REVIEW ARTICLE

Bradykinin-mediated angioedema

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KEY WORDS

angioedema, bradykinin, C1 inhibitor, renin–angiotensin–aldosterone system blockers

ABSTRACT

Angioedema and urticaria often constitute a challenge in daily clinical practice. They may either co-occur or present as independent conditions. They are characterized by a complex pathomechanism, and their symptoms may be triggered by diverse factors. These differences are crucial for developing a successful treatment regimen. Both conditions may have an allergic origin (immunoglobulin [Ig] E and non-IgE-related), usually induced by histamine, or a nonallergic one, such as bradykinin-mediated angioedema in patients with C1 inhibitor (C1-INH) deficiency or angioedema induced by certain drugs (eg, angiotensin-converting enzyme inhibitors). Currently, we distinguish 5 types of nonallergic angioedema: hereditary angioedema (HAE) due to C1-INH deficiency, acquired angioedema (AAE), and angioedema induced by the renin–angiotensin–aldosterone system, all of which are mediated by bradykinin, as well as pseudoallergic angioedema and idiopathic angioedema. Bradykinin-mediated angioedema (eg, laryngeal angioedema) may be life-threatening because of resistance to corticosteroids and antihistamine drugs. C1-INH concentrates are the drugs of choice in the treatment of HAE and AAE. In recent years, some new drugs have been introduced in the treatment of bradykinin-mediated angioedema, such as bradykinin B_2-receptor antagonist, icatibant, and kallikrein inhibitor, ecallantide, which allow to improve treatment outcomes.

Introduction Angioedema and chronic urticaria are the most common skin diseases. They may either co-occur or present as independent conditions. Their prevalence is estimated at approximately 15% to 20% of the population.[1] Incidental acute forms of these disorders are more common in children, while chronic forms develop in approximately 5% of the population, mainly adults.[2,3]

Angioedema is a result of increased vascular permeability in the deeper layers of the dermis and in the subcutaneous tissue,[4,5] and urticaria—in the superficial parts of the dermis. Statistical data indicate that 50% of patients present with concomitant urticaria and angioedema, while 40% of patients develop only urticarial lesions.[4,5] In 10% of patients, angioedema develops without concomitant urticaria. An angioedema attack is a serious clinical challenge due to its complex pathomechanism, difficulty in determining the causal factor, and varied response to symptomatic treatment among patients.[1,2,5] Clinical diagnosis is based on a history and characteristic features of edema.[3,5]

Angioedema is classified as allergic (immunoglobulin [Ig] E-dependent or non-IgE-dependent) or nonallergic (TABLE 1). Allergic angioedema often occurs with an inflammatory focus (including a parasitic focus) and an allergy to food, drug, or insect venom. Histamine is an essential mediator in this type of edema.[1,2,5] Effective treatment includes antihistamine drugs, glucocorticosteroids (GCS), and adrenaline. Nonallergic angioedema[1] is classified into 5 different types (TABLE 2): 1) hereditary angioedema (HAE); 2) acquired angioedema (AAE) due to C1 inhibitor (C1-INH) deficiency; 3) angioedema associated with the renin–angiotensin–aldosterone system blockade (RAE), for example, after the use of angiotensin-converting enzyme inhibitors (ACEIs); 4) pseudoallergic angioedema, in which the increase in bradykinin occurs as a result of direct kallikrein activation at normal levels and the activity of C1-INH; and 5) idiopathic angioedema. Bradykinin is the main mediator of HAE, AAE, and RAE.[1,5-10]

Pseudoallergic angioedema is a reaction that cannot be explained by allergic mechanisms despite the similarity of symptoms to allergic angioedema and similar susceptibility to medications. It is mostly the result of a drug action (eg, acetylsalicylic acid, nonsteroidal

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TABLE 1 Types of angioedema

Type of angioedema		Mediators	Efficient drugs
allergic	IgE-related	histamine, PAF bradykinin (late phase reaction)	–
	non-IgE-related	cysteine LTs, PAF	–
nonallergic	bradykinin-mediated without urticaria and pruritus	bradykinin	C1-INH, icatibant, ecallantide
	non-bradykinin-mediated often with urticaria	cysteine LTs	GCS, adrenaline

Abbreviations: C1-INH, C1 inhibitor; GCS, glucocorticosteroids; IgE, immunoglobulin E; LTs, leukotrienes; PAF, platelet activating factor

TABLE 2 Clinical types of nonallergic angioedema (bradykinin-mediated and non-bradykinin-mediated angioedema)

Type of angioedema	Cause	Mediator	Efficient drugs
hereditary angioedema	C1-INH deficiency FXII, kallikrein HMW heparin	bradykinin	C1-INH, recombinant C1-INH, kallikrein blocker bradykinin B_2-receptor inhibitor
acquired angioedema	C1-INH deficiency anti-C1-INH	bradykinin	as above
RAAS blocker-induced angioedema	ACEIs, AT1 blockers	bradykinin	as above
pseudoallergic angioedema	eg, NSAIDs	LTs	GCS, adrenaline
idiopathic angioedema	?	?	as above

