

Angioedema

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Although first described more than 130 years ago, the pathophysiology, origin, and management of the several types of angioedema are poorly understood by most dermatologists. Although clinically similar, angioedema can be caused by either mast cell degranulation or activation of kinin formation. In the former category, allergic and nonsteroidal anti-inflammatory drug-induced angioedema are frequently accompanied by urticaria. Idiopathic chronic angioedema is also usually accompanied by urticaria, but can occur without hives. In either case, an autoimmune process leading to dermal mast cell degranulation occurs in some patients. In these patients, histamine-releasing IgG anti-FcεR1 autoantibodies are believed to be the cause of the disease, removal or suppression by immunomodulation being followed by remission. Angiotensin-converting enzyme inhibitor-induced angioedema is unaccompanied by hives, and is caused by the inhibition of enzymatic degradation of tissue bradykinin. Hereditary angioedema, caused by unchecked tissue bradykinin formation, is recognized biochemically by a low plasma C₄ and low quantitative or functional C₁ inhibitor. Progress has now been made in understanding the molecular genetic basis of the two isoforms of this dominantly inherited disease. Recently, a third type of hereditary angioedema has been defined by several groups. Occurring exclusively in women, it is not associated with detectable abnormalities of the complement system. Angioedema caused by a C₁ esterase inhibitor deficiency can also be acquired in several clinical settings, including lymphoma and autoimmune connective tissue disease. It can also occur as a consequence of specific anti-C₁ esterase autoantibodies in some patients. We have reviewed the clinical features, diagnosis, and management of these different subtypes of angioedema. (*J Am Acad Dermatol* 2005;53:373-88.)

Learning objective: After completing this learning activity, participants should be aware of the classification, causes, and differential diagnosis of angioedema, the molecular basis of hereditary and non-hereditary forms of angioedema, and be able to formulate a pathophysiology-based treatment strategy for each of the subtypes of angioedema.

WHAT IS ANGIOEDEMA?

Angioedema refers to abrupt and short-lived swelling of the skin, mucous membranes, or both including the upper respiratory and intestinal epithelial linings.¹ The swelling is nonpitting, erythematous or skin-colored, and shows a predilection for areas where the skin is lax rather than taut (especially the face and genitalia). In the skin, heat and pain are variable additional symptoms, but there is rarely any itching. There is no desquamation or staining of the skin although scratching or rubbing may cause bruising.

Abbreviations used:

ACE:	angiotensin-converting enzyme
COX:	cyclo-oxygenase
HAE:	hereditary angioedema
NSAID:	nonsteroidal anti-inflammatory drug
TNF:	tumor necrosis factor
IL:	interleukin
LI:	leukotriene
NAP:	neutrophil activating protein
TAFI:	thrombin-activated fibrinolysin inhibitor

Pathophysiology

The pathophysiology of angioedema consists of rapid onset of local increase in permeability of the submucosal or subcutaneous capillaries and post-capillary venules, causing local plasma extravasation and consequent ephemeral swelling. A variety of vasoactive molecular mediators cause plasma extravasation. Preformed mast cell-derived mediators include histamine and proteases such as tryptase. These are classically associated with acute allergic angioedema, but mast cell mediators synthesized

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Table I. Comparison of features of angioedema and urticaria

Feature	Urticaria	Angioedema
Pathology	Papillary dermal, vasodilation +++, edema +, sparse perivascular infiltrate of mainly neutrophils, eosinophils, monocytes and T-lymphocytes	Reticular dermal, subcutaneous/submucosal edema +++ vasodilation +/-; little or no cellular infiltrate, except in allergic angioedema where eosinophils may be seen
Clinical Location	Skin only	Skin and mucosae
Duration	Transitory (<24 h)	Transitory (24-48 h)
Color of lesions	Red	Pink or skin colored
Itch	Almost invariable	Variable
Pain, tenderness	Rare	Common

de novo including cyclooxygenase (COX) products, especially prostaglandin D₂, cysteinyl leukotrienes, cytokines and chemokines may also be involved. Apart from allergic angioedema in which eosinophils may be prominent, there is a paucity of cellular infiltration in angioedema. However, the participation of mediators released by immigrant cells including macrophages, lymphocytes, eosinophils, and neutrophils is probable. Some forms of angioedema are mediated by vasopermeability agents derived from plasma and tissue fluids, notably bradykinin and complement components. These will be discussed in more detail in later sections.

Historic

Although a number of earlier published accounts mentioned conditions apparently resembling angioedema, in 1876 the first detailed account was by Dr John Laws Milton,² the founder of St John's Hospital for Diseases of the Skin, London, United Kingdom, entitled "On Giant Urticaria" and published in *The Edinburgh Medical Journal*. Therein he described in detail 6 patients with typical angioedema and, in closing, noted that he "wished to be understood as merely suggesting the title (giant urticaria)." Twelve years later William Osler³ distinguished hereditary angioedema (HAE) as a separate entity from the commoner acquired types after a study of episodes of angioedema in 5 generations of a single family. The most recent major advance in terms of origin was in 1963 when Donaldson and Evans⁴ published the first report of an inherited deficiency of C'1 esterase inhibitor in this condition.

Epidemiology

The epidemiology of urticaria and angioedema has been poorly studied. Champion et al,⁵ in a study of 554 patients, found 49% of all patients with urticaria also had angioedema. Angioedema

occurred alone in 11%. In a recent series⁶ from England, angioedema occurred in 93 of 107 (87%) patients with chronic urticaria. Women are more frequently affected than men, and the condition most commonly affects those 40 to 50 years old. There are some data to suggest that angioedema, which is idiopathic (ie, no identifiable cause), is actually more common in men⁷ provided there is no concomitant urticaria.

How do urticaria and angioedema differ?

Urticaria, unlike angioedema, rarely affects mucosal surfaces, but the incidence of mucosal involvement varies with the cause. However, there are no fundamental differences between lesions of angioedema and urticaria. Urticarial wheals involve the papillary dermis and mid-dermis, whereas angioedema involves the reticular dermis and subcutaneous or submucosal tissue. In both cases the main change is local vasodilation and increased vascular permeability. Itch is an almost invariable symptom of urticaria, but is inconstant in angioedema, which may instead manifest pain and tenderness. The main differences and similarities between urticaria and angioedema are summarized in Table I.

Differential diagnosis

Referral of patients to the dermatology or allergy clinic with swollen skin or mucosae erroneously labeled as angioedema is a frequent occurrence. Conditions that masquerade as angioedema are listed in Table II.

Classification of angioedema

Angioedema is conventionally classified into those clearly mediated by bradykinin and those dependent on mast cell degranulation or other unknown mechanisms (Table III). With the notable

exception of angiotension-converting enzyme (ACE) inhibitor-induced angioedema, acquired forms are typically associated with concurrent urticaria, but patients with angioedema associated with C1 esterase inhibitor depletion, even when acquired rather than hereditary, are typically devoid of urticaria (Table III).

