Urticaria and Angioedema

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Definitions

Urticaria is a transient erythematous swelling of the skin, associated with itching, which usually resolves within 24 hours.

Angioedema (previously known as angioneurotic edema) is characterized by swellings caused by edema in the deeper dermal, cutaneous and sub-mucosal tissue. The overlying skin may appear normal.

Symptoms

Urticarial lesions itch, have a central white wheal that is elevated, and are surrounded by an erythematous halo. The lesions are typically rounded and circumscribed. Characteristically, hives should blanch with pressure; they generally resolve within 24 hours, leaving no residual change to the skin. The redness, which is augmented by local neural reflexes, is due to dilated blood vessels in superficial layers of the skin; the wheal is due to leakage of these vessels as fluid extravasates and compresses the vessels beneath it so that the central area appears clear.

Swelling of deeper layers of the skin, angioedema, commonly accompanies urticaria. This swelling often results from the same inflammatory processes that cause hives. The redness that is seen surrounding superficial lesions is not observed, though the swelling is readily appreciated. Angioedema generally occurs on the extremities and digits as well as areas of the head, neck, face, and in men, genitalia. It is often described as being painful or burning.

Classification

Urticaria and angioedema are commonly classified by duration. Lesions of less than six weeks' duration are considered acute; episodes that persist beyond six weeks are designated chronic. The causes and mechanisms of hive formation are different in each instance, as are the prognosis and approaches to treatment.

Acute urticaria can be divided into two general types, depending on the rate at which hive formation occurs and the length of time it is evident. One type produces lesions that last 1-2 hours and is typically encountered in physically induced hives. The inciting stimulus is present only briefly, and there is prompt mast cell degranulation. Biopsy of such lesions reveals little or no cellular infiltrate. The second type produces a prominent cellular infiltrate, and individual lesions can last as long as 36 hours. This type is encountered with food or drug reactions, delayed pressure urticaria, chronic spontaneous urticaria, and urticarial vasculitis.

Chronic spontaneous urticaria is characterized by a non-necrotizing perivascular mononuclear-cell infiltrate (CD4 positive T lymphocytes and monocytes) with variable accumulation of eosinophils, neutrophils, and mast cells. Patients with vasculitis and urticaria appear to be a

separate sub-population in whom the cause and pathogenesis of hive formation probably involves immune complexes, complement activation, anaphylatoxin formation, histamine release, and neutrophil accumulation, activation, and degranulation.

Causes

Acute urticaria

Acute urticaria, which is an allergic (IgE-mediated) reaction, is common in both children and adults. This type of urticaria is a self-limiting process that occurs when mast cells in the skin are activated, degranulate, and secrete histamine, leukotrienes, platelet activating factor (PAF), enzymes such as tryptase and chymase, cytokines, and chemotactic cytokines (chemokines). When an allergen (for example, a food) to which the person is allergic arrives via the bloodstream to mast cells in the skin, it binds to the IgE, and the mast cells become activated, and degranulate. Allergens that can result in acute urticaria include foods, drugs (particularly antibiotics such as penicillin), and venoms from bee, wasp, yellow jacket, hornet, or fire ants. Virtually any allergen that can be disseminated throughout the body, and to which there is an IgE response, has the potential to cause generalized urticaria.

In general, if an allergic reaction causes hives or swelling, it is usually ingested (food, oral drug) or injected (drugs, stings). If an allergen can penetrate the skin locally, hives will develop at the site of exposure. For example, contact urticaria may occur following exposure to latex gloves if sufficient latex penetrates through the skin.

Non-specific stimuli

Acute urticaria can result from "non-specific" stimulation of mast cells, when there is degranulation of mast cells in the absence of a defined allergen. An example is exposure to certain radiocontrast media which changes the osmolality of the environment in which the mast cell resides and can result in degranulation. Patients who develop acute urticarial eruptions can have other accompanying manifestations of a systemic anaphylactic reaction such as wheezing, laryngeal edema, cramps, diarrhea, and hypotension.

Acute viral illnesses in children can be associated with urticarial eruptions which last a few weeks and then spontaneously subside. This typically accompanies symptoms of viral rhinitis, pharyngitis, or bronchitis. When such patients are given an antibiotic, the cause of the hives becomes less clear because a drug reaction becomes an alternative possibility. If penicillin or related antibiotics have been given it is worth performing skin testing for penicillin and/or cephalosporin allergy, rather than making an unsubstantiated assumption that the child is "penicillin allergic." Hepatitis B, infectious mononucleosis (EB virus) and a large number of helminthic parasites may be associated with hives in all age groups.