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; FXII, factor XII; HMW, high-molecular-weight; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system; others, see **TABLE 1**

anti-inflammatory drugs) and is likely to be caused by leukotrienes.[1,4,5] Nonallergic idiopathic angioedema, whose pathomechanism is usually unknown, develops in patients with chronic nonallergic urticaria.[1] The mediators of angioedema and urticaria are various vasoactive inflammatory substances[1,2,3,5] released from effector cells (basophils, mast cells). Their characteristic features are presented in Supplementary material online (*Table S1*).

The clinical features of angioedema and its susceptibility to medications depend on the mediators that induce symptoms. Histamine and platelet activating factor (PAF) induce pruritus and edema that is susceptible to antihistamine drugs. Bradykinin does not cause pruritus and bradykinin-mediated angioedema is resistant to antihistamine drugs and to GCSs (Supplementary material online, *Figure S2*).

Bradykinin is a tissue hormone (autacoid), which was discovered in 1949 (Supplementary material online, *Table S2*). Similarly to histamine, it is a vasodepressor that relaxes vascular smooth muscles and, consequently, lowers blood pressure and increases vascular permeability.[1,3-5,8-10] Its vasodilating activity corresponds to the release of 3 potent mediators: tissue plasminogen activator , prostacyclin, and endothelium-derived vascular relaxing factor (**FIGURE 1**).

Bradykinin is generated from high- and low-molecular-weight kininogen via kallikrein (**FIGURE 2**). The inactive precursor, called bradykininogen, is present in plasma. The normal serum level of bradykinin is very low (0.2–7.1 fmol/ml).[10] Released bradykinin is inactivated very quickly. Bradykinin acts via the receptor-dependent mechanism (**FIGURE 1**). Bradykinin B_2-receptors (B_2R) are constantly present, while B_1-receptors (B_1R) are actively formed in the damaged tissue. The activation of B_2Rs has a bidirectional action because it induces angioedema as a consequence of vascular leakage, and it can provoke a cough as well as act as a cardioprotective factor.

Most authors recognize the essential role of B_2R of bradykinin in the induction of bradykinin angioedema. However, recent studies of Bossi et al[12] have indicated that the best inhibitory effect of vascular leakage induced by bradykinin is achieved with the combination of B_1R and B_2R antagonists. The authors have also emphasized a possible role of bradykinin degradation products on the worsening of acute edema.

The physiological activity of bradykinin is multidirectional[1,10-13]: 1) it increases the permeability of capillaries, leading to the development of local edema, warming, and erythema; 2) it irritates nerve endings, causing burning pain; 3) it dilates blood vessels (in the skin, striated muscles, kidneys, brain, and viscera); 4) it dilates coronary vessels by paralyzing vascular smooth muscles, thus reducing arterial blood pressure; 5) it constricts smooth muscles of other organs such

