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Angioedema Associated with Urticaria can be a Silent Killer

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Abstract

Urticaria and angioedema are common diseases in children and adults. Erythematous swelling of the deeper cutaneous and subcutaneous tissue is called angioedema. Urticaria is characterized as the appearance of erythematous, circumscribed, elevated, pruritic, edematous swelling of the upper dermal tissue. Urticaria may occur in any part of the body, whereas angioedema often involves face, extremities or genitalia. Urticaria is considered acute if symptoms are present for less than 6 weeks. In chronic urticaria symptoms are longer than 6 weeks. Acute urticaria has been reported to be the common type in childhood and chronic urticaria is more frequent in adults. Urticaria and angioedema are a frequent cause of emergency room visit but few patients need to be admitted. The basic mechanism involves the release of diverse vasoactive mediators that arise from the activation of cells or enzymatic pathways. Histamine is the best known of these substances, and response consisting of vasodilatation (erythema), increased vascular permeability (edema) and an axon reflex that increases reaction. The most common etiological factors for angioedema and urticaria have been identified as infection, physical urticaria, food allergy, drug adverse reaction, parasitic infestation and papular urticaria. The aim of this study is to define, describe and discuss etiology, diagnostic, treatment and severity.

Keywords: Etiology; Diagnostic approach; Treatment

Introduction

Allergic manifestations have become more and more frequent lately because of the organism's way of reaction, the wide spread of allergens in the environment and because of a higher level of hygiene. Statistic studies reveal that 1 in 4 Europeans suffer of a form of allergy [1]. Allergic manifestations are more frequent in western countries, where hygienic conditions are higher. Angioedema and urticaria rank high among allergic manifestations [1,2].

Hives is an allergic skin reaction that comes on suddenly. The hives themselves are slightly raised, smooth, flat-topped bumps called wheals and welts that are usually slightly more reddish in color than the surrounding skin and cause severe itching. Hives look somewhat like mosquito bites [2-4].

Angioedema is like hives; only the welts are larger and form at a deeper layer in the skin. Angioedema causes severe swelling, usually in the face, near the eyes and mouth. The swelling can also occur in the inside of the throat, which is a dangerous situation because it can close off the passage of air into the lungs [3,5,6].

Classification of Hives and Angioedema

Hives

1. Acute urticaria
2. Chronic urticaria [2,3]

Angioedema

1. Hereditary angioedema type1 (HAE1)
2. Hereditary angioedema type2 (HAE2)
3. Hereditary angioedema type3 (HAE3)
4. Acquired angioedema type1 (AAE1), (very rare)
5. Acquired angioedema type2 (AAE2), (very rare)
6. Non Histaminergic angioedema (INAE), (5% of cases)
7. Idiopathic angioedema
8. Allergic angioedema (most common form)
9. ACE inhibitor-induced angioedema (4-8% of cases) [5-11]

Hereditary angioedema accounts for only 0.4% of angioedema cases; however, the specific diagnostic tests and high mortality rate associated with hereditary angioedema deserve special attention [1,6,7].

Hereditary angioedema is an autosomal dominant disease usually associated with a positive family history of angioedema. However, numerous cases are due to a new mutation of the gene [5,8]. In approximately 80-85% of hereditary angioedema cases, serum levels of C1 inhibitor (C1-INH) are decreased to approximately 30% of reference range values. In contrast, about 15% of patients with hereditary angioedema have reference range levels of antigenic, but mostly nonfunctional, C1-INH [8,9]. Missing or nonfunctional C1 INH leads to failure in controlling the enzymatic activity of C1, resulting in lower levels of the early-acting complement components C4 and C2 because of overconsumption.

The structural abnormalities in the SERPING1 genes in patients with hereditary angioedema have been found to be very heterogeneous. More than 150 mutations have been reported in unrelated patients [5,8].

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HAE3 is the most recently described type of hereditary angioedema. In HAE3, C1-INH function and complement components are normal [5-7]. AAE1 is usually linked to an underlying lymphoproliferative disorder. The onset of angioedema can precede other symptoms of a lymphoproliferative disease [5-8]. AAE2 is associated with autoantibodies that directly inhibit C1INH function. AAE1 and AAE2 are very rare in the pediatric population [5-8]. INAE angioedema is angioedema without urticaria. Patients usually do not respond to antihistamines. [5-8]. The idiopathic form of angioedema may be associated with swelling, hives that persist longer than 6 weeks, or both [5-8,10]. Allergic angioedema is characterized by swelling, hives, or both in reaction to environmental factors such as food, an insect sting or bite, cold, heat, latex, or a drug. Usually, these environmental factors provoke histamine release that leads to swelling, hives, or both [5-8] (Table 1).