Acute allergic angioedema

Acute allergic angioedema is almost invariably accompanied by urticaria and both usually occur within 1 to 2 hours of exposure to the offending allergen. Its onset is reliant on prior sensitizing exposure. It is commoner in patients who are atopic but allergic reactions to foods or medications may be seen in the absence of diseases associated with atopy, ie, allergic rhinitis, extrinsic asthma, and atopic dermatitis. Reactions are self-limited, typically 1 to 3 days, but will recur with repetitive exposures or exposure to cross-reactive substances.

Pathophysiology

The target cell in the skin is the dermal mast cell. The reaction is dependent on sensitization of the mast cells by specific IgE that is bound to the high-affinity IgE receptor FcεR1. Exposure to specific antigen causes cross-linking of adjacent high-affinity IgE receptors, which leads to activation of intracellular tyrosine kinases by immunoreceptor tyrosine kinase activation motifs located in close relation to the γ-chains of FcεR1. Subsequent steps including protein kinase C activation, and increase in intracellular calcium leads to release of preformed mediators by degranulation followed by secretion of synthesized mediators. Histamine, tryptase, and chymase are among the granule-associated products. Mast cell activation also leads to transcription of a variety of cytokines including TNF-α and IL-3, IL-4, and IL-5 synthesis of eicosanoids including the lipooxygenase products LTC₄ and LTD₄ and the COX product PGD₂, and transcription of chemokines such as IL-8 (NAP-1).

Causative factors

Common causative factors are listed in Table IV.

Clinical features

Sites of predilection include the face, especially the lips and periorbital area; the extremities; and the genitalia, but the swellings can occur anywhere. In severely affected patients mucosal edema may involve the tongue, throat, and larynx occasioning dyspnea and acute distress. Acute allergic angioedema may be accompanied by anaphylaxis with acute dyspnea (asthma as a result of bronchospasm or stridor caused by laryngeal edema), and signs and

Table II. Differential diagnosis of angioedema: pseudoangioedema

Facial cellulitis	Lasts for several days, painful, often associated with fever, followed by peeling
Acute contact allergic or photodermatitis	Associated with itching, vesiculation, scaling, lasts longer than 24-48 h
Crohn's disease of mouth and lips	Causes granulomatous swelling of lips complicated by lymphoedema. Patients often show cobblestone thickening of buccal mucous membrane
Dermatomyositis	Presents with heliotrope (violaceous) edema of the eyelids, which is persistent
Facial lymphoedema	Classically associated with rosacea, or rarely Melkersson-Rosenthal syndrome
Tumid discoid lupus	Red edematous plaques on light-exposed areas of the face, persistent, may cause scarring
Ascher syndrome ⁸	Recurrent episodes of eyelid edema leading to blepharochalasis
Melkersson-Rosenthal syndrome	Granulomatous swelling of lips that is persistent; can be associated with lingua plicata and/or Bell's palsy.
Superior vena cava syndrome	Edema of the eyelids, lips, associated with venous engorgement

symptoms of shock, but there is no fever. There may be associated abdominal pain and vomiting, especially if an offending allergen was ingested.

Swellings will normally subside in around 24 hours but relapses are common and unpredictable, and concomitant urticaria can sometimes last for 1 to 3 weeks with some drug reactions. Most patients show associated urticarial wheals and experience itching. The swellings of angioedema resolve without staining of the skin unless vigorous rubbing and scratching occurs. Investigations are normally unremarkable. Contact urticaria (in which contact of the skin with an allergen causes immediate hives at the site of contact) may be complicated by angioedema and even severe anaphylaxis. In these cases the reaction is IgE mediated.⁹

Table III. Classification of angioedema¹

Angioedema	Comment
Allergic	IgE mediated, usually with urticaria
NSAID-induced	Frequently accompanied by urticaria
Idiopathic angioedema	No urticaria
Associated with idiopathic or autoimmune chronic urticaria	60% idiopathic; 40% autoimmune
Associated with urticarial vasculitis	—
Infections and infestations	Usually with urticaria
Angioedema with eosinophilia	—
Associated with some physical urticarias and with cholinergic urticaria ⁴¹	See Table VI
Associated with allergic contact urticaria ⁹	—
C'1 INH deficiency-hereditary angioedema	Types 1 and 2, no urticaria
Hereditary angioedema with normal C'1 INH in women	No urticaria
Angiotensin-converting enzyme inhibitor-induced	No urticaria
Acquired C'1 INH deficiency	Autoimmune, or secondary to lymphoma, no urticaria

Table IV. Common causes of acute allergic angioedema

Foods, especially peanuts, shellfish, milk, eggs, tree nuts, and foods containing allergens cross-reactive with latex (eg, kiwi fruit, banana, avocado, and chestnut)
Drugs, especially penicillin and sulfa drugs and their derivatives
Insect venoms (stinging) and the fire ant
Radiocontrast media (may be allergic or pseudoallergic)

Diagnosis and differential diagnosis

Like acute urticaria, diagnosis of acute angioedema depends principally on the history. Most patients or their care givers are fully aware of the association of one or other of the allergens or drugs listed in Table IV with the onset of acute angioedema.

Virus infections are a rare cause of angioedema although parvovirus B19 infection is a recognized cause of angioedema in neonates (vide infra).¹⁰

Exercise-induced anaphylaxis, with or without relationship to foods, although rare, may be a source of confusion.^{11,12} Patients with this condition have angioedema with or without urticaria and acute systemic symptoms associated with exercise. It is commonly associated with jogging and the exercise required to produce symptoms is often substantial; it is far less predictable than is cholinergic urticaria. In some patients, reactions occur only if exercise is preceded by eating. In one group of patients the reaction to food is specific; ie, only selected items cause the reaction and they have evidence of positive skin tests (ie, IgE-mediated hypersensitivity) to the food. In others the reaction is provoked by exercise after any meal. Ingestion of food alone without exercise does not provoke symptoms, and

likewise exercise alone is insufficient to evoke a response.^{12,13} In general, a 5-hour interval between eating and exercise prevents anaphylaxis, except for angioedema, onset of which is provoked by exercise but unrelated to food.

Skin prick testing, which demonstrates the existence of specific IgE-mediated hypersensitivity, may provide supportive information in some instances, especially where a food allergen or penicillin is thought to be involved. However, this procedure is not devoid of risk, especially in patients with a history suggestive of anaphylactic hypersensitivity, and should be carried out with caution and ready availability of cardiopulmonary resuscitation equipment. Radioallergosorbent serum testing to detect circulating specific IgE antibodies is occasionally helpful, mainly for suggested penicillin allergy, although these only give evidence of reactivity to the major determinant, analogous to the skin testing reagent penicilloyl polylysine. But reagents to test minor determinant reactivity that is often associated with anaphylaxis are not available. One minor determinant is penicillin itself, which can be used as a skin test, and a mixture of minor determinants may be prepared by alkaline hydrolysis of penicillin.