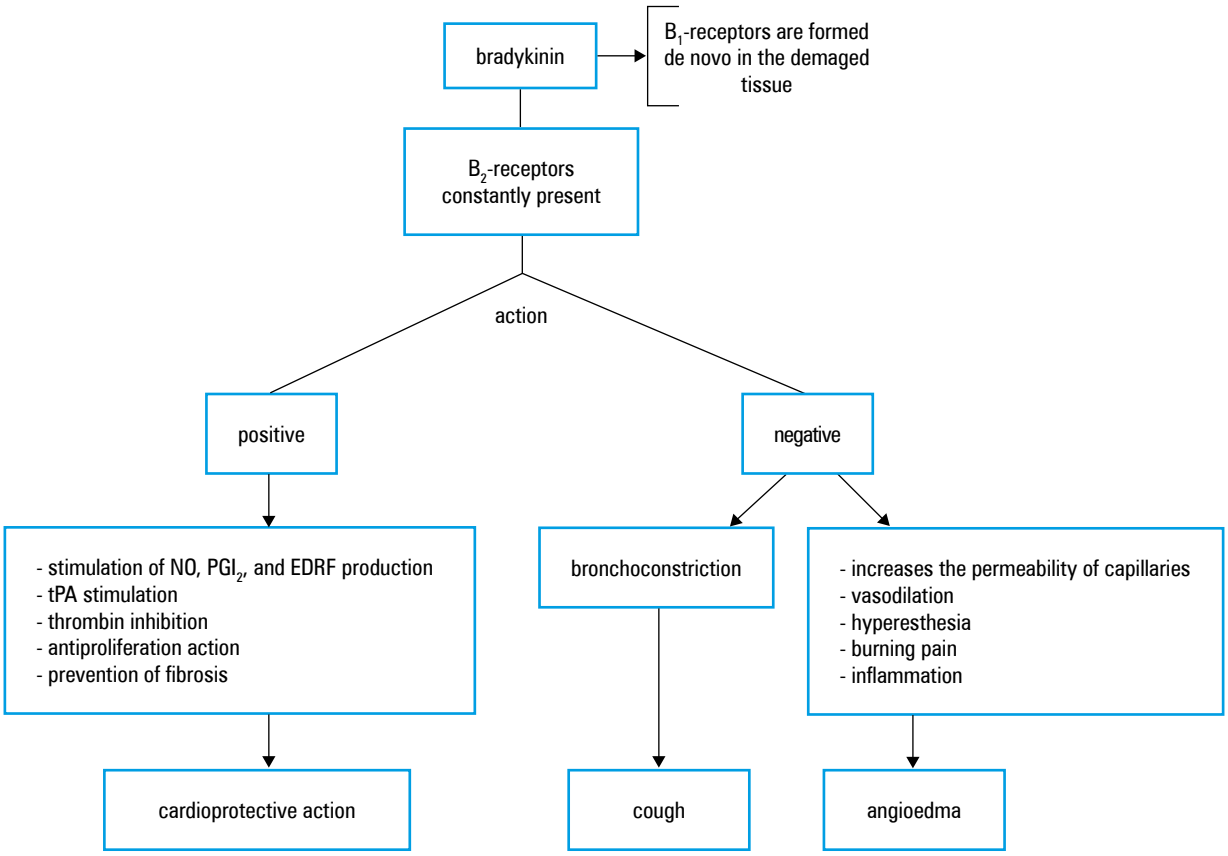
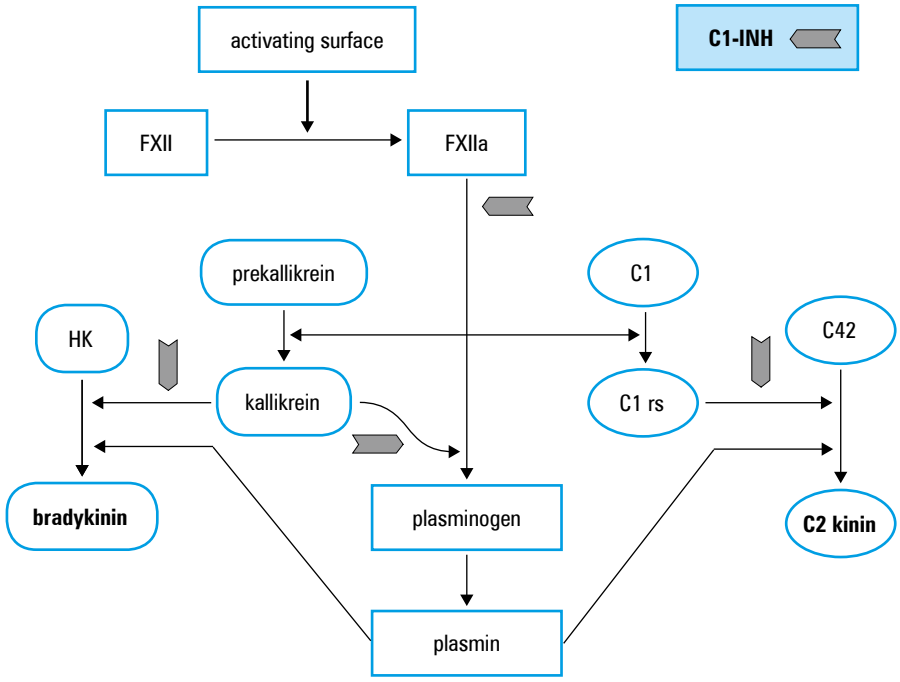


FIGURE 1 Bradykinin receptor action

Abbreviations: NO, nitric oxide; tPA, tissue plasminogen activator; PGI_2, prostacyclin; EDRF, endothelium-derived vascular relaxing factor

FIGURE 2 Bradykinin production in the body
Abbreviations: see TABLES 1 and 2



as the bronchi and uterus; 6) it increases the release of catecholamines from the adrenal glands; 7) it activates the contact system[7,13,14]; 8) it induces bradykinin-mediated edema[1,10]; and, finally, 9) it stimulates the production of potent vascular mediators by the endothelium.

