



Life-threatening severe allergic reactions: urticaria, angioedema, and anaphylaxis

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Abstract Urticaria, angioedema and anaphylaxis are life threatening skin diseases. Allergological emergencies are common; drugs, food, food ingredients/additives, insects, and many other factors have been reported to elicit anaphylactic reactions. The severity of symptoms ranges from pruritus to generalized skin eruptions, gastrointestinal, bronchial problems to systemic anaphylaxis and cardiovascular emergencies. The pathomechanisms and treatment of urticarias, angioedema and anaphylaxis are described. In some situations emergency kit: antihistamines, steroids, betamimetics and adrenaline is needed. Familiarity with the early diagnosis and correct management should be acknowledgeable for dermatologists to recognize these allergic reactions and must be prepared to administer emergency kit.

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Introduction

Anaphylaxis, acute urticaria, and angioedema are severe allergic reactions and represent life-threatening skin diseases which dermatologists must be able to identify and treat. It is necessary to distinguish them from other severe conditions, such as anaphylactic reaction from heart arrest, an epileptic-form attack, and syncope, to treat generalized acute urticaria and angioedema as soon as possible. Allergology and clinical immunology are elements of dermatovenereology, and all dermatologists must be familiar with these conditions and the best therapeutic options available.

Allergological emergencies are common events, with a plethora of drugs, foods and food ingredients, additives,

insects, and many other factors having been reported to elicit anaphylactic reactions. Every year there are about 500 deaths from penicillin allergy in the United States alone and 5 to 10 deaths from insect venom in Austria.¹ Allergological emergencies range in severity, arising from pruritus to generalized skin eruption and bronchial and gastrointestinal problems to systemic anaphylaxis with cardiovascular features. The pathomechanism of these reactions is also variable and include immunoglobulin (Ig) E-mediated reactions to drugs, foreign antigens (latex, blood, etc), other well-known antigen-immune complexes and complement-mediated reactions, blood and x-ray substances, direct histamine liberation (by opiates), and modulators of arachidonic acid metabolism (nonsteroidal anti-inflammatory drugs [NSAIDs]), all of which are frequent causes of anaphylaxis. Many reactions remain unclassified despite vast numbers of investigations that have been conducted: some triggers are hidden antigens, and reactions are

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sometimes augmented by drugs (eg, aspirin or food intolerance) or combinations of physical strain and food intake (exercise-induced anaphylaxis).¹ Disease like cold urticaria and hereditary angioedema may manifest as an anaphylactic reaction or may exacerbate reactions caused by other triggers. Clinical signs, associations, and interactions (eg, with angiotensin-converting enzyme [ACE] inhibitors, β -blocking agents) are variable and pathologic findings are nonspecific in most situations. The responsible physician must always be vigilant. Although anaphylactic reactions are rare, practicing dermatologists must be prepared for the worst.¹⁻⁴ Familiarity with the correct management should be a matter of course, and a standby emergency kit must include adrenaline, antihistamines, steroids, and betamimetics. The management should consist “of more than just epinephrine”.^{1,4-7} According to Ring, the ABC rule (*Atemwege*—airway, *Beatmung*—breath, Circulation) should be AAC (Antigen weg—remove the antigen, Adrenaline—epinephrine, Cortisone).³

Urticaria

Urticaria (synonyms: hives, *Nesselfieber*) is a form of monomorphic dermatosis, with characteristic lesions (urtica = wheal) of sudden and rapid development and appearance (acute urticaria).^{5,6} Urticaria means hives, which in chronic urticaria the wheals persist for a long time (ie, weeks, months, even years). In German, the name *Nesselfieber* refers to the typical skin reaction to nettles (*Urtica dioica*).⁶ Hippocrates (460-377 BC) described pruritic lesions caused by nettles and mosquitoes.³ Angioedema was described by Donato in 1586 and hereditary angioedema by Osler in 1888.³

Epidemiology and pathogenesis

Urticaria/angioedema is considered to be acute if it lasts less than 6 weeks and chronic if the lesions persist beyond 6 weeks. In the United States between 1990 and 1997, women accounted for 69% of patient's visits for this condition.³ In the UK, 15% to 20% of college students reported having urticaria, and it was the reason for 1% to 3% patient referrals to hospital dermatologic clinics.³ Urticaria is the result of edema in the dermis and increased vascular permeability, with diffusion of serum and various mediators into the tissue.⁶ The typical triple response of Lewis can be seen when the histamine is injected into the skin. The most commonly observed feature in most cases of urticaria is the activation of cutaneous mast cells and their release of mediators after degranulation in blood vessels (histamine, heparin, various enzymes, prostaglandins, and leukotrienes) which are responsible for urticarial lesions. Ordinary angioedema has the same pathogenic mechanism and is often clinically associated with urticaria.^{3,5,6} Typical sites of involvement are the eyelids, lips, genitalia, and distal extremities. The

mast cell is the major effector cell in most forms of urticaria and angioedema, although other cell types may be involved. Cutaneous mast cells adhere to fibronectin and laminin through the very late activation (VLA) of β_1 integrins, VLA-2, VLA-4, and VLA-5, and to vitronectin through the $\alpha v \beta_3$ integrin. Cutaneous mast cells release histamine in response to compound 48/80, C5a, morphine, and codeine. The neuropeptides substance P, vasoactive intestinal peptide, and somatostatin—but not neurotensin, neurokinins A and B, bradykinin, or calcitonin gene-related peptide—activate mast cells for histamine secretion.³ Vascular permeability in skin is produced predominantly by H_1 histamine receptors, although H_2 histamine receptors may sometimes participate. The possibility that chronic idiopathic urticaria may be an autoimmune disorder arose from data that suggested an association of chronic idiopathic urticaria with autoimmune thyroids, and, more specifically, with the presence of IgG autoantibodies to thyroglobulin and peroxidase.³ Immunoglobulin G antibodies to the α subunit of the high-affinity IgE receptor Fc ϵ RI α were then detected in about 30% of patients with chronic idiopathic urticaria.

The autoantibodies to Fc ϵ RI α and IgE are associated with IgG₂ and IgG₃.³ Immunoglobulin G alone is effective at plasma concentrations, but the reaction is augmented in the presence of C5a in serum. Blocking antibody to the C5a receptor inhibits the ability of serum to augment basophile histamine release caused by the patient's IgG autoantibodies; therefore, the complement agonist is C5a.