Treatment

If the respiratory tract is involved the first priority must be to secure the airway that occasionally may require intubation or rarely a tracheostomy and to administer oxygen. An intravenous line should be established. For these and other patients subcutaneous or intramuscular adrenaline will reduce the edema and should be given in dosage 0.3 mg repeated every 10 minutes (0.3 mL of 1:1000

dilution). Diphenhydramine (50 mg) administered intramuscularly or intravenously is helpful and hydrocortisone (200 mg) or solumedrol (40 mg) given intravenously may reduce the possibility of relapse. Patients with severe angioedema should be admitted for at least 24 hours' observation particularly where laryngeal edema has occurred. Patients in whom a cause for the angioedema is proven or strongly suggested should be advised to wear a Medic Alert bracelet inscribed with this information.

Nonsteroidal anti-inflammatory drug-induced angioedema

A variety of the nonsteroidal anti-inflammatory drugs (NSAID) can cause angioedema, aspirin being the most common. True allergic reactions to aspirin or other NSAIDs are rare. However, reactions to these drugs superficially resemble allergic urticaria or angioedema and are often termed "pseudoallergic."^{14,15} The reactions can often be explained by the pharmacologic properties of the drugs.

Epidemiology

Precise figures for incidence of aspirin or other NSAID reactivity for patients presenting with angioedema are unknown. However, in patients with urticaria, aspirin reactivity can be documented in a small percentage.¹⁶

Pathophysiology

Pseudoallergic angioedematous reactions to aspirin and other NSAIDs are generally considered to be caused by inhibition of COX, the enzyme pathway that causes prostaglandin synthesis from its substrate arachidonic acid. This results in redirection of transformation down the lipoxygenase pathway, leading to compensatory increased synthesis of cysteinyl leukotrienes and other highly vasoactive hydroxy fatty acids (Fig 1). The main classes of culprit NSAIDs are listed in Table V. Only COX 1 inhibitors cause pseudoallergic angioedema, COX 2 inhibitors being suggested to be inactive.¹⁷ The mast cell is presumably the main cellular target in these reactions. Paracetamol (acetaminophen) is generally tolerated, even for patients sensitive to aspirin, most likely because of very weak COX 1 inhibition.

Clinical features, diagnosis, and differential diagnosis

The clinical features of NSAID-induced angioedema do not differ significantly from those of acute allergic angioedema, and like allergic angioedema, mucosal and/or cutaneous angioedema occurs within minutes of ingestion or injection of the offending NSAID. Diagnosis is based on the history, and most patients are aware of sensitivity to

these compounds. Skin prick testing is not of value. Although NSAIDS pseudoallergy can also lead to bronchospasm, there is a curious separation of the two presentations because most patients with urticaria/angioedema to NSAIDS have no respiratory symptoms and those with NSAID-induced asthma typically lack skin manifestations.

Treatment

Emergency measures are as for acute allergic angioedema. Patients should be warned to avoid these drugs as a class. Intradermal injection of cysteinyl leukotrienes causes increased inflammatory responses in patients with chronic urticaria¹⁸ and leukotriene antagonists or lipoxygenase inhibitors might be assumed on theoretic grounds to be helpful in patients with NSAID-induced angioedema.¹⁹ Use of leukotriene antagonists to prevent exacerbations as a result of NSAIDS has been advocated, but recent work sheds doubt on their efficacy.²⁰ Furthermore, administration of leukotriene antagonist concurrently with aspirin has been reported to provoke an acute anaphylactic episode with urticaria and angioedema.²¹ One of us (M. W. G.) has encountered a similar patient with an identical adverse event after montelukast. We advise against the use of leukotriene antagonists for patients with a history of NSAID-induced angioedema or urticaria. That patients with NSAID-induced angioedema can safely be given COX 2 inhibitors has been proposed.¹⁷ We believe more data from controlled studies are required before unreservedly advising this measure.

Angioedema as a result of ACE inhibitors

ACE inhibitors, developed from peptides found in venom from the Malayan snake *Bothrops jararaca* and known to enhance bradykinin activity, were first introduced in 1981 for treatment of hypertension and congestive heart failure. Unlike true allergic angioedema or pseudoallergic angioedema caused by NSAIDS, angioedema as a result of ACE inhibitors is not associated with urticaria. Furthermore, although angioedema may occur during the first week of therapy, some patients may have taken the ACE inhibitor without any problem for weeks or months before angioedema develops.²² ACE inhibitors are often overlooked as a cause of angioedema and this may lead to unfortunate consequences, because continuing administration tends to lead to more severe attacks.²³

Epidemiology

The overall incidence of ACE-induced angioedema is reported to be around 0.1% to 0.2% and is 5 times more common in African Americans than among white patients.²⁴ ACE inhibitor angioedema

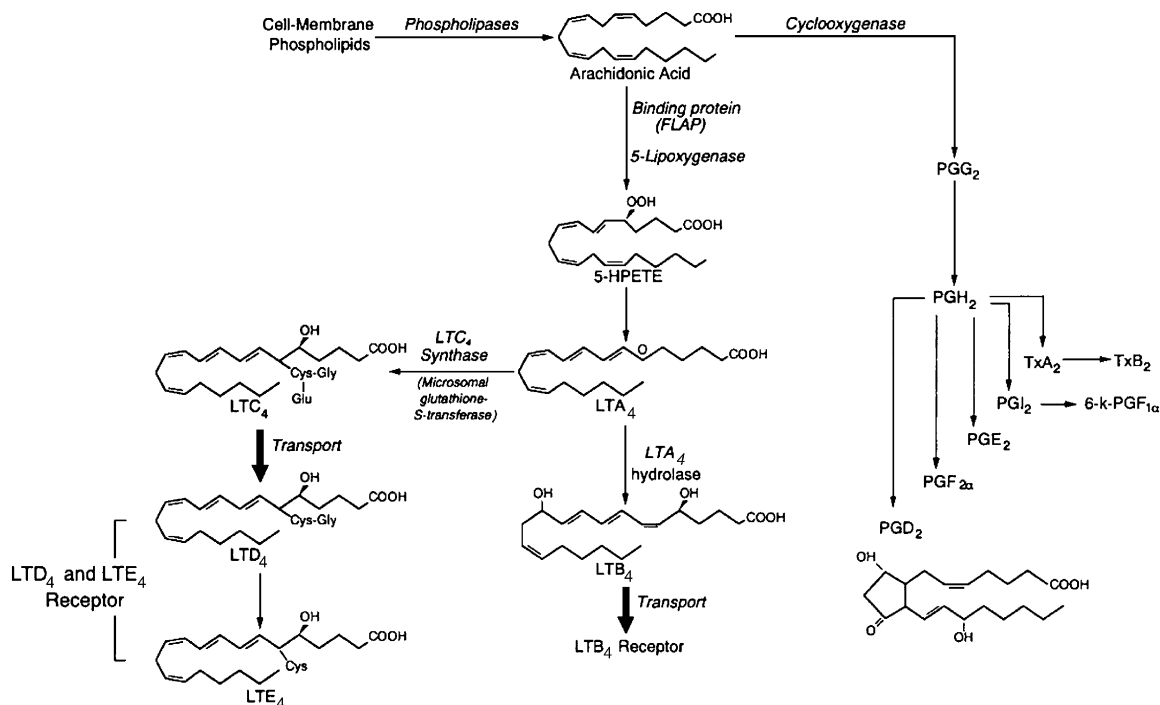


Fig 1. Pathways for production of prostaglandins and leukotrienes from mobilized arachidonic acid. 5 HPETE, 5 Hydroperoxyeicosatetraenoic acid; FLAP, five lipoxygenase activating factor; LT, leukotriene; PG, prostaglandin. Reprinted from: McNeil HP, Austen KF. The biology of the mast cell. In: Frank MM, Austen KF, Clamen HN, Unanue ER, editors. Samter's immunologic disorders. Vol 1. 5th ed. Boston: Little, Brown and Co; 1995. p. 199 (fig 13.4).