Bradykinin seems to be the basic mediator of nonallergic angioedema in patients with HAE and AAE caused by C1-INH deficiency.[1,4,5,7-10] Moreover, recent studies have suggested that bradykinin can also mediate the late phase of an immediate allergic reaction.[1,12]

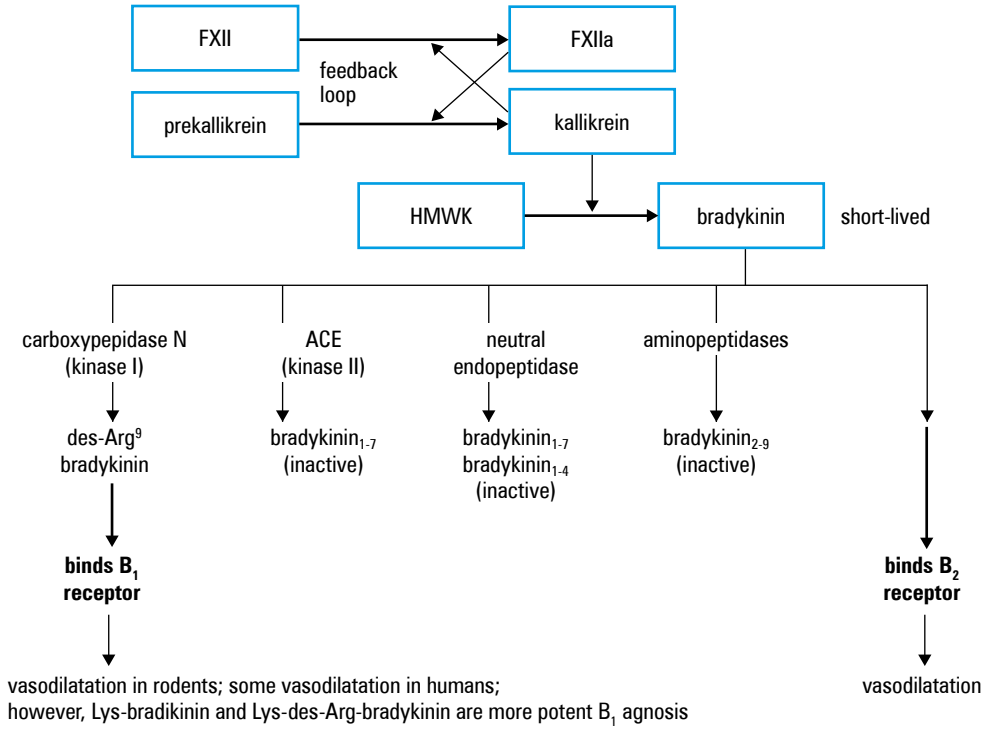


FIGURE 3 Bradykinin production and degradation
Abbreviations: ACE, angiotensin-converting enzyme; HMWK, high-molecular-weight kininogen; others, see TABLES 1 and 2

The serum level of bradykinin is affected by numerous factors[1,7-10] including the complement, contact, and kinin systems, fibrinolysis, inflammatory factors, as well as numerous endogenous substances, metabolites, and enzymes essential for bradykinin inactivation (Supplementary material online, *Table S3*).

In the proper inactivation of bradykinin and other kinins, angiotensin-converting enzyme (ACE), kinase II, plays the essential role (FIGURE 3). ACE is an exopeptidase that generates the formation of vasoconstricting angiotensin II (ATII) through the activity of the ATII-receptor (Supplementary material online, *Figure S1*).[1,14-17] ACEIs and AT1 inhibitors (renin–angiotensin–aldosterone system [RAAS] blockers) may cause bradykinin-mediated angioedema by blocking the destruction of bradykinin and by activating B_2R.[1,8-11] They inhibit the formation of ATII by interfering with the RAAS, thus blocking the destruction of bradykinin. An increase in kinin-like substances (especially Des-Arg-bradykinin) often manifests itself in an angioedema attack on the tongue. Such angioedema is resistant to antihistamine drugs. Only from 0.1% to 0.5% of patients treated with ACEIs develop bradykinin-mediated edema.[4,15,18,19]

Recent studies[1,7-10,12] have indicated that bradykinin-mediated edema can be induced by numerous substances, including drugs that affect the formation of bradykinin or the reactivity of its receptors, especially those with effects on the RAAS system (Supplementary material online, *Table S3*). This activity can be potentiated by the concomitant administration of other drugs with a similar action, for example, ACEIs with other drugs that block the natural degradation of bradykinin (eg, aliskiren) or with ATI receptor antagonists.[1,15,17-20] The risk of developing bradykinin-mediated edema, which can be life-threatening, after taking such drugs is significantly higher in individuals with C1-INH deficiency.[1,15]

Currently, there is a substantial body of evidence documenting significant associations between bradykinin-mediated edema and the RAAS.[1,17-19] This is also found in individuals with a normal function of the complement system.

Clinical forms of bradykinin-mediated angioedema Bradykinin-mediated angioedema is a non-allergic type of edema. The diagnosis is based on its characteristic clinical features. The edema increases slowly (up to 24 hours), is self-limited, usually achieves a large size, and disappears spontaneously within 2 to 5 days. It is not accompanied by either itchiness or hives and is resistant to treatment with GCSs and antihistamine drugs. Usually, during an attack, the edema develops at 1 site in the body. However, it may develop simultaneously at several sites. Most frequently, it appears on the feet, hands, face, or genitals as external angioedema. Submucosal edema of an internal organ usually affects the larynx and gastrointestinal tract.

