The name "idiopathic histaminergic angioedema" has been proposed for this type of angioedema.²² The author prefers the name "angioedema of unknown cause responding to antihistamines" (AE-UC-h). This type of recurrent angioedema obviously is mast-cell driven. Most probably these cases correspond to antihistamine-sensitive CSU.

The problem may arise that angioedema does not respond to antihistamines, even at high doses. The author prefers the name "angioedema of unknown cause not responding to antihistamines" (AE-UC-nh) for this condition. The response to antihistamine is a clinical feature pointing toward the pathomechanism. If patients with AE-UC do not respond to antihistamines, other pathomechanisms can be taken into consideration. It is possible that subtypes exist according to the following pathomechanisms. First, recurrent angioedema could develop from mast-cell mediators other than histamine. This type of angioedema might correspond to those patients with CSU who do not respond to antihistamines. Second, the main mediator could be bradykinin. In bradykinin-induced angioedema, such as HAE-C1-INH, AAE-C1-INH, and HAE-nCI (HAE type III), histamine plays a minor role, if any. Accordingly, urticarial lesions are usually not observed in these diseases. If bradykinin was the main mediator in AE-UC-nh, a response to icatibant would be expected. Information about this proposal is still sparse. Third, other and hitherto unknown pathways might play a role that differs from that of from mast-cell mediators and bradykinin.

Diseases with Urticaria Without Angioedema

Several forms of urticaria are not associated with angioedema.

Cholinergic urticaria

Cholinergic urticaria is a frequent form of urticaria, clinically characterized by tiny urticarial lesions that occur simultaneously with or shortly after an increase of body core temperature attributable to physical exercise or spicy food. In most patients the lesions do not occur in the face. In severely affected patients, however, the face may also be involved and swollen, simulating angioedema. In rare cases, patients may contract angioedema of the skin or mucous membranes.²³

Factitial urticaria

Further subtypes of urticaria without angioedema include factitial urticaria (dermographic urticaria) and delayed-pressure urticaria.

Delayed-pressure urticaria

Delayed-pressure urticaria is clinically characterized by localized deep erythematous skin swellings developing 3 to 12 hours after pressure. The lesions persist for up to 2 days. Although of delayed-pressure urticaria involves deep swelling of the skin, it is not identical to angioedema.

Other subtypes of urticaria

Heat-contact urticaria and solar urticaria are usually not associated with angioedema. The same is true for aquagenic urticaria and contact urticaria elicited by contact with urticariogenic substances.

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