Table V. Nonsteroidal anti-inflammatory drugs that cause pseudoallergic angioedema

Class of nonsteroidal anti-inflammatory drug (derivative)	Example
Salicylic acid	Aspirin
Propionic acid	Ibuprofen, naproxen, ketoprofen
Anilin	Paracetamol (acetaminophen)
Acetic acid	Indomethacin, sulindac
Heteroaryl	Tolmetin, diclofenac, ketorolac
Enolic acids	Piroxicam, meloxicam
Anthranilic acids	Mefenamic acid, meclofenamic acid

is the most common cause of acute angioedema in accident and emergency hospital departments (17%-38%)²⁵ and up to 20% may be life-threatening.^{25,26} There is no preponderant age or sex bias.

Pathophysiology

ACE inhibitor—induced angioedema is not dose-related; however, it may occur almost immediately after the first dose, and is class- but not drug-specific and is, therefore, unlikely to be immunologically mediated. ACE catalyses the transformation of angiotensin I to angiotensin II (which is vasoconstrictive and increases the blood pressure).²⁷ It also inactivates bradykinin by cleavage of C-terminal

Phe-Arg, followed by Ser-Pro. ACE inhibitor effects on both these enzymatic pathways leads to lowering of blood pressure and a potential elevation of bradykinin levels.²⁸ Bradykinin, a nonapeptide, is powerfully vasoactive in human skin²⁹ and angiotensin convertase inhibition has been demonstrated to cause elevation of plasma kinins in human subjects.²⁸ A new dual ACE and neutral peptidase inhibitor, omapatrilat, carries an even higher risk of angioedema than pure ACE inhibitors alone.³⁰ Captopril has also been shown to inhibit degradation of the vasoactive neuropeptide substance P in the rabbit³¹ but this is probably a less important pathway in human beings. Why only a tiny minority of patients receiving ACE inhibitor treatment develop this dramatic complication is unclear but genetic factors may be relevant.³² The proposed mechanism of angioedema as a result of ACE inhibitors is illustrated in Fig 2. ACE is the predominant inactivator of bradykinin and is found along the endothelial cells of the pulmonary vasculature.³³ With ACE inhibition bradykinin accumulates and interacts with vascular B-2 receptors to cause vasodilatation and to increase vascular permeability with a concomitant increase in C-GMP and release of nitric oxide. When ACE is inhibited, bradykinin inactivation is slow, and dependent on plasma or serum carboxypeptidases,

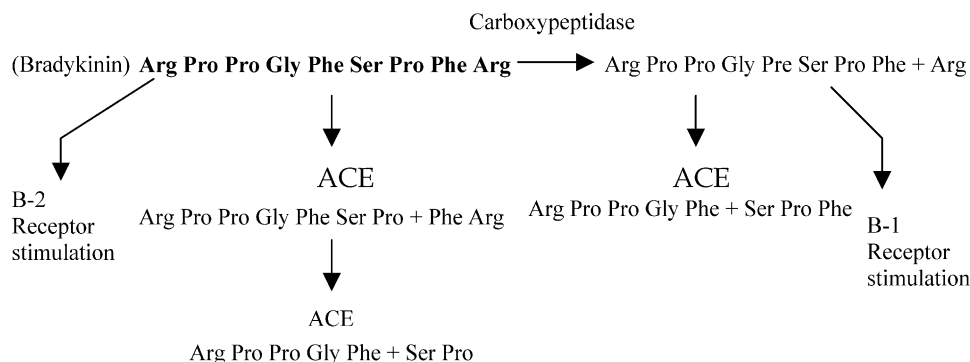


Fig 2. Nonapeptide bradykinin is digested by angiotensin-converting enzyme (ACE) to release Phe Arg and then Ser Pro. Those products have no activity on kinin receptors. Carboxypeptidase N and/or TAFI (carboxypeptidase U) remove C-terminal Arg leaving octapeptide that interacts with B₁ receptors. ACE degrades this to pentapeptide + tripeptide.

which remove C-terminal Arg,³⁴ leaving an octapeptide which, during chronic inflammatory states, can interact with B-1 receptors. The other products of ACE do not react with either bradykinin receptor.

Clinical features and differential diagnosis

Around 50% of patients with ACE inhibitor—induced angioedema occur within the first week of treatment. It shows a predilection for the head, neck, lips, mouth, tongue, larynx, pharynx, and subglottal areas³⁵ without urticaria. Mouth involvement may not only compromise the airway but cause dysarthria, thus preventing an adequate case history. Intestinal edema may also occur, causing abdominal pain that may not be accompanied by visible mucocutaneous angioedema. Thus, sudden abdominal pain, diarrhea, and vomiting in an adult should prompt questioning about recent intake of an ACE inhibitor.^{36,37} HAE (vide infra) may present with an identical history and clinical picture and, like ACE inhibitor—induced angioedema, is not associated with urticaria. These both appear to be a presentation associated with bradykinin-mediated swelling; ACE inhibition leads to an abnormality in bradykinin degradation whereas C1 INH deficiency causes over production. Other possible sources of diagnostic confusion include those listed in Table II plus tonsillitis, peritonsillar abscess, and pharyngeal foreign body.

Treatment of angioedema as a result of ACE inhibitors

Emergency treatment should take into account the risk of relapses after apparent recovery from the initial episode, despite withdrawal of the offending drug.^{38,39} Therefore, patients should be admitted for observation at least overnight. The severity of angioedema has occasionally necessitated admission to an intensive care department.³⁹ Other emergency procedures and drug administration are essentially

as for treatment of acute allergic angioedema (vide supra). The patient should not be subsequently prescribed another ACE inhibitor as the reaction is class- but not drug-specific and a Medic Alert bracelet should be worn. It is also advisable to check the complement C₄ level as patients with pre-existing angioedema, including HAE as a result of C₁ esterase inhibitor deficiency, are predisposed to develop angioedema in response to ACE inhibitors.⁴⁰ In general, angiotensin II receptor antagonists are tolerated by patients who have reacted to ACE inhibitors.