Some patients with chronic urticaria and thyroid autoimmunity have IgG autoantibodies to thyroglobulin and peroxidase, and 88% of these individuals also exhibit IgE autoantibodies to peroxidase.³

Etiology

The most common immunologic mechanism is IgE-mediated, a type I reaction. For the development of hives, it is important that there be IgE or IgE receptor-dependent reactions in association with abnormalities of the complement system and activation of other cytokines. Nervous system stimulation, physical stimuli and various chemicals (eg, histamine), substance P in axonal reflex, and the liberation of histamine after mast cell degranulation can also interact to modulate nerve reactivity and vessel tone. In cholinergic urticaria (ChU), the stimulus for urticaria appears almost entirely neural. Urticaria may also be associated with a variety of infectious disorders (hepatitis B, infectious mononucleosis, etc). In contact urticaria, application of the allergen to the skin causes mast cell degranulation. Non-inflammatory agents, preservatives, and additives cause hives on a nonimmunologic basis. In cold urticaria, pressure urticaria, and urticaria with pseudoallergy, other mediators appear to be important, among them serotonin, bradykinin, leukotrienes C₄, D₄, and E₄, prostaglandins, and proteolytic enzymes.³ HLA-DRB1*04,

HLA-DQB1*0302, HLA-DRB1*15, and HLA-DQB1*06 are present with increased frequency in patients with chronic idiopathic urticaria.³

Clinical findings

Hives develop rapidly and suddenly with a pruritic raised, prominent, patchy erythema (urticaria rubra) usually over minutes. They are sometimes white (porence), hemorrhagic, hyperpigmented (chronic urticaria), annular, or circinal. The size may range from a few millimeters to the more typical lesions that are several centimeters in diameter. Each hive lasts a few hours before fading without a trace, rarely persisting longer than 24 to 48 hours; it may continue to recur for indefinite periods.³ New areas may develop as old areas fade and they can vary in size from a small dot to as large as a dinner plate to form larger swellings. Hives usually are itchy, but they may also burn or sting.

Most episodes of hives disappear quickly (within a few days to a few weeks). The tissue may swell excessively when they form around the eyes, lips, or genitals. The swelling usually goes away in less than 24 hours, but the affected person should go to the emergency department if there is difficulty in breathing or swallowing. Hives that form by firmly stroking, excessively rubbing or scratching the skin are called "dermographism." These hives can also concomitantly occur with other forms of urticaria and appear more frequently in young women, lasting for months or even years. Dermographism is the most common form of physical urticaria.

Classification of urticaria/angioedema is based on immunologic (type I and III reaction), nonimmunologic, and idiopathic factors.^{6,7} Clinical classification of urticaria can be according to etiology, duration, and immunopathogenesis and be based on kinetics and etiopathophysiology. There are different types of urticaria according to etiology: allergy (food, inhalant, contact allergens, drugs, blood derivatives); toxic (insect bites, plants, ASA, analgesic drugs, additives, preservatives); pseudoallergic (NSAIDs and other inflammatory drugs, contrast agents); focal infections (parasitic infections, mycotic, bacterial, virus infections); paraneoplastic; physical (mechanic, thermal, cholinergic, water, light, UV light); enzymatic defects (angioneurotic edema, hereditary edema, serum carboxypeptidase); autoimmune diseases (urticaria vasculitis associated with systemic lupus erythematosus [SLE], cryoglobulinemia, paraproteinemia); psychosocial factors (stress, depression); hormonal disturbance (eg, thyroid disease); mastocytosis; idiopathic urticaria.⁷

Hein's⁸ clinical classification of urticaria is based on kinetics: acute (lasting <6 weeks), chronic (>6 weeks), episodic (intermittent), allergic, and etiopathophysiologic. Allergic urticaria occurs at some time in 20% to 30% of patients with chronic allergic diseases. A focal reaction is consequent to a localized chronic infection. Idiopathic describes a nonidentifiable cause, although up to half of

these cases have autoantibodies to IgE and/or IgE receptor. The irritative-toxic is the result of contact with a triggering agent (eg, nettles). The physical type results from cholinergic, pressure, solar, cold, heat, or aquagenic sources, while the psychosocial form follows a conflict situation that amplifies the urticarial symptoms. In urticarial vasculitis, the skin biopsy shows deposits of immune complexes, while cases stemming from enzyme defects involve hereditary angioedema and autosomal dominant disease that afflicts 1 in 10,000 to 150,000 persons. Finally, mastocytosis is characterized by an abnormal increase of mast cells in tissues, most frequently the skin.

Urticaria and angioedema may act as clinical manifestations of immunologic and inflammatory mechanisms or they may be idiopathic.³ According to the consensus of the European Society of Dermatological Research on definition, classification, routine diagnosis, and management of urticaria, and modification by Zuberbier⁹ in 2003, the urticaria can be spontaneous, physical, a special type, and different diseases related to urticaria for historical reasons.

Acute urticaria

The prevalence of acute urticaria is higher in persons with atopic disease: they comprised 50.2% of the acute urticaria cases in the study by Zuberbier.⁹ As for etiology, food was suspected as being the cause in 63% of the patients: food is of high importance in children, and cow's milk seems to be relevant for acute urticaria in 10 of 12 affected babies. In older children with urticaria (5-16 years), the prevalence of food intolerance was 15% as the eliciting factor for the acute urticaria.⁹ Drugs can elicit acute urticaria as allergens (penicillin) and as pseudoallergens (acetylsalicylic acid). The most frequent reason for acute urticaria is viral infections in the upper respiratory tract, usually a few days before the onset of wheals.⁹

Chronic urticaria

There are no reliable data regarding the prevalence of chronic urticaria. Type I allergic reactions are only rarely responsible for the development of chronic urticaria.⁹ There are different subsets of patients with chronic urticaria, pseudoallergic reactions against food additives, infections, and autoimmune etiology. Apart from anti-IgE receptor autoantibodies, thyroid autoantibodies are also apparently associated with chronic urticaria, although the pathomechanism is unclear. *Helicobacter pylori* of the gastrointestinal tract in urticaria is still controversial: there are reports of patients with chronic urticaria who went into remission after the elimination of *H pylori*. Candidosis has been regarded as a highly important eliciting factor for chronic urticaria.⁹ Hepatitis virus infections are a more frequent cause for chronic urticaria in southern Europe but a rare cause in northern Europe.⁹ Noninfectious chronic inflammatory process has also been identified as causing urticaria-like

gastritis, reflux esophagitis, inflammation of the bile duct or bile gland, and, rarely, autoimmune disorders, for example, SLE and neoplasia.^{3,6,7,9,10}