Pathophysiology

Urticaria and angioedema partly have the same pathophysiology. Urticaria results from the release of histamine, bradykinin, leukotriene C4, prostaglandin D2, and other vasoactive substances from mast cells and basophils in dermis. These substances cause extravasation of plasma into the dermis, leading to the urticarial lesion. The intense pruritus of urticaria is a result of histamine released into the dermis [12-14].

In terms of immune reactions, urticaria and allergic angioedema admit 2 types of reactions: immune mediated and non-immune mediated. Histamine is the most frequently involved mediator. It is released from the mastocyte along with leukotriene (LT) and prostaglandin through a directly immune mediated mechanism, mediated by IgE, which is characteristic to food products, medicine and insect bites. It can also be released directly in viral and bacterial infections and in certain medicine's case (antibiotics, AINS, opioids, radiocontrast agents). It can also be released from food products containing histidine, which is found in fish, cheese and red wine.

Histamine is the ligand for 2 membrane-bound receptors, the H1 and H2 receptors, which are present on many cell types. The activation of the H1 histamine receptors on endothelial and smooth muscle cells leads to increased capillary permeability. The activation of the H2 histamine receptors leads to arteriolar and venule vasodilation.

In the immune mechanism of urticaria and allergic angioedema there are involved 3 types of reactions [12-14]:

1. The type I allergic immunoglobulin IgE response is initiated by antigen-mediated IgE immune complexes that bind and cross-link Fc receptors on the surface of mast cells and basophils, thus causing degranulation with histamine release.

2. The type II allergic response is mediated by cytotoxic T cells, causing deposits of immunoglobulins, complement, and fibrin around blood vessels. This leads to urticarial vasculitis.

3. The type III immune-complex disease is associated with systemic lupus erythematosus and other autoimmune disease that cause urticaria.

Urticaria	Angioedema
- A rash of smooth, raised, pink or reddish bumps of different sizes, called wheals	- Describes marked swelling, usually around the eyes and mouth
- Appear suddenly	
- May cover all or part of the body	- It may also involve the throat, tongue, hands, feet and genitals
- Usually appear first on the covered areas of the skin such as the trunk and upper parts of the arm and legs	- The skin may appear normal, without hives or other rash - The eyes may appear swollen shut
- Wheals appear in batches; each wheal may last from a few minutes to six hours	- The swelling may not be symmetrical
- Are usually patchy at first, but the patches may run together until the urticaria cover most of the body	
- The patches can be small or large; they are usually irregular in shape	
- The itching is often very intense [22]	- The swelling usually do not itch but may be painful or burning [22]

Table 1: Urticaria and angioedema symptoms and signs.

Bradykinin is an important swelling mediator. Kallikrein forms from C1-INH under prekallikrein action. It acts upon kininogens, turning it into bradykinin.

In some patients with chronic urticaria the disease appears to be an autoimmune disorder. Thus about 35-40% of patients have circulating IgG antibodies directed against a subunit of the IgE receptor, and another part of patients (5-10%) have antibodies against a subunit of IgE. These antibodies and complement fixation increase histamine release. In the last decade predominantly allergic and autoimmune diseases were found. This is due to stimulation of T cells toward T helper 2 growing and encourages the release of IgE antibodies. Changing the ratio of T helper 2 lymphocytes and T helper 1 lymphocytes in favor of T helper2 cell can be explained by the hygiene measures supported with decreased infections and thereby stimulate T lymphocytes lack helper 1. Autoimmune diseases such as thyroiditis, vitiligo, type I diabetes, rheumatoid arthritis, pernicious anemia, are frequently associated with chronic urticaria. Recently, a strong association was found between basophil-histamine-releasing activity and HLA-DR4 and DQ8. The basophil histamine release assay is the "gold standard" for detecting functional autoantibodies in the serum of patient with chronic urticaria. The finding that peripheral blood basophils are reduced or absent in patients with chronic urticaria histamine-releasing autoantibodies suggests that chronic urticaria has an autoimmune origin [15].