Angioedema in physical urticarias and cholinergic urticaria

Physical urticarias that may be associated with mucocutaneous angioedema are listed in Table VI. The reader is referred to a recently published comprehensive account of physical urticarias by Black⁴¹ for a more detailed discussion.

Cholinergic urticaria is usually a relatively trivial but annoying pruritic monomorphic transitory urticarial eruption provoked by exercise, heat, and emotion. But occasionally it may be associated with severe systemic symptoms and angioedema.⁴¹

Idiopathic acquired angioedema

This is frequently chronic and relapsing, and usually associated with urticaria. As its name implies it normally cannot be attributed to an identifiable cause. However, recent research has shown that, in 30% to 50% of patients both the urticarial wheals and the angioedematous lesions are a result of an autoimmune process.⁴²

Epidemiology

Champion et al⁵ reported that of 554 patients with urticaria, angioedema and urticaria occurred together in 49% and angioedema alone in 11%. In a more recent series⁶ of 104 patients with chronic

Table VI. Physical urticarias and mucocutaneous angioedema

Physical urticaria	Frequency of angioedema
Symptomatic dermographism	Absent
Delayed pressure urticaria	Absent
Cold urticaria	Fairly common (mucocutaneous)
Solar urticaria	Occasional (cutaneous)
Contact heat urticaria	Rare (mucocutaneous)
Vibratory angioedema	Invariable (cutaneous)
Aquagenic urticaria	Absent

idiopathic urticaria, angioedema occurred concurrently with urticaria in 93 (87%). The median duration of angioedema was 18 months, and angioedema occurred less than once weekly in 72% (54 of 75). Kozel et al⁴³ found that 10 of 220 patients had angioedema alone of whom only two were free of symptoms after 1 year. However, 59% of patients with idiopathic urticaria also had concurrent angioedema. Most recently, Nettis et al⁴⁴ found that in 562 patients with urticaria, angioedema, or both, 49 (9%) had angioedema alone.

Pathophysiology

Chronic urticaria and angioedema has long been known to be associated with autoimmune thyroid disease.⁴⁵ The first definitive report was that of Leznoff et al⁴⁶ who described 140 patients with chronic urticaria, angioedema, or both, 17 of whom had elevated antithyroid autoantibodies and 8 of these had thyroid dysfunction. Gruber et al⁴⁷ proposed a possible functional role for anti-IgE autoantibodies in chronic urticaria; as was also observed in some patients with cold urticaria. In 1993 Hide et al⁴⁸ published *prima facie* evidence demonstrating the presence of functional (histamine-releasing) IgG anti-high affinity IgE receptor (anti-FcεR1) autoantibodies (or less commonly IgG anti-IgE autoantibodies) in some patients with chronic idiopathic urticaria and angioedema. This work has been repeatedly confirmed.⁴⁹⁻⁵¹ In this model, specific IgG autoantibodies bind to and cross-link adjacent FcεR1 (alpha chain) (or the Fc portion of IgE) leading to activation of dermal mast cells and release of histamine, cytokines, and other mediators. Recent work indicates that complement activation augments the reaction in many patients,⁵² which is dependent on release of C5a.⁵³ Further evidence for the autoimmune basis of chronic idiopathic angioedema and urticaria in 30% to 50% of cases derives from the successful use of immunomodulatory approaches in

this disorder⁵⁴⁻⁵⁶ such as plasmapheresis, intravenous gamma globulin, or cyclosporine. The cause of whealing and itching in the remainder is unclear but a nonimmunoglobulin mast cell—specific factor⁵⁰ may be involved in some of these. Other workers have suggested a role for nonimmunoglobulin histamine-releasing factors in idiopathic cases⁵⁷ or an abnormality in signal transduction involving the Ras/MAPkinase pathway.⁵⁸

Clinical features and diagnosis

The clinical features of autoimmune and non-autoimmune angioedema (with or without associated urticaria) do not differ significantly and there are no clear differences in the histologic appearances of the affected skin.⁵⁹ Accordingly, identification of patients with angioedema as a result of an autoimmune mechanism relies on a screening skin test, the autologous serum skin test⁶⁰ or *in vitro* testing using an assay that depends on measurement of evoked release of histamine or other mediator from human donor basophils, dermal mast cells, or a rat basophil leukemia cell line.^{50,51} The autologous serum skin test is normally performed when antihistamines have been withdrawn from the patient for at least 2 full days. Serum is obtained from blood withdrawn during an active stage of the disease. It is then injected intradermally into clinically uninvolved skin of the flexor surface of the forearm, along with saline and histamine controls. The responses are read 30 minutes later. A positive response consists of a wheal the diameter of which is more than 1.5 mm greater than that of the saline control. This test has a sensitivity and specificity of about 80%.⁶⁰ However, it is no more than a screening test for autoimmune urticaria and a positive response should be validated by *in vitro* testing.

Blood basophil leukocytes in patients with autoimmune urticaria are usually extremely low and demonstration of basopenia has been proposed as a screening test for autoimmune urticaria,⁶¹ but is as yet not validated.

Associated symptoms in autoimmune angioedema are rare and if they are prominent (dyspnea, gastrointestinal upset, flushing) then an alternative diagnosis of idiopathic anaphylaxis should be considered. Urticarial vasculitis can also present with angioedema. In this case the swellings will normally last for several days and may leave residual staining of the affected skin. A skin biopsy specimen will be needed to confirm this diagnosis. The strong association between chronic urticaria and angioedema and autoimmune thyroid disease has already been alluded to and the relationship is statistically associated with chronic autoimmune urticaria

(ie, with anti-IgE receptor antibody) rather than the 60% with chronic idiopathic urticaria.^{62,63}

The issue of role of dietary factors in the origin of idiopathic chronic angioedema and urticaria has been debated. That food allergy can cause acute angioedema is not in dispute. Nonallergic (pseudoallergic) reactions to food preservatives and dyes have frequently cited as causes of chronic urticaria and angioedema.^{64,65} These studies were mainly inadequately controlled and reproducibility was not established. In a series of 1200 patients from 1995 to 2003, Kaplan found the incidence of food allergy as a cause for chronic urticaria and angioedema to be zero (unpublished data), and the experience of one of us (M. W. G.) is similar. We tend to agree with Mathews⁶⁶ who stated that "as a cause for chronic urticaria or angioedema food allergy can only rarely be implicated" and challenge tests, exclusion diets, and other food allergy tests are rarely indicated.

Treatment

Routine treatment for autoimmune and non-autoimmune chronic angioedema with or without urticaria is the same. Patients should be advised to avoid provoking factors (aspirin, overtiredness, overexcitement, overvigorous exercise, alcohol overconsumption).