Chronic urticaria and autoimmune syndrome

As mentioned earlier, chronic urticaria by definition lasts for more than 6 weeks. It predominantly affects adults and is about twice as common in women as men. It tends to follow a remitting and relapsing course and is an extremely distressing and disabling condition. When it appears to have no identifiable cause, the condition is termed *idiopathic* and 52.7% of autoimmune diseases—particularly thyroid diseases—have been implicated in its occurrence. Chronic urticaria is sometimes associated with other autoimmune disorders, such as lupus erythematosus, or dermatomyositis, as well as with antithyroid autoantibodies, anti-IgE autoantibodies, and anti-FcεRI autoantibodies. The latter two autoantibodies are capable of directly causing mast cell degranulation.¹¹ Most cases of chronic urticaria are considered an autoimmune rather than an allergic disease.¹² Functional autoantibodies against FcεRI and IgE have been demonstrated in 30% to 50% of sera in chronic urticaria. Circulating antibodies have been recognized in the sera of patient with chronic idiopathic urticaria, leading to the term *autoimmune urticaria* in 35% to 40% of patients. These patients have wheals with wider distributions and more severe pruritus accompanied by flushing and abdominal pain. Recombinant anti-IgE antibodies as a therapeutic agent has been shown to have a beneficial effect. Autoimmunity and autoimmune syndrome can be associated with or without lymphoproliferative disorders in chronic urticaria. Treatment of autoimmune urticaria consists of nonsedating antihistamines and immunomodulators (corticosteroids, cyclosporine A, or tacrolimus) as well as hormonal treatment of associated endocrine diseases.¹³

Chronic idiopathic urticaria

Chronic idiopathic urticaria (CIU) is a dermatologic disorder that may severely impair quality of life and a common skin condition that affects 0.1% to 3% of Americans and Europeans,^{14,15} accounting for nearly 75% of all chronic urticaria cases.¹⁶ Chronic idiopathic urticaria is classically defined as the appearance of hives/wheals on most days for more than 6 weeks, in the absence of a causative physical or environmental trigger.¹⁷ Therefore, the diagnosis of CIU is mainly one of exclusion, and the clinical investigative process can be lengthy. Hematologic, biochemical, immunologic, and endocrine assays are needed to provide direct or indirect evidence of systemic allergic, inflammatory, infectious, or autoimmune processes that may cause chronic urticaria. Thereafter, sensitivity to foods, environmental agents/pollutants, and the presence of chronic infection or occult malignancy must all be excluded before a diagnosis of CIU can be finally established.¹⁸

The wheals of chronic urticaria have a characteristic appearance, namely, a pinkish-red center that merges into a red surrounding. These wheals are itchy and edematous and may coalesce to form giant wheals that are very uncomfortable and unsightly. Many cases of chronic urticaria are accompanied by angioedema with infiltration and swelling at the lower dermal and submucosal levels. Macroscopically, the wheals of CIU bear a striking resemblance to the cutaneous late-phase response to allergen.¹⁴ This implies that CIU may be predominantly an illness in which symptoms are produced by autoimmune targeting of the body's allergen defense system. Basophiles, which also express FcεRI, are affected in CIU, and basophile numbers and immunologic reactivity are decreased in CIU,¹⁹ possibly via autoimmune mechanisms. Desloratadine, a third-generation antihistamine, has a low affinity for both the H₂ and the muscarinic receptors as well as novel antiallergic activity.¹⁴ A significant part of patients with CIU have functional autoantibodies. There is an increased expression of tumor necrosis factor α and IL-3 on endothelial cells and perivascular cells, expression of CD11b and CD18 cells, secretion of major basic protein and eosinophil cationic protein around blood vessels in the dermis, free eosinophil granules in the dermis, and P-selectin, E-selectin, intracellular adhesion molecule-1, and vascular adhesion molecule-1 on the vascular endothelium. The pathogenesis of CIU in more than 50% of cases, however, remains unclear. Because CIU can decrease quality of life significantly, the aim of treatment is to provide rapid and durable symptomatic relief. Despite the wide availability of nonsedating antihistamines, many patients continue to experience troublesome symptoms, sometimes for decades. Clinical experience in CIU has so far shown desloratadine to be a safe and effective treatment, providing rapid onset of action and long duration of symptom relief.¹⁴

Urticaria eruption in infancy

Urticaria in infancy is rare and mostly associated with food allergy, drug eruptions, infections, insect bites, or idiopathic occurrence.^{20,21} It may be the first sign of multisystemic inflammatory disease (eg, Still disease, SLE, Kawasaki disease, mastocytosis, dermatitis herpetiformis, lymphoma, leukemia, metabolic disorders, and genetic disorders). If, after delivery, a newborn develops a macular or urticarial eruption that varies in distribution and intensity within the following days, the questions to be asked are: are there known heritable diseases in the family and did the mother transfer infection/or antibodies, such as SSA/Ro, to her child? The laboratory tests will indicate the correct diagnosis (circulating immune complexes, rheumatoid factor, antinuclear antibody, blood test, liver enzymes, etc) of perhaps a chronic inflammatory disease and therapy consisting of steroids as potent anti-inflammatory drugs and antiphlogistics having the most beneficial effect.

Physical urticaria

Physical urticaria whealing occurs in response to a specific physical stimulus. It can be divided into whealing responses to mechanical stimuli, change in temperature, exposure to water, and exposure to light. Angioedema occurs in addition to whealing in 3 conditions. Physical urticarias are frequently present concurrently with CIU, and delayed-pressure urticaria is almost invariably associated with CIU. Physical urticarias are very common, and 20% of all patients attending urticaria clinics will suffer from one type or another. Indeed, 2 or more physical urticarias can sometimes be present in the same patient. Lesions on the buttocks and thighs can be caused by sitting and lesions on the trunk by any one of a number of activities, such as leaning against a chair, lying on a hard bed, carrying bags over the shoulder, wearing a seat belt, and others. Angioedema of the hands can occur after carrying bags, using a screwdriver, or holding a steering wheel, while angioedema of the feet can occur because of climbing, walking, running or jogging.

Cholinergic urticaria is a special type of urticaria provoked by exercise, emotion, and warming of the body. Jogging, cycling, housework, and dancing can cause itching and eruption. Taking a hot bath or shower, going into a warm room, and eating spicy or hot food can provoke eruption or itching. Brief, intense, and usually unpleasant emotions can also cause itching and eruption. Interestingly, the combination of sports and social activities are the major offenders: cholinergic urticaria is characterized by pinpoint-sized highly pruritic wheals that are typically provoked by these physical stimuli. Cholinergic receptors are found at the neuroglandular junction of the sweat glands, and various mediators, including histamine, serotonin, and eosinophil chemotactic factors, have been implicated. The therapeutic choice for ChU is atropine sulfate. Oral scopolamine butylbromide (10 mg), 3 times a day for 3 weeks, is useful in the therapy for ChU.