Non-Immune-Mediated Urticaria

Complement-mediated urticaria includes viral and bacterial infections, serum sickness, and transfusion reactions. Urticarial transfusion reactions occur when allergenic substances in the plasma of the donated blood product react with preexisting IgE antibodies in the recipient. Certain drugs (opioids, vecuronium, vancomycin, and others) as well as radiocontrast agents cause urticaria due to mast cell degranulation through a non-IgE-mediated mechanism [12-15].

Etiology

In 50% of patients with acute urticaria, a specific etiology can be identified. Brief episodes of urticaria can be associated with identifiable causes, and the method of exposure (direct contact, oral or intravenous routes) is usually known. Urticaria is often associated with a recent infection [16-20].

Food allergens

The most famous food products involved in the appearance of urticaria are: nuts, peanuts, eggs, fish, milk and tomatoes. Fish, cheese and red wine can contain histidine, which can eventually cause urticarial reactions or allergic angioneurotic edema.

Medical allergens

A list of medicine, such as aspirin, NSAIDs, opiates, succinylcholine, antibiotics (beta-lactams, polymyxin, ciprofloxacin, vancomycin, and rifampin) can cause urticaria and angioneurotic edema through a non-

allergic mechanism, but with participation of IgE. Mainly, any drug is capable of inducing an allergic reaction.

Contact allergens

These refer to those allergens which appear during daily activities in some professions. In this case, exposure to eggs, nuts and a whole list of other products can cause urticaria manifestations.

Insect bites

In this case, the most common are the bites of mosquitoes, bees and spiders.

Hypersensitivity

Urticaria may be caused by other immediate hypersensitivity allergic reactions to an ingested, inhaled, or percutaneously inoculated substance (e.g. Latex, stinging insects, and occupational exposures).

Medical causes

Urticaria has been reported with infectious diseases. Viral infections associated with acute urticaria include acute viral syndromes, hepatitis (A, B, and C), Epstein-Barr, and herpes simplex virus. Streptococcal infection has been reported as the cause of 17% of acute urticaria cases in children. Urticaria has also been reported with chronic parasitic infections. Although sinusitis, cutaneous fungal infections, Helicobacter pylori infection, or other acute infections have been reported in the literature to cause urticaria, the data are not strongly supported [19]. Hormonal causes via endocrine tumors or ovarian pathology are rare. Oral contraceptive use or changes in the menstrual cycle have been reported as a possible cause of urticaria; patients commonly report worsening of hives with the menstrual cycle. This may be hormonally mediated, and the cyclical use of analgesics should also be considered as a possible etiology.

Recurrent urticaria includes the following: crioglobulinemia, serum sickness, other immune complex-mediated inflammation, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, hypothyroidism and hyperthyroidism, although euthyroid patients with antithyroid antibodies, lymph reticular malignancies, pregnancy.

Physical causes

They include the following: cold, pressure, vibration, cholinergic, sunlight, water, dermographism, exercise [3,21,22].

Epidemiology

Urticaria (acute and chronic) affects 15-25% of the population at some time in their lives. The incidence of acute urticaria is higher in people with atopy, and the condition occurs most commonly in children and young adults [2,6].

Some patients can have both urticaria and angioedema, occurring simultaneously or separately. Approximately 50% of patients have both urticaria and angioedema, whereas 40% have urticaria alone, and 10% have angioedema alone. Hereditary angioedema accounts for only 0.4% of cases of angioedema but is associated with a high mortality rate [2,6,7,13].

The II Pediatric Clinic's cases, from January 2011 until January 2012, have noted 1180 patients who presented different allergic manifestations of teguments, representing 18% out of the total of 6400 patients that were interned over the course of that year. Urticaria caused by food was diagnosed in 35% of the 1180 allergic patients, meaning 436 patients. The rest of the urticaria manifestations appeared as results of infections, medicine use or specific disease. Of the patients with urticaria, 51%, i.e. 601 patients also presented angioneurotic edema manifestations. To identify the allergens, the specific IgE pediatric panel was made for 20 allergens.

Hereditary angioedema

Lack of pruritus and urticarial lesions, recurrent GI attacks of colic and episodes of laryngeal edema are the most commonly symptoms and signs.

Appearance of linear wheal at site of brisk stroke with firm object suggests dermographism.

Serum sickness

It is an immune complex–mediated hypersensitivity reaction characterized by urticaria, pyrexia, lymphadenopathy, myalgia, and arthralgia or arthritis.