Low sedation antihistamines (loratidine [10 mg], cetirizine [10 mg], fexofenadine [180 mg], desloratidine [5 mg]) are best prescribed for relief during the daytime. We regularly prescribe any of these in off-label dosage in treatment of resistant severely affected cases. These newer compounds do not cause impairment of cognitive function even in double or triple the dosage used for allergic rhinitis. However, sedative antihistamines such as hydroxyzine (10-50 mg) can be added at night and patients refractory to nonsedating agents may respond to hydroxyzine, diphenhydramine, or doxepin in high dosage. One of us (A. P. K.) uses diphenhydramine (50 mg 4 times a day) effectively for severe angioedema to prevent frequent and/or severe episodes⁶⁷ for patients with idiopathic angioedema (no urticaria) or for chronic urticaria (idiopathic or autoimmune) in association with angioedema. Although systemic steroids are unsatisfactory on a long-term basis, they can be used in short tapering courses for acute relapses.

Patients with autoimmune urticaria and angioedema are frequently treatment-resistant and for them the paradigm illustrated in Fig 3 is useful. After trying off-label dosage of fexofenadine or unsatisfactory control with sedating antihistaminics, patients can be offered cyclosporine⁵⁵ or methotrex-

ate⁶⁸ to be taken concurrently with antihistamines. Cyclosporine, in dosages of 2.5 to 4 mg/kg/d, is given for up to 3 months in the first instance. Renal function (serum urea nitrogen, creatinine, urinalysis), lipid and cholesterol profile, and blood pressure need to be carefully monitored. Data⁵⁵ from a controlled randomized study show that 80% of patients respond either completely or almost completely, and after withdrawing the treatment about two thirds of cases either remain in remission or can be successfully controlled by routine antihistamines. The remainder may require a further course of cyclosporine or a trial of methotrexate.⁶⁸ Additional immunomodulatory treatments that can be used include intravenous immunoglobulin infusions⁵⁶ and plasmapheresis.⁵⁴ One of us (A. P. K.) has used cyclosporine effectively for patients with chronic urticaria and angioedema who are in the idiopathic group without evidence of autoimmunity. Corticosteroid use on a daily basis is to be deplored for patients with any type or combination of urticaria/angioedema unless the dose is 10 mg/d or less. Every other day corticosteroid (20-25 mg q.o.d.) with a gradual tapering of 2.5 to 5.0 mg only 2 to 3 weeks is an effective alternative to use of cyclosporine and one option can be used when the other is ineffective or relatively contraindicated. Addition of an H-2 antagonist adds protection of gastric hyperactivity with perhaps some minimal effect on any concomitant urticaria. Acute treatment for idiopathic angioedema or severe angioedema associated with chronic urticaria can use 40 to 60 mg of prednisone with a repeated dose for 1 to 2 days more if needed, and then discontinue without any taper.

Infections as causes of angioedema

The possible role of parvovirus B19 infection in acute angioedema of neonates¹⁰ has already been mentioned (vide supra). Virus infections such as infectious mononucleosis may have an accessory role by precipitating attacks of angioedema in patients with HAE.⁶⁹

There is little or no evidence that infestations or bacterial infections can cause angioedema, although there has been some recent interest in the possible role of *Helicobacter pylori*. Exacerbations of HAE have been attributed to *Helicobacter*,^{70,71} and it has been suggested that the episodes of abdominal pain characteristic of HAE may in some instances be caused by *H pylori* gastritis. Eradication of *Helicobacter* in 18 patients was associated with lessening of episodes of abdominal pain in 9.⁷¹ Given the controversy regarding a role for *H pylori* in any type of urticaria, such data should be viewed with some skepticism until reproduced by many observers.

1. Non-sedating antihistamines
 fexofenadine 180 mg daily or twice daily
 or cetirizine 10 mg daily or twice daily
 or desloratadine 5 mg daily or twice daily
2. Sedating antihistamines
 hydroxyzine 25-50 mg four times daily
 or diphenhydramine 25-50 mg four times daily
 or doxepin 25 mg four times daily
3. Alternate day corticosteroid and immune suppressants
 - a. 20 mg prednisone every other day for 3 weeks, decrease dose by 2.5-5.0 mg every 2-3 weeks as tolerated. An H-2 receptor antagonist should be added which provides some additional antihistamine effect and protects against steroid induced hyperacidity.
 - or b. cyclosporine 200-300 mg daily
 - or c. methotrexate 10-15 mg weekly

Fig 3. Treatment of angioedema with chronic autoimmune or chronic idiopathic urticaria. Each step is added to previous one if inadequate response is obtained. Goal is to reduce itch, urticaria, and angioedema to tolerable levels to maintain function (eg, work, sleep, school), not to necessarily eliminate symptoms completely.

Episodic angioedema associated with eosinophilia

In 1984 Gleich et al⁷² described 4 patients with angioedema, urticaria, and fever. During these attacks massive peripheral blood and skin eosinophilia was found. Subsequently other patients with this syndrome were described, all of whom showed hypereosinophilia and, in one report,⁷³ IgG antienothelial antibodies. These patients responded well to systemic steroids and the condition is probably closely related to the hypereosinophilic syndrome.

Angioedema in urticarial vasculitis

Although less frequent than in chronic idiopathic urticaria, angioedema is a recognized complication of urticarial vasculitis, especially the hypocomplementemic form. This subject has been well reviewed by Wiesnieski et al.⁷⁴

Hereditary angioedema

Having encountered, in 1887, a 24-year-old woman with recurrent attacks of angioedema,

Osler³ obtained a history of similar episodes of edema in no less than 5 generations of the patient's family, beginning with the woman's great grandmother born in 1762. Thus, Osler³ established the dominantly inherited basis of a subset of patients with relapsing angioedema.

Epidemiology

HAE is a dominantly inherited disease that affects about 1:50,000 persons. It has been reported in all races, and there is no sex bias in the classic forms (types 1 and 2). The classic type of HAE is a result of a quantitative (type 1) or functional (type 2) defect in the plasma inhibitor of the first component of complement (C1 INH). The C1 INH gene has been mapped to chromosome 11 (11q12-q13.1) with considerable genetic heterogeneity when mutations responsible for the diseases are defined.

However, recently a third (type 3) form of HAE has been reported by several groups occurring exclusively in women with quantitatively and functionally

normal C1 INH activity with a relationship to estrogenic activity.