Idiopathic cold contact urticaria is characterized by itching and whealing of the skin when exposed to cold weather, including wind and rain or a combination of both as well as swimming in cold sea or outdoor pool. The inside of the mouth and tongue are affected in 25% of patients when drinking cold liquids. Swimming in cold water has caused syncope and death from drowning and these activities must be forbidden to susceptible individuals. The patients with delayed-pressure urticaria are more disabled by such exposure, and those with ChU, symptomatic dermographism, and cold contact urticaria have special problems which are related to the factors which provoke their disease (as mentioned above).²²

Delayed-pressure urticaria

Typical lesions of this type of urticaria are deep, painful areas of swelling that develop 4 to 8 hours after exposure to vertical pressure and persist 8 to 48 hours. Palms and

soles as well as buttocks are the typically involved areas. Men are more frequently affected, and the average age of onset is 30 years with duration of 6 to 9 years.⁹ Pressure urticaria can become a disabling disease in jobs that require physical exertion.^{6,9}

Cold urticaria

Urticarial reaction after exposure to cold can be manifested as an immediate or a late localized reaction as well as by generalized responses in areas of skin not directly exposed to cold. There are acquired and inherited forms of cold urticaria/angioedema. Idiopathic or primary acquired cold urticaria may be associated with headache, hypotension, syncope, wheezing, nausea, vomiting, or diarrhea. Attacks occur within minutes after exposure to cold objects, and passive transfer of cold urticaria with serum of IgE to the skin of a normal recipient has been documented after an experimental challenge with released mediators (histamine, PGD₂, tumor necrosis factor, chemotactic factors, etc) into the circulation.³ Autosomal dominant disorder is familial cold auto-inflammatory syndrome.³ In most of these patients, cold water, and cold air provokes symptoms. Cold urticaria is frequent in young women and can last for years. Infectious diseases can also induce cold urticaria (eg, syphilis, borreliosis, measles, hepatitis, human immunodeficiency virus, and mononucleosis). In 20% to 50% of patients, it can be idiopathic with an unrecognized bacterial infection that responds to antibiotic therapy.⁹

Heat urticaria

Heat urticaria is a rare form of physical urticaria elicited after exposure to temperature ranges from 38°C to 50°C.

Solar urticaria

Solar urticaria is elicited by light in wavelengths ranging between 285 and 760 nm. Young women are more frequently more affected. It was demonstrated that serum factors acting as IgE-dependent photoallergens may be involved in its pathogenesis. The affected areas of the body are those which are not usually exposed to sunlight. Although solar urticaria can be associated with SLE and polymorphous light eruption, it is usually idiopathic. Histamine and chemotactic factors for eosinophils have been identified in blood.

Adrenergic urticaria

Adrenergic urticaria is an extremely rare type of urticaria. Wheals are elicited by stress and not by exercise. Treatment with β -adrenoreceptor blocker and propranolol is useful in preventing attacks.

Contact urticaria

Contact urticaria is caused by chemical substances in contact with the skin and is strictly confined to exposed areas of the body. Food, plants, drugs, cosmetics, industrial chemicals, and textiles can be eliciting factors.

Aquagenic urticaria

Aquagenic urticaria must be differentiated from contact urticaria. Water-soluble allergens from the corneal layer act as allergens. This condition is 5 times more frequent in young women. The wheals resemble those of ChU.

Reactions to the administration of blood products

Urticaria/angioedema, which may develop after administration of blood products, is the result of immune complex formation and complement activation and leads to direct vascular smooth muscles alteration and, indirectly via anaphylatoxins, to mast cell mediator release. Urticarial or anaphylactic reactions to blood, plasma, or immunoglobulin in patients with antibodies to IgA may arise after transfusion or by placental transfer. Aggregates of IgG may activate mast cells by binding to Fc gamma R III or by activating complement. A soluble antigen present in a donor preparation that is transfused into a previously sensitized recipient can trigger the urticaria or angioedema.³

Urticaria/angioedema relating to abnormalities of arachidonic acid metabolism

Urticaria/angioedema occurs after intolerance to aspirin in both normal individuals and atopic patients (ie, those with allergic rhinitis or asthma). Nonsteroidal anti-inflammatory drugs were responsible for eliciting urticaria/angioedema in 10% to 20% of these patients in UK.³ Reactions to NSAIDs increase the levels of cysteinyl leukotrienes and this may be related to the appearance of urticaria and asthma.

Diagnosis and differential diagnosis

Urticarial eruptions are episodic and are characterized by multiple lesions that seldom persist for more than 48 hours. In contrast, angioedema may persist for several days. Several disorders need to be considered in the differential diagnosis: they include erythema esudativum multiforme, erythema migrans (in Lyme borreliosis), urticaria pigmentosa, renal insufficiency cellulitis, myxedema, and Melkersson-Rosenthal syndrome.

Diagnosis of urticaria

Guidelines for the diagnosis of urticaria are designed for classic cases, and unusual presentations will require special testing procedures. The standard diagnostic procedure for a number of urticaria subtypes according Zuberbier⁹ is designated for:

1. Acute urticaria: no routine diagnostic test (unless strongly suggested by patient history).
2. Chronic urticaria: differential blood count, erythrocyte sedimentation rate, and ruling out of suspected drugs,

for example, NSAIDs, especially drugs known to cause pseudoallergic reactions (the prototype being aspirin), as well as any aggravation of preexisting chronic urticaria.⁹ In addition, possible autologous serum skin test for *Helicobacter*, gastroscopy, antinuclear antibody, stool for worm eggs/parasites, skin test, specific IgE, thyroid hormones and autoantibodies, and pseudoallergens-free diet for 3 weeks. Dietary management consists of the avoidance of specific food allergens (food itself and food ingredients and additives). Diet in patients with pseudoallergic reactions to food must be prolonged to 3 to 6 months. Dietary avoidance of type I allergens is usually helpful and apparent within 24 to 48 hours, whereas a diet may often need to be maintained for 2 to 3 weeks before beneficial effects are noted in pseudoallergy. Diet in other subtypes of urticaria other than chronic continuous urticaria is usually not helpful.⁹

3. Physical urticaria can be diagnosed with a provocation test according to our experience: cold (water, ice), warm water, pressure (pressure test 0.2-0.4 kg/cm² for 10-20 min), and with exercise. A differential blood count and erythrocyte sedimentation rate measurement (as indications of severe systemic disease) must be carried out. For cold urticaria,⁹ the protocol consists of cold provocation tests (ice cube, cold water), the use of different temperatures to possibly identify the culpable threshold, exposure to cold wind (ventilator), and differential blood count, erythrocyte sedimentation rate, and cryoglobulin measurements.⁹ For heat contact urticaria, routine diagnostic tests include warm arm bath (42°C, varying temperature to detect the threshold) and for solar urticaria UV and visible light of different wavelength.
4. For special types of urticaria: ChU is provoked by exercise or hot bath according to patient history.
5. For urticarial vasculitis: biopsy, differential blood count, erythrocyte sedimentation rate, and antinuclear antibody.