Symptoms are related to the affected organ. Attacks of bradykinin-mediated angioedema occur in individuals with HAE and AAE C1-INH deficiency (because of an easy activation of the complement system, plasma contact system, and kinin system). Under some conditions, C1-INH deficiency may result in an uncontrolled overproduction of kallikrein and bradykinin. This causes a leakage of fluid from the capillaries to the surrounding tissue, resulting in painful angioedema.[8,16,18,21] The attacks are also observed in individuals with increased activity of factor XII and kallikrein due to the use of various agents (even in individuals without C1-INH deficiency)[1,10,12-14] and in individuals with impaired bradykinin inactivation

(Supplementary material online, *Table S2*) or increased expression of bradykinin B_2Rs.[1,7,8,10]

The findings from recent experimental and clinical studies[12-15,22-26] have contributed to a significant progress in our understanding of bradykinin-mediated angioedema. There is no doubt that genetic changes, especially those connected with mutations in the C1-INH and factor XII genes, play an essential role in the pathomechanism of this condition. The gene for C1-INH (ie, *SERPING1*) is particularly susceptible to mutation. More than 200 different mutations of the C1-INH gene have been identified[26] as the cause of hereditary angioedema in the gene governing the production of C1-INH,[1,18,21,26,27] located on the long arm of chromosome 11 (11q12-q13.1).

These genetic changes cause the C1-INH to be defective and predisposed to an uncontrolled kallikrein and bradykinin overproduction in the course of HAE due to C1-INH deficiency, which is a rare disease with autosomal dominant inheritance.[1,18,26] Bradykinin-mediated edema may also appear in cases of mutations in the factor XII gene, located on chromosome 5, in patients with normal functional and antigenic levels of C1-INH.[28-34] Mutations in factor XII (ie, Hageman factor) lead to its hyperactivity and, in consequence, to an increase in the bradykinin production, despite normal C1-INH, thus provoking an attack of bradykinin-mediated angioedema (HAE type III). The diversity of mutations in patients with HAE types I, II, and III suggests that HAE is a heterogeneous disease with similar clinical manifestations.

In recent years, numerous authors have also noted the essential role of the plasma contact system in the pathomechanism of HAE.[13,23,25,35] Zahedi et al[36] strongly suggested that the activation of the complement system alone (without the involvement of the contact system) does not cause angioedema. In the human body, there are numerous physiological activators of the plasma contact system (DNA/RNA, collagens, endotoxin, lipopolysaccharides, and fatty acid) as well as nonphysiological activators (polyethylene, dextran sulfate, microbial enzymes, and numerous other endogenous and exogenous agents[13,23,25]). They are often difficult to identify and may trigger bradykinin-mediated angioedema. Also, factor XII seems to be a very important activator of the contact system, which leads to the generation of bradykinin.[14,37]

The status of the endothelium—its continuity, tightness, and smoothness in responding to its normal function—is of fundamental interest to bradykinin-mediated angioedema.[38-41] Bossi and Bulla[12] indicated that the products of complement system activation can modulate endothelial function. Receptor C5a seems to play an important role by increasing endothelial permeability mediated by bradykinin and PAF. This effect is blocked by the B_2R antagonist (icatibant) and selective PAF receptor antagonist.

French studies indicated that the integrity of the endothelial cell–cell junction depends on the adhesive function, the cell-surface expression of vascular endothelial cadherin,[23,39] and the soluble E-selectin levels, which increase during the periods between attacks.[40]

Other authors indicated that the serum level of the atrial natriuretic peptide inversely correlates with the severity of HAE symptoms and may protect against HAE attacks.[41]

The results of some studies on the role of the lectin complement pathway in the pathomechanism of bradykinin-mediated angioedema[42-44] suggested an involvement of the ficolin-dependent lectin complement pathway in the pathophysiology of HAE-C1-INH. They confirmed the hypothesis that the ficolin–lectin pathway plays a more dominant role in the pathomechanism of HAE-C1-INH than mannose-binding lectin (MBL) does. Low concentrations of ficolin 2 (L ficolin) and ficolin 3 (H ficolin or Hakata antigen) were inversely correlated with the severity of HAE C1-INH, while this was not observed for MBL. The activation of the ficolin–lectin pathway via ficolin 2 and 3 by triggering C-activation pathogens may deplete the innately low level of C1-INH and provoke the uncontrolled activation of the plasma cascade systems and edema formation.[44-48]

The results from a study by Dobo et al[49] suggested a direct bradykinin release by a mannan-binding lectin serine protease 1 (MASP-1) in a mechanism independent of factor XII and kallikrein. According to a study of Matsushito and Fujita,[50] it seems that the overactivation of the MBL pathway, leading to C1-INH consumption by MASPs, might be an additional factor modifying HAE. Further studies on all activation pathways of the complement in the context of the clinical parameters of HAE may be worthwhile.