Codeine and other opiate-derived medications can cause degranulation of mast cells by stimulation of opiate receptors. Urticaria and angioedema can result from agents that alter the metabolism of arachidonic acid, such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). These responses to NSAIDs have the potential to be fulminant with generalized hives and swelling. Angiotensin-converting enzyme inhibitors (ACEIs), drugs used to treat hypertension, (eg, Captopril) can cause recurrent episodes of angioedema, but urticarial skin

lesions are not observed. Because ACE normally inactivates bradykinin, the angioedema is thought to be due to elevated bradykinin levels causing dilation and leaking of vessels in deep layers of the skin. This is the most common cause of angioedema seen in emergency rooms. Tongue, throat and laryngeal swelling can be extremely severe and intubation may be necessary. The swelling resembles that seen in hereditary or acquired C1 inhibitor deficiency where bradykinin is also the mediator of swelling.

Chronic spontaneous urticaria and angioedema

Chronic spontaneous urticaria and angioedema is diagnosed when hives and swelling are present for more than six weeks and when it has been determined that an apparent protracted episode of urticaria is not the result of recurrent episodes of acute urticaria.

It is typically diagnosed when chronic hives do not appear to be associated with any other systemic disease process, and are not due to one of the physically induced urticarias. Research during the past decade suggests an association with autoimmunity in 35-45% of patients. When severe, it can be resistant to therapy and there is a 40% incidence of accompanying angioedema. Angioedema may involve the face, lips, tongue, throat, or extremities but not the larynx. The remission rate is 65% within three years, 85% within five years and 98% within ten years. A form of angioedema in the absence of hives with no identifiable cause is termed idiopathic angioedema.

The physical urticarias

Physically induced hives and/or swelling share the common property of being induced by environmental factors such as a change in temperature or by direct stimulation of the skin by pressure, stroking, vibration, or light.

Cold-dependent disorders

Idiopathic cold urticaria is characterized by the rapid onset of pruritus, erythema, and swelling after exposure to a cold stimulus. The location of the swelling is confined to those parts of the body that have been exposed. When suspected, an ice-cube test can be performed in which an ice cube is placed on the subject's forearm for 4-5 minutes. A positive reaction leads to formation of a hive in the shape of the ice cube within 10 minutes after the stimulus is removed. The time course of this reaction (i.e., cold challenge followed by hive formation as the area returns to body temperature) demonstrates that a two-step reaction has occurred in which exposure to cold is a prerequisite, but hive formation actually occurs as the temperature increases.

One proposal to explain this phenomenon is that patients have an IgE autoantibody to a cold-induced skin antigen. Passive transfer (PK-testing) has been reported. Thus, sensitization might occur in the cold, and release of mediators proceeds as the cells warm. Studies to test this hypothesis have thus far been negative. High levels of IgM and IgG antibodies directed against the Fc portion of IgE have been found in patients with cold urticaria, although the clinical significance of such autoantibodies is questionable.

Localized cold urticaria, in which only certain areas of the body urticate with cold contact, has been reported after predisposing conditions such as cold injury; it has also been reported at sites of intracutaneous allergen injections, ragweed immunotherapy, or insect bites.

Systemic cold urticaria yields severe generalized hive formation resulting from systemic cold challenge occurring over covered or uncovered parts of the body. Symptoms are unrelated to exercise or other activities, and the ice-cube test is negative.

Cold-dependent dermatographism demonstrates prominent hive formation if the skin is scratched and then chilled.

Exercise-induced disorders

Cholinergic or generalized heat urticaria is characterized by the onset of small (1 mm) punctate wheals surrounded by a prominent erythematous flare associated with exercise, hot showers, sweating, and anxiety. Typically, lesions first appear about the neck and upper thorax; when viewed from a distance, hives may not be perceived and the patient appears flushed. Pruritus is a prominent feature of the reaction. Gradually the lesions spread distally to involve the face, back and extremities, and the wheals increase in size. In some patients the hives become confluent and resemble angioedema. Although uncommon, symptoms of more generalized cholinergic stimulation such as lacrimation, salivation, and diarrhea may occasionally be seen. These various stimuli have the common feature of being mediated by cholinergic nerve fibers. Cholinergic urticaria is the only form of hives in which emotional stimuli can, in some patients, initiate an urticarial reaction. One study suggests that a subpopulation of patients has IgE antibody to an antigen in sweat.