Treatment

The treatment follows basic principles by being aimed at the initiating stimulus, effector cells and inflammatory mediators, and at the receptor sites on target tissues. Therapy directed at mast cells involves blocking the release of the generation of mediators or blocking the effects of released mediators by stabilizing the membrane of mast cells and by modulating cyclic nucleotide levels or calcium flux.³

The most important factor in treating urticaria/angioedema is identification and removal of its cause, especially in acute urticaria, and the administration of H₁ antihistamines.

Treatment of CIU focuses on measures that provide symptomatic relief. The therapeutic approach for the other types is dependent upon the precise diagnosis and includes the avoidance of the provoking stimuli, removal of infectious

agents and treatment of inflammatory processes, and removal of the Fc ϵ RI autoantibody. Plasmapheresis has been shown to be of only temporary benefit because relapse occurred as the antibody formed again, while immunologic treatment with cyclosporine or high-dose Ig infusion has proven to be helpful. The dietary management mentioned earlier is useful in IgE-mediated food allergy as well as in pseudoallergy reactions in chronic urticaria to food.⁹

Mast cell-directed therapy

Systemic corticosteroids in high doses are frequently administered shortly because long-term treatment should be avoided. Allergists were found to be the least likely to use a systemic glucocorticoid (6% of visits), whereas internists were the most likely (29% of visits).^{3,23} The use of prednisone in the management of acute urticaria has been advocated in emergency departments, but this should not be the routine approach. Epinephrine is used widely, particularly in hospital emergency departments, but its use is indicated only in cases of laryngeal edema or cardiovascular collapse.

Prednisone is used at a dose of 15 to 20 mg every other day and is gradually tapered by 2.5 to 5.0 mg every 3 weeks depending on the patient's response. It can often be discontinued within a 4- to 5-month period. The alternate-day dose is 20 mg of prednisone or its equivalent.³ Cyclosporin A also has a moderate, direct effect on mast cell mediator release,^{9,24} but is reserved for alternative treatment because of high costs. Cyclosporine was effective in CIU in a randomized, double-blind study, but the appropriate dose has not yet been determined.²⁵

Psoralen-UV-A reduces the number of mast cells and has been successfully used in mastocytosis. UV-A and UV-B have also been studied as additive treatment in urticaria.⁹

Patients with the same forms of physical urticaria responded to treatment with broadband UV-B phototherapy and psoralen-UV-A photochemotherapy. Narrowband UV-B phototherapy was useful in CIU.³ The subcutaneous administration of interferon- α in 2 controlled trials was of no benefit.³

Therapy at the target organ

In urticaria, the main symptoms are mediated by H₁ receptors. H₁-type antihistaminic drugs are the mainstay in the management of urticaria/angioedema. Because the older classic, H₁-type antihistamines or first-generation H₁-type antihistamines were with sedation effect, never or low-sedating, second- and third-generation H₁-type antihistamines have become the therapeutic agents of choice. Initial treatment in acute urticaria is prednisone 50 mg/d for 3 days⁹ and nonsedating H₁-type antihistamines.⁹ The combination of H₁ and H₂ antihistamines may benefit patients with CIU¹⁴ as might terbutaline (a β -adrenergic agonist) in combination with H₁-type antihistamine. Nifedipine (as an adjunctive agent) with H₁ antihistamines has been shown to be useful, and zafirlukast and montelukast

had beneficial responses as well.³ Montelukast and cetirizine showed a benefit for patients with intolerance to food additives or acetylsalicylic acid.²⁶ Stanazol and sulfasalazine²⁷ were beneficial in some patients with CIU.

New-generation antihistamines have improved the quality of life of patients with urticaria. These medications should be preferred because they also exert anti-inflammatory effects such as the inhibition of cytokine release from basophils and mast cells. The effect of antihistamines in urticaria is dose-dependent,²⁸ and higher dosages are usually well tolerated, but care must be taken because of side effects. Second-generation antihistamines, with the exception of astemizole and terfenadine, having a good safety profile, should be considered as first-line symptomatic treatment of urticaria. Increasing the dosage in unresponsive patients is advised before choosing other drugs.

Other therapies

Propranolol hydrochloride may prevent attacks of adrenergic urticaria. Acupuncture has been reported to be of benefit in the treatment of urticaria in Asia. We believe, however, that alternative treatment should be reserved for unresponsive patients. Delayed-pressure urticaria may respond to NSAIDs, dapsone, cetirizine, sulfasalazine, and systemic glucocorticoids, but not to colchicine and rarely to H₁ antihistamines^{3,9} and leukotriene antagonist.⁹ In ChU, nonsedating H₁ antihistamines can be used in increased dosage if necessary, but hydroxyzine and cetirizine are the initial agents of choice.³ Danazol (initially 400-600 mg)²⁵ can be tried as well.

Nonsedating H₁ antihistamines are useful in solar urticaria,⁹ as is the induction of physical tolerance (hardening) with a UV light.²⁹ For cold urticaria, H₁ antihistamines,⁹ leukotriene antagonists,³⁰ the induction of physical tolerance (cold bath),³¹ and penicillin 3 $\times$ 1.2 mIU/d parenterally or doxycycline 2 $\times$ 100 mg/d PO,⁹ are useful.

Treatment for chronic urticaria according to Zuberbier⁹ includes nonsedating H₁ antihistamines, increasing the dosage if necessary and in combination with Dapsone (50-100 mg/d) and pentoxifyllin (2 $\times$ 600 mg/d),⁹ combination H₁ and H₂ blocker, combination H₁ blocker and β sympathomimetics or nifedipine, doxepin, danazol (initially 400-600 mg/d), leukotriene antagonists, such as montelukast (10 mg/d), sulfasalazine (3 $\times$ 500-1000 mg/d), corticosteroids, cyclosporin A (4 mg/kg), interferon, psoralen-UV-A, plasmapheresis, immunoglobulins, and cumarin.⁹

We have summarized the current standard treatments in different subtypes of urticaria.

In urticaria, the severity may fluctuate with spontaneous remission at any time. It is recommended to reevaluate therapy every 3 to 6 months for continuing drug treatment or administering an alternative one.⁹

Conclusions

Urticaria and angioedema are life-threatening disorders that require an individual approach because of their

complexity. Therapy needs to be administered on an emergent basis in acute urticaria with angioedema. Management is based on avoidance of triggering factors, treatment of concomitant diseases, and symptomatic pharmacological treatment. New-generation antihistamines can be used at increasingly higher doses in nonresponding patients.