In recent years, there has been increasing interest in the role of mast cell-derived high-molecular-weight heparin (MCH) in the pathomechanism of bradykinin-mediated angioedema. The studies of Bjorkqvist et al,[13] Renné et al,[14] and Oschatz et al[24] indicated that MCH is a potential trigger of factor XII activation resulting in bradykinin generation.[13,14,24,25] The authors suggested that in some patients with HAE, swelling attacks may even be triggered in allergic or direct reactions to food, drugs, or insect stings. Also the studies of other authors indicated an action of platelet-derived polyphosphate similar to that of MCH.[37,38] These results confirm earlier reports indicating that IgE-mediated mast-cell activation causes the release of MCH.[51,52] This reaction is inhibited by the B_2R antagonist (icatibant). MCH release mediated by various allergens (drugs, food products) may directly trigger factor XII and provoke bradykinin-mediated edema in vivo. Activated mast cells might be a trigger for an edema in inflammatory and allergic diseases[24] as well as a potential initiator of swelling attacks in HAE.

A recent study by Stephan et al[53] has pointed to factor VII-activating protease, which is a plasma serine protease activated by apoptotic cells, DNA, and glycosaminoglycan, as a factor that may also generate bradykinin from high-molecular-weight kininogen. It forms complexes with C1-INH and may be also crucial in the pathogenesis of inflammation as well as bradykinin-mediated edema.

New data have been reported by Bossi et al[12] who stressed the role of the increased activity of B_2R in the development of some types of bradykinin-mediated angioedema and on the inhibitory effect of vascular leakage in this type of angioedema with the combination of B_1R and B_2R antagonists. The authors also suggested a possible effect of degradation products of bradykinin on the worsening of acute attack of HAE or other types of bradykinin-mediated angioedema by the generation of B_1R-reacting substances from bradykinin. The possible accumulation of desAGR9 bradykinin (a ligand of B_1R) seems not to be inhibited by plasma-derived C1-INH.

Characteristic features of bradykinin-mediated edema

External edema Characteristic features of external edema, which usually affects the foot, hands, face, and genitals are as follows: it increases slowly (up to 24 hours), achieves large sizes, disappears spontaneously within 2 to 5 days, is not accompanied by pruritus or urticaria, is resistant to GCSs and antihistamine drugs, it usually develops locally at 1 site on the skin (rarely at several sites), and it may be accompanied by marginal erythema (Supplementary material online, *Figure S3*).

Internal organ edema Internal organ edema usually affects the larynx or gastrointestinal tract. Symptoms are similar to those of external angioedema in that it increases slowly, disappears spontaneously within 2 to 5 days, and is resistant to GCSs and antihistamine drugs.

Hereditary angioedema due to C1-inhibitor deficiency

HAE was first described in 1882 by Heinrich Quincke[16] as self-limited angioedema without hives and itchiness. The disorder develops in individuals with a hereditary deficiency of C1-INH that is responsible for numerous biological activities in the human body.[3,5,16] HAE is inherited as an autosomal dominant trait. A family history is positive in 75% of patients. In about 25% of patients, the mutations occur de novo, and their family history is negative.[26,54] The level and activity of C1-INH is decreased in about 85% of patients (HAE type 1), while in 15% of patients, the level is within the reference range but the activity is decreased (HAE type II).[55] The lowering of the C1-INH level and activity (>40% of the low border value) is a diagnostic criterion.[54] HAE is a rare disease (1 patient per 10 000–50 000 people), with autosomal dominant inheritance, caused by mutations in the gene governing the production of C1-INH,[3,5,16,21,54] located on the long arm of chromosome 11 (11q12-q13.1). Prenatal diagnosis is possible although rarely used. DNA analysis allows to establish the presence of a mutation in the *SERPING1* gene, confirming the diagnosis. More than 200 different mutations in this gene have been identified.[26]

C1-INH deficiency may cause an uncontrolled overproduction of kallikrein and bradykinin. Increased bradykinin levels result in leakage of fluid from capillaries to the surrounding tissue, resulting in painful swelling.