Pressure urticaria

It is typically delayed, most commonly occur 4 hours after the sustained stimulus (e.g., shoulder strap or belt, running, or manual labor). Often accompanies dermographism or chronic idiopathic urticaria [2-5].

Exercise-related anaphylaxis

It is characterized by the appearance of pruritic cutaneous erythema and urticaria. It may progress to angioedema of face, oropharynx, larynx, or intestine or to vascular collapse. Exercise-induced anaphylaxis represents a distinct form of physical allergy.

Cholinergic urticaria

In cholinergic urticaria, itching, burning, tingling, warmth, or irritation precedes the onset of numerous small (1 to 2 mm in diameter), pruritic wheals surrounded by large area of erythema. Patients who are affected with cholinergic urticaria may experience systemic symptomatology, such as fainting, abdominal cramping, diarrhea, salivation, headaches. Angioedema, asthma, anaphylactoid reactions, and even anaphylactic reactions are also reported [2-5].

Cold urticaria

Exposure to low ambient temperature or cold objects causes redness, itching, swelling and hives on the skin that has been in contact with the cold. Swimming in cold water is the most common cause of a severe, whole-body reaction - leading to vascular collapse [5-7].

Solar urticaria

It is characterized by pruritus, stinging, erythema, and wheal formation after a brief period of exposure to natural sunlight or an artificial light source emitting the appropriate wavelength.

Vibratory angioedema

It is a rare form of chronic hives; the stimulus is a strong vibration which can occur with cholinergic urticaria. Rare forms of physical allergy such as local heat urticaria, aquagenic urticaria and contact urticaria are also reported [2-5].

Diagnostic Approach

Detailed history is essential for diagnosis. Patients with angioedema

or urticaria should be questioned to identify the offending antigen. A personal or family history of atopy such as allergic rhinitis, asthma, and aspirin allergy should be sought.

Physical examination include: thyroid enlargement, lymphadenopathy or hepatosplenomegaly, joint, renal, central nervous system, skin, or serous surface abnormalities (suggesting a connective tissue disorder), dermographism.

Laboratory tests consist of IgE measurement, skin testing, monospot test if acute mononucleosis is suspected and complement studies to exclude hereditary or acquired C1 esterase inhibitor deficiency [2-5].

IgE-mediated reactions to environmental allergens can be confirmed by skin-prick testing and radioallergosorbent tests on blood. Results of both tests have to be interpreted in clinical context.

For diagnosis of acute urticaria clinical signs and medical history are important, without the need for specific tests. In chronic urticaria diagnostic medical history and clinical signs are necessary. For differential diagnosis it is important to exclude the drug-induced urticaria, autoimmune thyroiditis which determines TPO and TSH. To extend diagnosed chronic urticaria, tests are required for: infectious disease, type I allergy, autoantibodies, physical tests, pseudoallergen-free diet for 3 weeks and tryptase biobsy. To exclude other forms of urticaria such as cold contact urticaria, delayed-pressure urticaria, heat contact urticaria, aquagenic urticaria, cholinergic urticaria and dermographic urticaria provocation tests are made [15].

Differential diagnosis

➢ Contact dermatitis: It is characterized by vesicular eruption. It progress to chronic skin thickening with continued allergenic exposure.

➢ Atopic dermatitis: Major characteristics include the following: pruritus, facial and extensor involvement in infants and young children, chronic relapsing dermatitis and personal or family history of atopy.

➢ Cutaneous mastocytosis: It is characterized by reddish-brown macules or papules that respond to trauma with urticaria and erythema.

➢ Systemic mastocytosis: Patients with systemic mastocytosis can have episodic systemic flushing, with or without urticaria.

➢ Cutaneous necrotizing angiitis (urticarial vasculitis): It tends to run a chronic course. A patient presents an urticarial eruption, associated with burning rather than pruritus, lasting for more than 24 hours in a fixed location. Lesions have an erythematosus appearance and heal to a pigmented scar. Urticarial vasculitis is associated with arthralgias, an elevated erythrocyte sedimentation rate (ESR), and normo- or hypocomplementemia.

➢ Other causes of facial swelling include: superior vena cava syndrome, hypothyroidism, autoimmune disorders, lymphoma and other tumors of the head and neck [2,17].