Angioedema

Angioedema is a reaction characterized by swelling of subcutaneous tissue of the skin and mucosa of the respiratory and gastrointestinal tracts. The cardiovascular system may be involved as well.^{5,32,33} It can be fatal for patients who do not receive emergency care. Urticaria and angioedema may present with abnormalities of the serum complement system and they often occur together in many patients. This representation is seen most frequently with underlying cutaneous necrotizing vasculitis or SLE, or in the presence of a number of autoantibodies. Angioedema was first described by Donato in 1856 and hereditary angioedema by Osler in 1888.^{32,33}

Angioedema is a grave expression of urticaria. Common triggers for angioedema are bee and wasp stings, drug reactions, foods, and hypersensitization. Angiotensin-converting enzyme inhibitors have also been associated with life-threatening angioedema.

The classification of angioedema is same as that of urticaria described above: immunologic IgE and IgE receptor-dependent, mediated by the complement system and other plasma effector systems, hereditary, acquired with C1 INH deficiency and malignant disorders or autoantibody, appearing after direct mast cell degranulation, and related to abnormalities of arachidonic acid metabolism.³³ The current state of angioedema classification is according to the publication of Gigli and Rosen³³ and is based on:

1. normal or elevated serum complement levels (IgE-mediated: atopic, specific antigen, excise) induced by physical agents (cold pressure), aspirin and nonsteroidal anti-inflammatory agents, dyes, contrast media opiates, or polyanionic antibiotics;
2. low serum complement levels (low C1 INH protein function or both): genetic (hereditary angioneurotic edema [HAE]); C1 INH deficiency type I/no protein), C1 INH deficiency type II (dysfunction protein), acquired (acquired angioneurotic edema), lymphoproliferative disorders (type I, low protein), or anti-C1 INH antibodies (type II, dysfunctional protein);
3. normal C1 INH: serum sickness, blood products reactions, necrotizing vasculitis, idiosyncratics, dyes, contrast media.³³

Hereditary angioneurotic edema is a rare form of angioedema with life-threatening consequences. Osler identified the entity HAE as having a clear pattern of

inheritance.^{32,33} In 1962, Landerman et al³⁴ reported a biochemical abnormality in HAE, and Quincke reported swelling in members of 2 consecutive generations in the same family.³

Clinical manifestations of angioedema

Angioedema commonly affects the face or a portion of the extremities and may be painful, but not pruritic. The affliction can last several days. Involvement of the lips, cheeks and periorbital areas, genitalia, and distal parts of extremities are common, and the tongue and pharynx may sometimes be affected as well. Angioedema infrequently accompanies urticaria and an exacerbation of asthma, rhinitis, or atopic dermatitis. The prevalence of angioedema is not increased in atopic individuals. Angioedema represents an edematous process in deep dermis and/or subcutaneous and submucosal layers.^{32,33,35} Women are more often affected than men, and young adults are the major target group.

Course and prognosis

The outlook for any attack depends upon the presence and extent of involvement of the airways.

Vibratory angioedema

Vibratory angioedema may often occur as an acquired idiopathic disorder in association with ChU and in patients with occupational exposure to vibration. It has been seen in families with an autosomal dominant pattern of inheritance. An increase in the level of plasma histamine was registered in both forms.^{32,35}

Cold edema

There are acquired and inherited forms of cold angioedema. The elicitation of edema and whealing after the application of cold was considered a diagnostic cold contact test. In rare instances, cold urticaria/edema has been associated with underlying cryoglobulins, cryofibrinogens, cold agglutinins, and cold hemolysins, especially in children with infectious mononucleosis.^{32,35}

Whereas complement has no role in primary acquired cold urticaria, the challenge of patients with cold edema/urticaria who have circulatory immune complexes, such as cryoglobulins, can provoke a cutaneous necrotizing vasculitis with complement activation.

Physical angioedema/urticaria has the same stimulus and type of response as described in urticaria.^{32,35}

Angioedema with urticarial vasculitis is a severe clinical manifestation with serum complement abnormalities, with identified IgG autoantibody directed against the collagen-like region of C1_q (a low-molecular-weight 7S C1_q-precipitin).³² Urticarial vasculitis may occur in patients with serum sickness, connective tissue disorders, hematologic malignant conditions, and as an idiopathic disorder.

Laboratory findings

As in patients with hereditary angioedema, the C₄ levels should be reduced in patients with the acquired form, giving the first sign of angioneurotic edema diagnosis as well as C1 INH levels. C1 INH is reduced in 85% of patients and dysfunctional in 15%.^{33,35} In C1 INH deficiency in adults with no positive family history, Caldwell syndrome (1972) with underlying hematologic disorder and primary acquired angioneurotic edema (Bork, 1987) with developing of IgG or IgM antibodies directed against C1 INH⁵ must be excluded.³⁵

Angioedema has been associated with the administration of ACE inhibitors.³⁶ The frequency of angioedema occurring after ACE inhibitor therapy is 0.1% to 0.7% during the first week of therapy in up to 72% of affected patients.³² Therapy with ACE inhibitors is contraindicated in patients with a history of idiopathic angioedema, hereditary angioedema, and acquired C1 INH deficiency.^{32,36} Angioedema related to abnormalities of arachidonic acid metabolism (reactions to aspirin and NSAIDs) increases the levels of cysteinyl leukotrienes.³²

Idiopathic angioedema with urticaria is the most prevalent form. Cyclic episodic angioedema has been associated with fever and weight gain and has a benign course with peripheral blood eosinophilia.³⁷

There is no recommended diagnostic laboratory evaluation for angioedema, and routine screening laboratory tests are of no value.^{32,38} According to Soter and Kaplan,³² assessment of serum complement proteins may be helpful in identifying patients with urticarial venulitis and angioedema, as well as those with hereditary and acquired forms of C1 INH deficiency. There is little value for skin prick testing or the radioallergosorbent test in angioedema: inhalant materials are uncommon causes of this condition and food skin tests may be difficult to interpret. The radioallergosorbent test should be reserved for those patients in whom skin testing is contraindicated.

Pathology of angioedema

Angioedema involves the deeper dermis and subcutaneous tissues. There is dilatation of the venules and findings of inflammatory cells, major basic protein and eosinophil cationic protein, adhesion molecule (intercellular adhesion molecule-1, vascular adhesion molecule-1), P-selectin, E-selectin, T and B lymphocytes, and deposition of immunoglobulins and C3 complement, as described in the section on Urticaria.

Diagnosis

Clinically, angioedema is easily recognizable. It may persist for several days with episodic eruptions. Edematous plaques on predilection sites (lips, periorbital region, genital region) must be differentiated from erythema multiforme,

Melkersson-Rosenthal syndrome, dermatomyositis, allergic drug eruption, and cellulites.

Treatment

The ideal treatment of angioedema is identification or removal of its cause. H₁-type antihistaminic drugs are the mainstays in the management of angioedema (see the treatment description in the section on Urticaria).