In recent years, HAE type III has been described,[28,30,58] in which the level and the activity of C1-INH is within the reference range. HAE type III is caused by mutations in the factor XII gene, located on chromosome 5 (5q33-qter).[29,31,32] This type of HAE may be associated with the missense mutation 1032A/G on exon 9 of the factor XII gene, causing a gain in the function of factor XII and a predisposition to overproduction of bradykinin.[34]

HAE manifests itself in episodic attacks of self-limited subcutaneous swelling (Supplementary material online, *Figures S2* and *S3*), mainly affecting the hands, feet, and face, or as submucosal angioedema of the pharynx and larynx. It sometimes manifests itself as abdominal attacks because of angioedema of the gastrointestinal tract, urinary tract, or reproductive organs.[1,5,16-21,54] The first symptoms of HAE types I and II are most common in childhood and puberty.[16,21,54]

Bradykinin-mediated angioedema of the face and larynx is the most dangerous. In the case of a misdiagnosis and typical drug resistance, it may be life-threatening and may cause an individual to stop breathing for a period from 30 minutes up to a few hours[56] (Supplementary material online, *Figure S4*).

The precipitating trigger factors of bradykinin-mediated angioedema in patients with HAE include trauma, surgical procedures, tissue injury, pressure on the skin or mucous membranes, infections, stress leading to the activation of the complement system, contact system, or fibrinolytic cascades, increase of bradykinin and bradykinin edema.

Also estrogens,[18,19] which increase the reactivity of bradykinin B_2R, and ACEIs,[15,18] which diminish the metabolism of bradykinin, may provoke an attack of angioedema in patients suffering from HAE. In recent years, some allergens (food products, drugs) have also been suspected of triggering bradykinin-mediated angioedema[13,14,24] as a result of releasing MCH from activated masts cells, which directly activates factor XII and thus may induce bradykinin edema even in cases with normal C1-INH levels.

In diagnosing abdominal attacks in patients with HAE, an abdominal ultrasonography is recommended.[25,57] It may reveal a circumscribed edema (eg, of the intestines) and, often, the presence of fluid in the abdominal cavity[16,19,57] (Supplementary material online, *Figure S5*).

Symptoms of an edema attack in patients with HAE type III are similar to those in patients with HAE types I and II. An increase in factor XII activity and in FXII gene mutation allow to diagnose these types of HAE.[28-30,54] The first edema attacks in patients with HAE type III usually develop in adults. Their family history of angioedema is negative. Most often, it appears as an edema of the face, larynx, or tongue.[28,32,54] A lack of response to GCSs and antihistamine drugs may also be a characteristic feature.[58]

Acquired bradykinin-mediated angioedema The first AAE attack was described in 1972.[6] Clinical symptoms are similar to those observed in HAE. An edema develops in adults with a negative family history.[6,16,54] There are 2 subtypes of AAE.[6,16] AAE type I is connected with a decrease in C1-INH concentrations in the course of lymphoproliferative diseases usually connected with B lymphocytes and an increase in C1-INH wear-off. AAE type II, first described in 1986, develops in individuals with autoimmunization and the presence of autoantibodies against the C1-INH.

The activities of C1-INH and C4 in both types of AAE are usually very low. In contrast to HAE, in AAE, usually the C1q level is low.[6,54]

Bradykinin-mediated angioedema by renin–angiotensin–aldosterone system blockers The best known and most common RAE is an edema of the tongue after the use of ACEIs in patients treated for hypertension (Supplementary material online, *Figure S6*).[1,4,15,54] It can also be induced by AT1-receptor blockers.

The development of edema does not depend on the time of drug administration, although in 50% of patients, it develops within the first week of the therapy.[1,4,15] A 4-fold increase in the risk of angioedema has also been observed in patients treated for hypertension with concomitant administration of ACEIs and a peptidase inhibitor (omapatrilat).[1] An increase in bradykinin concentration and edematous reactions are also caused by the administration of AT1-receptor blockers.[1] The activation of AT1 receptors stimulates bradykinin production inhibiting ACEIs; however, the natural endopeptidase impairs bradykinin degradation by inhibiting the release of renin.[1,15,17] Estrogens[18,19] and antiandrogens[1,20] seem to exacerbate the symptoms of bradykinin-mediated edema by increasing B_2R activity.

Treatment of bradykinin-mediated edema in patients with hereditary angioedema In the case of an external edema attack of HAE, usually no treatment is required. Edema resolves in 2 to 4 days. If the edema is troublesome for the patient, then tranexamic acid at a dose of 3 × 500 mg/d may be administered or anabolic steroid (Danazol) at a dose of 200 to 400 mg/d for a few days.[18,22,54] In the case of children, the doses are adjusted to their weight.[59,60]

In severe and life-threatening attacks (edema of the face, neck, larynx, pharynx, or severe abdominal organ edema) C1-INH concentrate (Berinert, Cynryze) at a dose of 20 U/kg[59-67] should be administered immediately, or recombinant human C1-INH (Ruconest) at a dose of 50 U/kg.[54,68-70] Alternatively, icatibant, bradykinin 1 B_2R blocker, may be administered subcutaneously.[54,71-74] If none of these drugs are available, fresh frozen plasma should be used.[54,56,60] The treatment should be started as quickly as possible.