Treatment

Medical treatment

Acute urticaria may progress to life-threatening angioedema and/or anaphylactic shock in a very short time. If associated angioedema is present, especially if life-threatening obstruction of the airway is suspected, emergency treatment is needed. Treatment consists in airway management, glucocorticoids, H_1 and H_2 antihistamines and subcutaneous epinephrine.

The treatment of urticaria with angioedema depends on the severity of symptoms. For mild to moderately severe localized symptoms, a nonprescription antihistamine by mouth is usually adequate, along with skin-care measure for comfort. For more severe cases, an injection or short course of a corticosteroid may be needed to rapidly reduce swelling and itching.

As advised in the 2009 EAACI/GA(2)LEN/EDF/WAO management guideline, due to the fluctuating nature of acute urticaria and the chance that spontaneous remission can occur at any time, continued or alternative drug treatment should be reevaluated every 3-6 months.

Medications

H1 antagonists (first generation antihistamines): Short-acting type H1 antihistamines: These medications, including diphenhydramine, are the primary treatment of mild cases of hives and angioedema. The older, first-generation H1 antagonists are effective in reducing the lesions and pruritus but can produce a number of adverse effects, such as drowsiness, anticholinergic effects, and cognitive effects, which may continue until the next day. Many interactions have been described for these sedating antihistamines with alcohol and drugs affecting the central nervous system, such as analgesics, hypnotics, sedatives, and mood elevating drugs. Thus, these agents can be useful if administrated at bedtime [6,20,23,24].

Commonly used first generation agents include diphenhydramine, hydroxyzine, chlorpheniramine and cyproheptadine. For refractory cases, use a combination of H1 and H2 antihistamines plus PO glucocorticoids.

H1 antagonists (second-generation antihistamines): The second generation antihistamines are minimally sedating and free of anticholinergic effects, with very few adverse effects reported (cetirizine can cause drowsiness in up to 10% of patients). Considering their good safety profile, these agents should be considered as the first line symptomatic treatment for urticaria. Many specialists prefer the use of these agents for chronic urticaria. Second-generation agents are cetirizine, levocetirizine, desloratadine, loratadine and fexofenadine [23-25]. Most patients with chronic urticaria can use second-generation antihistamine administrated in single dose, preferred at bedtime.

H2 antagonists: H2 antagonists are not effective when used as single agents for urticaria, however, the combination of an H1 antagonist with an H2 antagonist has been shown to be more effective than an H1 antagonist alone. These drugs are usually used to decrease gastric acid secretion. Most commonly used agents are ranitidine and cimetidine [6,23].

Corticosteroids: The EAACI/GA(2)LEN/EDF/WAO management guideline recommends the use of corticosteroids only in severely affected patients.

For acute urticaria nonresponsive to antihistamines and acute exacerbations of chronic spontaneous urticaria, a short course of an oral corticosteroid or a single dose of a long-acting injectable steroid is not usually associated with long-term sequelae. Corticosteroids stabilize mast cell membranes, inhibit histamine release and reduce the inflammatory effect of histamine and other mediators. These drugs may be helpful to reduce the chance of the rash coming back and to relieve symptoms, such as swelling and inflammation, but may take a few hours to work. Examples are prednisone, methylprednisolone and dexamethasone.

Sympathomimetic agents: Sympathomimetic agents cause vaso-

constriction, reduce erythema and swelling. The efficacy of epinephrine in acute urticaria remains controversial. If angioedema is present with urticaria intravenous epinephrine should be used [26-28].

Immunomodulatory and anti-inflammatory therapy: Cyclosporin is recommended only for patients with severe disease refractory to any dose of antihistamine. This drug cannot be recommended as standard treatment due to a high incidence of adverse effects. Intravenous immunoglobulins (IVIG), plasmapheresis and antagonists of tumor necrosis factor α (TNFα) are recommended only to be initiated by specialists with considerable expertise in urticaria as last options. IVIG and plasmapheresis can be a consideration in chronic spontaneous urticaria that is unresponsive to medication and anti-TNFα for delayed pressure urticaria [17,23].

Colchicine and dapsone modulate polymorphonuclear lymphocyte function; for this reason they can be useful for refractory urticaria and urticarial vasculitis in which PMNs and mixed infiltrate can be present.

Omalizumab (monoclonal antibody to IgE) has now been shown to be effective in selected patients with chronic spontaneous urticaria, cholinergic urticaria, cold urticaria and solar urticaria, but considerable further study is needed [29].

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