Idiopathic angioedema

The cause is unknown in at least 70% of chronic idiopathic urticaria/angioedema cases. The common cause, sometimes easily recognized in angioedema, is frequently associated with concomitant events (infections, metabolic and hormonal abnormalities, emotion factors, malignant conditions). Proof of their etiology often is lacking, as in peripheral blood eosinophilia.

Hereditary angioedema

Hereditary angioneurotic edema is a genetic C1 INH deficiency and a rare form of angioedema with life-threatening consequences.^{33,39} Osler described HAE as having a pattern of inheritance angioedema,³³ and Landerman et al³³ reported a biochemical abnormality in HAE. Urticaria does not accompany the angioedema in patients with genetic or acquired deficiency of C1 INH.⁴⁰

Clinically, HAE is characterized by recurrent, circumscribed, nonpruritic, and nonpitting subepithelial edema. Angioedema may develop over several hours, and patients frequently are aware of a peculiar tingling or twitching sensation in the affected area. The skin swells progressively within hours, returning to normal in 1 to 3 days. Angioedema of the small bowel is associated with abdominal pain, and copious watery diarrhea may ensue. Urinary retention and central nervous system involvement (headaches, transient aphasia) are often present. The onset of HAE is variable, from a mild degree in early childhood to a dramatically worse degree at pubescence.

The classification of HAE is given above. The precipitating factors are not clear. Hereditary angioneurotic edema responds to stress and trauma. Systemic lupus erythematosus, lupuslike disorders, and Sjögren syndrome have been diagnosed in members of families with HAE.^{33,40}

There are 2 genetic variants of HAE.⁴⁰ In the more common form, type I (up to 30% of the cases), normal antigenic and functional C1 INH protein is present in the blood, whereas 15% have type II with normal or increased amount of an abnormal, dysfunctional C1 INH protein together with low levels of the normal protein.³³ The gene encoding the C1 INH maps to the long arm of chromosome 11.2-q13.³³ Although C1 INH is the only serum inhibitor of the first component of complement (C1) and the esterase activity of 2 of its subcomponents, C1r and C1s, it also inhibits factors XIa, XIIa, and XIIIf, kallikrein, and plasmin.^{33,41}

Many studies support the view that uninhibited C1 can elicit angioedema. Other studies suggest that the source of the kininlike activity in HAE plasma is bradykinin rather than C2. It is possible that mediators generated during activation of complement also play a role. In patients with acquired C1 INH deficiency in the fifth and sixth decades of life, without a family history of this disorder, there are 2 forms of angioedema, type I (entity with lymphoproliferative disorder) and type II (autoantibodies to the C1 INH are present in the sera of patients associated with systemic lupus, rheumatoid arthritis, and Sjögren syndrome).

The diagnosis of HAE is not straightforward. Decreased serum levels (type I) and decreased C₄ levels are identified in 85% of patients with HAE. In some cases, it is necessary to assay C1 INH functionally to confirm the diagnosis.

Differential diagnosis: IgE-mediated reactions in individuals with respiratory symptoms, hypotension or vascular collapse and angioedema/urticaria adverse reactions after ingestion of aspirin; cellulitis or erysipelas may sometimes resemble angioedema; congestive heart failure and obstruction of the superior vena cava.

Treatment

Prevention of acute attacks of HAE that are life-threatening is vital, and trauma must be avoided. Prophylactic therapy before surgery and dental procedures is warranted. The intravenous injection of purified C1 INH or recombinant C1 INH is the most effective therapeutic approach. Attenuated androgens with reduced virilizing effects but retained anabolic activity were also found to be prophylactic agents. Stanozolol (0.5-2 mg) and danazol (50-400 mg daily) are widely used to prevent attacks of HAE. The patients with acquired angioedema type I respond to attenuated androgens and those with type II (ie, with anti-C1 INH autoantibodies) respond to glucocorticosteroids.

Anaphylaxis

Anaphylaxis is the maximal (extreme) variant of an immediate IgE-mediated allergic reaction. There is massive release of mediators. An anaphylactoid reaction has the same clinical manifestation but in the absence of an acute type I reaction according to Coombs and Gell. The anaphylactic shock and anaphylactoid reactions are often subsequent to exposure to bee or wasp stings, insect bites, and drugs.

The most common causes (triggers) of anaphylaxis are: medicaments (penicillin, hyposensitization injections), bee and wasp allergens, food allergens (nuts, fish, shellfish, poppy seeds), latex (probably the most common cause of anaphylaxis), insect toxins, seminal fluid, aeroallergens, insects (echinococcal cysts), contact allergens, C1 INH deficiency, systemic mastocytosis, exercise-induced anaphylaxis alone or in combination with food allergens

ingested before strenuous exercise, a combination of the above factors, and idiopathic causes.

It is known that widely prescribed analgetic-antipyretic drugs can induce drug eruptions. Anaphylactic shock due to acetaminophenol (paracetamol) is rare but it was reported by Bachmeyer et al⁴² in 2002. Some European groups have published data on series of patients with idiopathic anaphylaxis. In Spain, Tejedor et al⁴³ found that 9% of the patients had vascular involvement, 48% had atopic disease, 20% had food allergy, and 15% had episodes of anaphylaxis with a nonidentifiable cause. They recorded a high frequency (58%) of idiopathic urticaria, with 62% of the affected patients having acute urticaria. Immediate transfusion reactions in recipients of 15,990 red blood cells, 18,013 platelets, 409 single donor platelets, 3451 FFP, and 1507 units of cryoprecipitates were found low (0.2%; 40 patients) in South America.⁴⁴

Exceedingly rare cyclical anaphylactoid reactions associated with menstruation were found in 2 sisters in Australia because of an abnormal reaction to prostaglandins (perhaps produced by COX-2 enzyme activity in the endometrium).⁴⁵ Exercise-induced anaphylaxis and ChU were differentiated in a select group of persons with an erythematous and irritating skin eruption to a life-threatening anaphylactic reaction.⁴⁶ Mast cell degranulation with release of vasoactive substances was the inciting factor for symptoms, and the diagnosis was based on history and examination of the morphology of the lesions. Management of acute episodes of exercise-induced anaphylaxis includes cessation of exercise, administration of epinephrine and antihistamine, vascular support, and airway maintenance. Prophylactic use of antihistamines and mast cell stabilizer is recommended.⁴⁶ Anaphylaxis or angioedema in response to recombinant tissue-type plasminogen activator or urokinase has been reported in only a few isolated cases: both agents were endogenous proteins and thus considered non-antigenic.⁴⁷ The 25-year-old patient developed protracted anaphylactoid reactions during recombinant tissue-type plasminogen activator continuous intravenous infusion. After changing treatment to urokinase, the same symptoms recurred with a more severe intensity despite corticosteroid premedication. Histamine receptor blockers seem to be an effective treatment, but steroids do not prevent this unusual complication of thrombolytic therapy.⁴⁷