Pathophysiology

Classic HAE was first demonstrated by Donaldson and Evans⁴ to be a result of a defect in the serpin (serine protease inhibitor) C1 INH. For HAE to be clinically expressed the C1 INH plasma level should be quantitatively or functionally less than 40% of normal (Table VII).^{75,76} This deficiency causes an abnormal increase in activation of C1, leading to consumption of C2 and C4, and correspondingly low plasma levels of these proteins. It also causes excessive formation of the enzyme kallikrein, resulting in increased transformation of kininogen to kinins including the highly vasoactive nonapeptide bradykinin. The evidence is now substantiated that bradykinin is the cause of the swelling^{28,77-92} rather than any vasoactive peptide resulting from complement activation. Biochemical pathways believed to be involved in the pathogenesis of HAE types 1/2 are illustrated in Fig 4. A total of 15% of patients have a normal immunoreactive but functionally defective C1 INH (type 2 HAE) (Table VII). The 85% with one inactive gene have transsuppression of the functional gene or hypermetabolism of synthesized C1 INH⁸³⁻⁸⁵ with mutations consisting of deletions, insertions, stop codons, or frameshifts so that messenger RNA is not produced or any protein degraded intracellularly; whereas inactive proteins synthesized are typically a result of point mutations.⁸⁶ HAE type 2 includes two variants, one with a functionally inactive protein present in normal immunoreactive amounts and a second with a nonfunctioning inhibitor in increased concentration and bound to albumin.⁸⁷

As can be seen from Table VII, patients with either type 1 or 2 HAE have a low C4 level, even when asymptomatic, and functional C1 INH is very depressed. Immunoreactive C1 INH is diminished in type 1 disease, and generally proportional to the function observed whereas immunoreactive C1 INH is normal (or increased) in type 2 HAE.

Clinical features and diagnosis

Patients are usually asymptomatic up to puberty. Although swellings may develop without any preceding trauma, more than half of patients with HAE report some, usually minor, localizing injury such as dental maneuvers.⁸⁷ Other precipitating factors include vigorous exercise, alcohol consumption, emotional stress, and hormonal factors.⁸⁸ Coadministration of ACE inhibitors and estrogens is contraindicated in HAE. There is also a transitory prodromal nonpruritic urticarial eruption in some patients. The main sites of cutaneous involvement

Table VII. Mean laboratory values (% of normal) for 226 patients with classic (types 1 and 2) hereditary angioedema

Type of hereditary angioedema	Immunoreactive C1 INH	Functional C1 INH	C4
1	16.2	15.0	20.4
2	112.5	18.0	23.8
Normal range*	63-137	68-119	67-130

Adapted from Agostoni and Cicardi.⁷⁶

*Normal values from normal human pooled plasma.

are the face, hands, arms, legs, genitalia, and buttocks and the swellings may slowly spread and persist for 3 to 4 days.

Involvement of the mucosae is especially feared, and glossal, pharyngeal, or laryngeal involvement can result in respiratory obstruction, asphyxia, and a fatal outcome. In one large series⁷⁶ 10% of 235 patients had required intubation or tracheostomy at least once. Presentation with abdominal pain and symptoms of intestinal obstruction are also common and any patient presenting to the emergency department with these symptoms, and evidence of multiple abdominal surgical scars, should be screened for HAE.⁸⁹ That pulmonary involvement is very rare is probably a result of high tissue levels of kininases that rapidly inactivate kinin-like peptides. Diagnosis can be supported during or between attacks by measuring the C4 plasma level that is rarely above 50% of normal in HAE. A normal value essentially excludes HAE but a low value should prompt measurement of the quantitative and functional plasma C1 INH activity, because a low C4 can be a result of a variety of other causes including autoimmune connective tissue diseases.

HAE-associated diseases

There is an increased frequency of several autoimmune diseases with HAE. These include glomerulonephritis, Sjögren's syndrome, thyroiditis, and lupus.⁹⁰ Associated coagulopathies have also been reported^{91,92} caused, at least in some cases, by an abnormally high levels of C4 transporting protein that also binds and inactivates protein S,⁹¹ a cofactor for the protein C inactivation of activated coagulation factors V and VIII.

Treatment

For acute emergency episodes, antihistamines and corticosteroids are ineffective although subcutaneous adrenaline (0.3 mg every 10 minutes) may be helpful. If the patient has serious respiratory obstruction intubation or tracheostomy should be carried out and may be life-saving. However, most acute episodes are nonlife-threatening and the mainstay of emergency medical treatment is

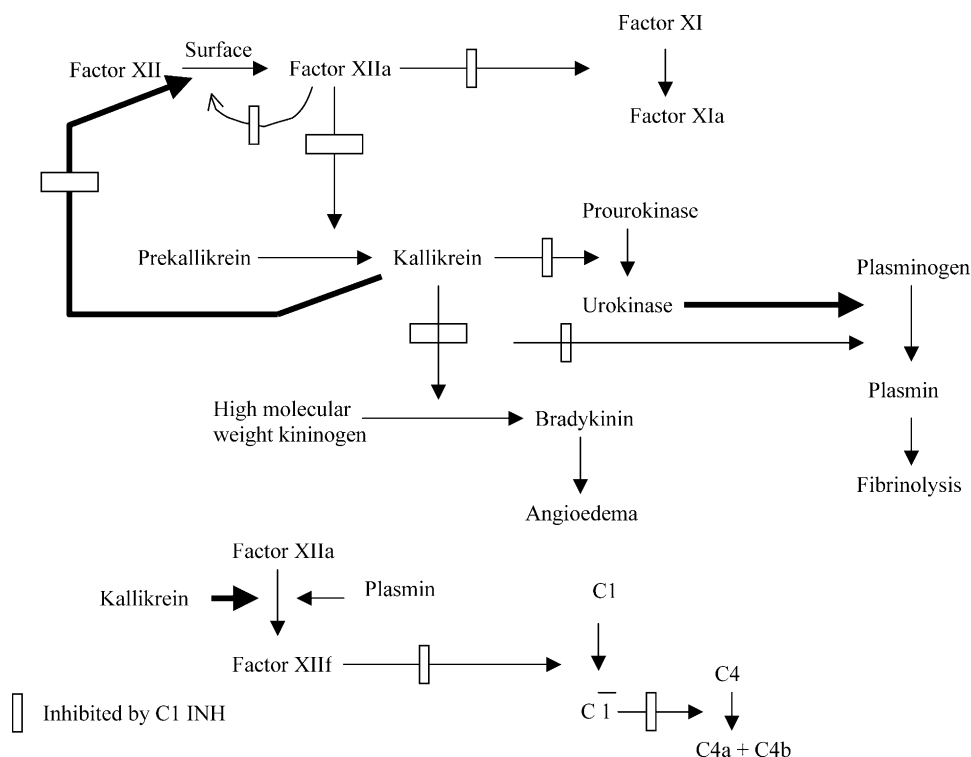


Fig 4. Diagrammatic representation of plasma kinin-forming cascade indicating steps inhibitable by C1 INH. All functions of factor XIIa and kallikrein are affected. *Lower figure*, Further digestion of factor XIIa by kallikrein and plasmin generates factor XII fragment (XIIIf), which is initiator of complement cascade. Both factor XIIIf and C1 are inhibited by C1 INH.

intravenous fresh frozen plasma or C1 inhibitor concentrate.⁹³ The recent availability of lyophilized vapor-heated C1 inhibitor concentrate⁹⁴ has largely removed concerns about transmission of HIV, viral hepatitis, and other infections. In this study, the product used (Immuno; Aventis Behring, Vienna, Austria) after reconstitution with saline contained 550 plasma U in a 10-mL vial and was administered at a dose of 25 plasma U/kg body weight to a total of 1000 plasma U repeated once if necessary. It is usually effective in diminishing swelling within 3 to 4 hours, and often within minutes.