Exercise-induced anaphylaxis was first described in a series of patients in whom combinations of pruritus, urticaria, angioedema, wheezing, and hypotension occurred as a result of exercise. The hives seen with exercise-induced anaphylaxis are large (10-15 mm), in contrast to the small punctate lesions characteristic of cholinergic urticaria. Subtypes of exercise-induced anaphylaxis have been described that are food-related. In one of these hives is seen only if exercise takes place within 5 hours after eating a food to which the patient is allergic. In a second subtype, hives occurs if exercise is within 5 hours of having eaten but the identity of the food is irrelevant.

Other physically induced forms of urticaria or angioedema

The remaining forms of physically induced hives or swelling are, with the exception of dermatographism, relatively rare disorders.

Dermatographism

Dermatographism, the ability to write on the skin, can occur as an isolated disorder that often presents as traumatically induced urticaria. It can be diagnosed by observing the skin after stroking it with a tongue depressor or fingernail. A white line secondary to reflex vasoconstriction is followed by pruritus, erythema, and a linear wheal, as is seen in a classic wheal-and-flare reaction. It is rarely severe enough to require treatment.

Pressure-induced urticaria/angioedema

Pressure-induced urticaria typically occurs 4-6 hours after pressure has been applied. Patients may complain of swelling secondary to pressure with normal-appearing skin (i.e., no erythema or superficial infiltrating hive), so that the term angioedema is more appropriate. Others are predominantly urticarial and may or may not be associated with significant swelling. Symptoms occur about tight clothing; the hands may swell with activity such as hammering; foot swelling is common after walking in patients with normal heart function; and buttock swelling may be prominent after sitting for a few hours.

Solar urticaria

Solar urticaria is a rare disorder in which brief exposure to light causes the development of urticaria within 1-3 minutes. Typically, pruritus occurs first, in about 30 seconds, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone caused by an axon reflex. The lesions usually disappear within 1-3 hours.

Aquagenic urticaria

Patients develop small wheals after contact with water, regardless of its temperature.

Chronic Spontaneous urticaria and angioedema (CSU)

This is a common disorder of unknown origin, whose subjects need not be atopic individuals; that is, they do not have an increased incidence of atopic dermatitis, allergic rhinitis, or asthma compared to the incidence of these disorders in the absence of chronic urticaria although their IgE level, as a group, is higher than normal. Some patients are dermatographic, although this is usually of milder degree than is seen with the IgE-dependent dermatographism described earlier. The dermatographism may wax and wane, and the urticaria may vary from severe to mild or may intermittently subside. These individuals have a normal white-blood-cell count and erythrocyte sedimentation rate (ESR) and have no evidence of systemic disease. CSU does not appear to be an allergic reaction in the classic sense, because IgE antibody is not involved and no external allergen is needed to initiate or perpetuate the process. It differs from allergen-induced skin reactions or from physically induced urticaria (e.g., dermatographia or cold urticaria) in that histologic studies reveal a prominent cellular infiltrate around small venules, with an increased number of mast cells. External examination reveals hives with palpably elevated borders, sometimes varying greatly in size and/or shape but generally being rounded.

Association with autoimmune thyroid disease

Patients with CSU have an increased frequency of Hashimoto's thyroiditis. An association has been noted with the presence of antibodies to thyroglobulin, or a microsomal-derived antigen (peroxidase) even if patients are euthyroid. The incidence of thyroid autoantibodies in patients with chronic urticaria is approximately 24%. Thyroid function and thyroid antibodies should be checked in all patients with chronic urticaria. There are no data to suggest that either of these antibodies are pathogenic in terms of hive formation and it is believed that these are associated, parallel, autoimmune events.

Antibodies to IgE or IgE receptor

Studies have shown that a substantial number of patients with chronic urticaria have a positive autologous skin test, meaning that injection of the patient's serum in a skin test leads to a significant wheal and flare reaction. A proportion of such patients (about 35%) have been found to have an IgG antibody directed against the alpha- subunit of the IgE receptor which experimentally can cause degranulation of histamine-containing cells (blood basophils or mast cells). A smaller proportion have anti-IgE antibodies (5%). This accounts for 40% of patients with CSU. Fifty percent of patients with CSU have circulating basophils that are hyporesponsive to activation by anti IgE due to high intracellular phosphatase levels and this reverts to normal during therapy or remission. Mechanisms for histamine release caused by the aforementioned autoantibodies have been described but proof of their pathogenicity is lacking. Yet virtually all diseases strongly associated with autoimmunity turn out to be autoimmune.