Anaphylaxis after ingestion of sharon fruit (edible fruit of the persimmon tree—*Diospyros kaki*) was reported in a 33-year-old man. It was proven to be the cause of anaphylaxis by a skin prick test, serum-specific IgE with enzyme immunoassay, and sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting that suggested an IgE-mediated hypersensitivity reaction.⁴⁸ Fatal anaphylaxis after eating wild boar meat in a patient with pork-cat syndrome was reported by Drouet et al.⁴⁹ They documented pork-cat syndrome developing in the form of anaphylaxis and then ending in the death of the patient after consumption of wild boar meat.⁴⁹

Berrocal and Schuman⁵⁰ described a female patient who developed a systemic anaphylactic reaction to a subconjunctival injection of cephalosporin. The patient required intensive therapy, including airway intubation. She had a history of penicillin allergy. Even as little as 50 mg of cephalosporin antibiotic injected locally can produce a life-threatening anaphylactic reaction.⁵⁰

Severe drug-induced cutaneous reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis as well as related mucocutaneous disorders, with high rates of morbidity and potential mortality. Hällgreen et al⁵¹ reported 2 cases of Stevens-Johnson syndrome associated with ciprofloxacin treatment, demonstrating the drug as being capable of provoking severe skin reactions.

IgE allergy due to formaldehyde paste during endodontic treatment was reported by Braun et al⁵² in 4 cases, 2 with anaphylactic shock and 2 with generalized urticaria. These infrequent but potentially severe reactions after root canal treatment led the authors to examine the involved mechanisms, the diagnostic procedure, and the possibility of prevention of these events in stomatology.

Idiopathic anaphylaxis, a type of anaphylaxis in which no external allergen can be identified, is a corticosteroid-responsive disease, which suggests that it may have an immunologic pathogenesis. Grammar et al⁵³ compared patients with acute episodes of idiopathic anaphylaxis in healthy subjects and in patients with chronic idiopathic urticaria and found that there were more activated T cells in patients with acute episodes of idiopathic anaphylaxis than in patients in remission. The authors speculated that the activated T cells might have a role in the pathogenesis of idiopathic anaphylaxis.⁵³

Penicillin is the drug that most often leads to allergic reactions and anaphylaxis. The incidence of adverse events triggered by penicillins is believed to be between 1% and 10%.⁵⁴ Up to one tenth of these episodes are life-threatening, with the most serious reactions occurring in patients with no history of allergy. da Fonseca⁵⁴ recently reported a case of a 5-year, 3-month-old girl who had a severe allergic reaction to amoxicillin before a dental appointment.

Nitrate and nitrite salts are commonly used to preserve and sustain color in a number of processed meats. Hawkins and Katelaris⁵⁵ reported a 22-year-old patient with recurrent anaphylaxis after eating take-out food. Nitrate anaphylaxis was proven and documented by a double-blind, placebo-controlled capsule challenge test: the patient had an acute anaphylactic reaction after a challenge to nitrates and nitrites. Of the 177 patients who had suffered an adverse reaction to 1 or more NSAIDs reported by Quarantino et al,⁵⁶ 55 had urticaria, 52 had angioedema, 39 had a combination of urticaria/angioedema, and 1 had a maculopapular eruption. Respiratory symptoms were displayed by 3.9%, cutaneous and respiratory symptoms by 9%, Stevens-Johnson syndrome by 2.3%, and an anaphylactoid reaction by 1.7%. When the tolerability of meloxicam, a new NSAID that selectively inhibits the

inducible isoform of cyclooxygenase, was assessed in a group of NSAID-sensitive patients, positive reactions were observed in only 2 cases (1.1%).⁵⁶

Among 105 patients given recombinant tissue plasminogen activator (alteplase) intravenously for acute stroke, 2 (1.9%) patients had lingual angioedema which progressed to a fatal anaphylactoid reaction in one of them. The authors reviewed these 2 cases of patients and suggested that it was the concomitant ACE inhibitors that increased their risk.⁵⁷

Anaphylaxis to pine nuts and immunologic cross-reactivity with pine pollen proteins was published in only a few reports. Senna et al⁵⁸ presented a patient with food allergy to pine nuts who showed no clinical symptoms to pine pollen despite the presence of specific IgE antibodies in her serum. Based on the cross-reactivity between pine nut and pine pollen extracts, they stated that cosensitization to these 2 allergens could be possible.

A 17-year-old Japanese adolescent boy was referred due to acute urticaria and anaphylaxis after the administration of a PL (combination of salicylamide, acetaminophen, anhydrous caffeine, and promethazine methylene disalicylate) and Bufferin (aspirin and dialminate) for headache and high grade fever. In vitro released interferon- γ in the diagnosis of drug-induced anaphylaxis (lymphocyte stimulation test with PL and Bufferin) were useful for identifying delayed-type hypersensitivity and for predicting anaphylactic shock reaction to drugs according to Kubota et al.⁵⁹

Torres et al⁶⁰ studied 59 patients (30 with anaphylactic shock and 29 with urticaria), with immediate allergic reactions to penicillin, comparing urticaria and anaphylactic shock. Positivity to minor determinants of penicillins was associated more with anaphylactic shock than urticaria, but the role of IgG antibodies in helping to prevent the development of anaphylactic shock could not be confirmed.

A novel wheat gliadin as allergen and as a cause of exercise-induced anaphylaxis in 18 adult patients was studied by Palosuo et al.⁶¹ All 18 patients had experienced recurrent episode of generalized urticaria during exercise, 17 patients in association with collapse, and 15 patients with an anaphylactic reaction. Testing (enzyme-linked immunosorbent assay, immunoblotting) with 65- and 40-kDa wheat protein, and in vivo by positive skin prick test responses, as well as in follow-up on a gluten- or wheat-free diet, the authors demonstrated the major allergen of exercise-induced anaphylaxis as being gamma-like gliadin. The authors recommended skin prick testing with crude gliadin for screening of this life-threatening allergy and a gluten-free diet for treatment.

Adverse potentially life-threatening symptomatically and cosmetically unappealing side effects (especially Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and anaphylaxis) of various psychotropic drugs were reported by Kimyai-Asasi et al.⁶² True (IgE-mediated) allergic reactions to crustaceans are relatively common and can be serious. The anaphylactic reaction in a young

woman developed immediately after kissing a boyfriend who had eaten shrimps just before the kiss.⁶³

Conclusions

Anaphylaxis, acute urticaria, and angioedema are true life-threatening skin diseases. The dermatologists must be knowledgeable about them to recognize these allergic reactions, and the responsible physician must be prepared to administer adrenaline, antihistamines, steroids and betamimetics and otherwise implement the correct management according to the nature and the severity of allergic reactions.

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