Androgens were first demonstrated to be effective for prevention of episodes of HAE by Spaulding in 1960⁹⁵ and antifibrinolytic agents⁹⁶ have also been used. These are now superseded by oral attenuated 17 α -alkylated androgens including danazol and stanazolol. These anabolic steroids increase the circulating levels of normal functional C1 INH in both type 1 and type 2 HAE. Because they are known rarely to cause hepatotoxicity and liver tumors⁹⁷ danazol and stanazolol should be prescribed in the lowest effective dosage⁷⁶ (stanazolol 2-4 mg/d; danazol 50-300 mg/d). There is no need to bring about complete normalization of C4 and C1 INH levels.⁹⁸ Other reversible side effects in women

include deepening of voice, menstrual irregularities, acne, and hirsutism. For patients in whom attacks are infrequent and not life-threatening it may be sufficient to restrict treatment to avoidance of known provoking factors including estrogens and ACE inhibitors together with administration of C1 inhibitor concentrate or fresh frozen plasma prophylactically before dental treatment or other minor surgical procedures.

HAE with normal C1 INH activity in female patients (HAE type 3)

In 2000 Bork et al⁹⁹ reported 36 women from 10 families with HAE but with normal quantitative and functional C1 INH and C4 levels. The clinical picture, including mucocutaneous swellings, respiratory obstruction, and abdominal symptoms, did not differ significantly from type 1 and 2 HAE. There was no urticaria and C1 inhibitor concentrate therapy was ineffective. Provoking factors included estrogens and pregnancy. These and other authors propose an X-linked inheritance for this new entity.¹⁰⁰

Angioedema as a result of acquired C1 INH deficiency

That angioedema clinically identical with the hereditary varieties can be caused by acquired C1

INH deficiency has been recognized only recently. In 1969 Costanzi et al¹⁰¹ reported a patient with cold urticaria who had acquired C1 INH deficiency associated with a monoclonal cryoglobulin. Subsequently a large number of other patients with a similar syndrome were reported mostly occurring in the setting of lymphoproliferative disease. Occurring in older age groups and without a family history, the underlying mechanism appears to be overconsumption of C1 INH.

Acquired C1 inhibitor deficiency

An acquired form of this disease has been described in patients with lymphoma who have circulating low molecular-weight IgM and depressed C1 inhibitor levels. This entity has an unusual complement use profile because C1q levels are low, which differentiates this condition from the hereditary disorder.¹⁰²⁻¹⁰⁴ The depressed C1 inhibitor level may be caused by depletion secondary to C1 activation by circulating immune complexes or C1 interaction with a tumor cell surface antigen. For B-cell lymphoma, the most common associated malignancy, C1 fixation, and C1 inhibitor depletion are caused by an anti-idiotypic antibody bound to immunoglobulin on the surface of the B cell.¹⁰⁵

Patients with connective tissue disorders such as systemic lupus erythematosus or carcinoma^{106,107} can present with acquired C1 inhibitor deficiency and, like patients with the hereditary form, will respond to androgen therapy, which enhances C1 inhibitor synthesis. A second form of C1 inhibitor deficiency results from the synthesis of an autoantibody directed to C1 inhibitor itself.^{108,109} These patients also have low levels of C4, C1q, and C1 inhibitor protein and function, and no family history. This form of acquired C1 inhibitor deficiency appears to be increasingly recognized. Under normal circumstances, C1 inhibitor is a substrate for the enzymes it inactivates: the active enzyme cleaves C1 inhibitor, which exposes the active site in the inhibitor. The cleaved C1 inhibitor then binds stoichiometrically to the enzyme and inactivates it. When antibody to C1 inhibitor is present, the C1 inhibitor is cleaved and it is unable to inactivate the enzyme.¹¹⁰⁻¹¹² Thus cleaved, functionless C1 inhibitor circulates and unopposed activation of the complement- and kinin-forming cascade takes place.

One circumstance in which the two forms of acquired C1 inhibitor deficiency merge is in an occasional patient with monoclonal gammopathy, in which the monoclonal immunoglobulin is in fact an antibody to C1 inhibitor.^{113,114} The immune complex-mediated depletion of C1 inhibitor and the autoantibody directed to C1 inhibitor represent

Table VIII. Assays for C1 inhibitor deficiency

	C1 INH protein	C1 function	C4	C1Q	95kD C1 INH
Hereditary type 1	↓	↓	↓	N	No
Hereditary type 2	N or ↑	↓	↓	N	No
Acquired type 1	↓	↓	↓	↓	No
Acquired type 2	↓	↓	↓	↓	Yes

types I and II acquired C1 inhibitor deficiency, respectively. The type II variety can be most readily determined by immunoblot with antibody to C1 inhibitor. The presence of a C1 inhibitor cleavage product at 95 Kd differentiates the two forms of the acquired disorder, and it is not present in the hereditary disorder.

Table VIII is a summary of the laboratory tests that may be used to identify the different forms of C1 inhibitor deficiency. If a family history is present, one needs to differentiate the two types of HAE. Because the C4 level will be diminished in both, the distinction is usually made by comparing C1 inhibitor protein level and C1 inhibitor function. Both protein and function will be low in parallel in type 1 HAE, whereas the protein level will be normal or elevated in type 2 form of this disorder with functional C1 inhibitor diminished. Because a low C1q level and a 95 Kd cleaved C1 inhibitor protein characterize types I and II acquired C1 inhibitor deficiency, the absence of either abnormality or of any family history of swelling, for patients with low C4 and abnormally low functional C1 inhibitor, would define a patient with a probable new mutation. Occasionally this pattern may be obtained in someone who does not have any of the aforementioned predisposing immune conditions. Such patients need to be evaluated carefully over time because there have been reports of angioedema of this sort preceding the diagnosis of the underlying disorder.

Treatment

Treatment of acquired C1 inhibitor deficiency requires, first, treatment of the underlying disease, if one has been identified, plus treatment with the aforementioned drugs, which is essentially the same as that for treatment of the hereditary disorder. Treatment of type II acquired C1 inhibitor deficiency with an autoantibody directed to C1 inhibitor is indeed more difficult because the ability to replete C1 inhibitor is significantly compromised. Plasmapheresis and use of a cytotoxic agent in addition to the use of prophylactic androgenic compounds or ϵ -aminocaproic acid may be necessary for chronic treatment, and infusion of plasma or C1 inhibitor concentrate used for emergency

treatment. The latter is clearly preferable to prevent volume overload and to be able to give enough C1 inhibitor to bind the autoantibody so as to raise the C1 inhibitor level significantly. In a practical sense, this is often not feasible. Tranexamic acid has also been successfully used in the treatment of type II acquired C1 inhibitor deficiency in which activation of the bradykinin-forming cascade and fibrinolysis (the latter determined by elevated levels of plasmin- α_2 antiplasmin complexes) was observed.¹¹⁵

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