In cases of severe hereditary angioedema attacks, the patient may be trained in home treatment. This type of treatment is highly appreciated by patients.[75] Home treatment with self-administration of C1-INH is a feasible option. Early C1-INH treatment during an attack shortens its duration and reduces its severity more effectively.[76-80] In addition, this might facilitate prophylactic treatment in patients with very frequent angioedema attacks.[81-85]

In life-threatening bradykinin-mediated edema of the pharynx or larynx, if the threat of asphyxion is present, conicotomy is necessary. Intubation is not indicated because of an increase in plasma contact system activity. The patient requires immediate treatment with C1-INH concentrate.

In the case of severe abdominal attack and after the exclusion of other reasons for acute abdominal symptoms, the patient should be given analgesics and relaxants.[16,57] Natural or recombinant human C1-INH concentrate or a bradykinin B_2R blocker is needed according to international recommendations.[54]

If there are any further diagnostic problems in patients with HAE before laparotomy, human or recombinant C1-INH concentrate should be administered prophylactically for diagnostic purposes. GCSs, antihistamine drugs, tranexamic acid, and anabolic steroids may be administered only as adjuvant therapy.

The treatment of edema in patients with RAE due to the use of ACEIs and AT1-receptor blockers is symptomatic.[15-18] Prevention includes the withdrawal of the drugs provoking the attack.[1,4,20,54] ACEIs and AT1-receptor antagonists may be replaced by calcium antagonists or β-adrenolytic drugs.

Chronic treatment in patients with hereditary angioedema is instituted if the frequency of attacks is more than once a month.[18,54] The following orally administered hormonal anabolic drugs are used at a minimum efficient dose: anabolic steroid or tranexamic acid.

Short-term preventive treatment is used in patients with HAE and AAE to prevent an edema during or after surgical, dental, and diagnostic procedures with the use of instruments (endoscopy). Before the surgery (2–6 hours), patients are administered C1-INH or anabolic drugs for 3 to 5 days.[18,54,86-88] Chronic preventive treatment is considered in patients with the severe course of HAE or AAE, when the number of attacks is higher than once a month.[18,54,88] In milder cases, oral anabolic drugs are used in a long-term treatment

(anabolic steroid, stanazolol, or tranexamic acid). In more severe cases, a chronic treatment with C1-INH formulations should be considered. In such cases, the drugs are administered twice a week for a few months.[54]

Recently, a novel plasma kallikrein inhibitor (ecallantide, DX88) has been applied in the treatment of patients with HAE in the United States. This mediator is essential for the production of bradykinin and in the development of angioedema in patients with HAE.[89-93] The results from double-blind clinical trials concerning the efficacy of subcutaneous treatment for acute attacks of HAE are promising and indicate new treatment possibilities of bradykinin-mediated angioedema.[54,94,95]

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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ARTYKUŁ POGLĄDOWY

Bradykininowy obrzęk naczynioruchowy

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SŁOWA KLUCZOWE

bradykinina, inhibitor C1, inhibitory układu renina–angiotensyna–aldosteron, obrzęk naczynioruchowy

STRESZCZENIE

Obrzęk naczynioruchowy i pokrzywka stanowią częsty problem w codziennej praktyce lekarskiej. Schorzenia te mogą występować równocześnie lub niezależnie od siebie. Charakteryzuje je złożony patomechanizm, a ich objawy mogą być wywoływane przez różne czynniki – różnice te są istotne dla opracowania skutecznego planu leczenia. Zarówno obrzęk naczynioruchowy, jak i pokrzywka mogą mieć podłoże alergiczne (IgE-zależne i IgE-niezależne), zwykle indukowane histaminą, lub niealergiczne, jak np. obrzęk naczynioruchowy indukowany bradykininą u chorych z niedoborem inhibitora C1 lub obrzęk naczynioruchowy indukowany niektórymi lekami (np. inhibitorami konwertazy angiotensyny). Obecnie wyróżnia się 5 odmian niealergicznego obrzęku naczynioruchowego: wrodzony związany z niedoborem inhibitora C1 (*hereditary angioedema* – HAE), nabyty (*acquired angioedema* – AAE) i indukowany inhibitorami układu renina–angiotensyna–aldosteron (wszystkie 3 indukowane bradykininą) oraz pseudoalergiczny i idiopatyczny. Obrzęki mediowane bradykininą (np. obrzęk krtani) mogą stanowić zagrożenie życia wskutek oporności na glikokortykosteroidy i leki przeciwhistaminowe. Lekami z wyboru w leczeniu HAE i AAE są koncentraty inhibitora C1. Ostatnio do leczenia obrzęków bradykininowych wprowadzono nowe leki, jak ikatybant (antagonista receptorów B2 bradykininy) czy ekalantyd (inhibitor kalikreiny), które pozwalają poprawić wyniki leczenia.

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