Treatment

Treatment of acute urticaria and angioedema

Identification of causative allergens, from the clinical history and blood testing for specific IgE antibodies, will enable the individual with urticaria and angioedema to avoid pathogenic allergens. Where a reaction to medication has been implicated, for example, NSAID's or antibiotics, the physician should identify alternative drug groups for future treatment, and if possible perform skin testing with antibiotics to confirm or refute the diagnosis of specific antibiotic allergy. Acute attacks of urticaria or angioedema can be treated with H1 antihistamines. Treatment with 1% menthol in aqueous cream may suppress itching. As wheals can occur where tight clothing is in contact with the skin, loose clothing should be recommended. Itching is worse in warm conditions, and a cool temperature, particularly in the bedroom, is recommended. If urticaria and angioedema have occurred during a systemic anaphylaxis reaction, the patient should be prescribed an auto-injector of epinephrine to carry. Very often an episode of urticaria occurs without any explanation or lasting clinical significance, and without any risk of recurrence. Patients unresponsive to antihistamines can be treated with a tapering course of corticosteroid.

Physically-Induced Urticaria

Disorders such as cold urticaria, cholinergic (generalised heat) urticaria, and dermatographism can be treated with antihistamines such as fexofenadine, cetirizine or loratidine. If so severe that responsiveness to these is insufficient, higher than normal doses can be used (example fexofenadine 180 mg twice daily; cetirizine 10 mg up to 4 times a day). The next step is higher concentrations of antihistamines such as hydroxyzine or diphenydramine at 25-50 mg four times a day. In some instances, when severe, a particular drug is tried, eg, cyproheptadine 4-8 mg, 3-4 times a day, to treat cold urticaria or hydroxyzine 50 mg four times a day for cholinergic urticaria. Solar urticaria (light-induced urticaria) is treated with antihistamines and sun-screens, if sensitivity is to u.v. wavelengths. Sensitivity to visible light wavelengths is particularly difficult since symptoms can occur indoors as well as outdoors. Delayed pressure urticaria is an exception where symptoms more closely resemble CSU (with which it is commonly associated) and responds poorly to antihistamines. It can be treated with cyclosporine or, perhaps, omalizumab. It does respond to corticosteroid.

Chronic Spontaneous Urticaria

Treatment depends on severity, specific disease manifestations, and a balance between efficacy and drug toxicity and/or side effects. Ideally, non-sedating antihistamines should be tried first, including increased doses as described above for physical urticarias controlled trails demonstrate efficacy at 4 times the dose typically used for allergic rhinitis. The first generation antihistamines such as hydroxyzine or diphenydramine at 25-50 mg four times daily can be employed if the non-sedating, second-generation agents are insufficient. H2-receptor antagonists offer a little more global blockade of histamine receptors by inhibiting H2 receptors once H1 receptor blockage is maximal. There are 10-15% H2 receptors on venular endothelial cells. Leukotriene antagonists (montelukast, zafirlukast) can be tried in patients with severe symptoms but they may still not be satisfactorily controlled with the above-mentioned combinations. Alternate-day corticosteroids, eg, prednisone 10-25 mg every other day can be employed with gradual tapering at a rate of 2.5-5.0 mg every 2-3 weeks or 10-15 mg daily with taper of 1 mg/week. Another approach, and one that may be employed when use of corticosteroids is relatively contraindicated or when steroid side-effects prohibit their use, is cyclosporine. A typical dose range in adults is 200-300 mg/day, to be tapered to the lowest effective dose once a response is obtained. Monitoring of blood pressure and kidney function (urinalysis, BUN, creatinine) needs to be done on a regular basis. The latest therapy is omalizumab supported by phase 1, 2, and three phase 3 trials. It has the best efficacy to side effect profile and once approved for this indication (being reviewed currently) may supplant any use of sedating antihistamines once high-dose non-sedating agents fail. H_2 blockers and leukotriene antagonists may or may not be added next, but corticosteroids can be eliminated for chronic use, and cyclosporine reserved for omalizumab failures.

Urticarial vasculitis can be treated similarly but other agents (that are typically less effective for CSU) may be tried, such as dapsone, hyroxychloroquine, or colchicine. Hydroxychloroquine can be particularly helpful for the treatment of the hypocomplementaemic urticarial vasculitis syndrome. The various types of urticarial vasculitis account for less than 1% of all chronic urticarias.