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Current Concepts in the Pathogenesis and Management of Urticaria and Angioedema:

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Definitions

Urticaria is characterized by transient pruritic and erythematous or pale plaques and papules which fade without a trace. It is traditionally classified as acute or chronic depending on whether episodes of wealing occur repeatedly for less or more than 6 weeks duration, respectively.

Acute urticaria is more common than the chronic form and has a higher prevelance in children and persons with atopic background[1]. It is frequently attributed to allergic or non-allergic reactions caused by viral infections, medications and foods. Chronic urticaria is often difficult to evaluate and treat because an underlying cause can be found in less than 20% of patients, and had therefore been historically referred to as "idiopathic". However, recently it has been recognized that 40% to 50% of chronic urticaria patients have autoimmune antithyroid antibodies or specific lgG antibodies to IgE or its receptors on mast cells[2]. Furthermore, physical, vasculitic and contact types of urticaria are recognized subsets of chronic urticaria Angioedema is the term used to describe deep and painful urticarial lesions that develop as edematous swellings in subcutaneous or submucosal tissues. It is considered as a grave expression and/or progression of urticaria and occurs with urticaria in about 50% of patients. In significant numbers of patients angioedema occurs without urticaria and is associated with acquired or inherited complement abnormalities[2,3].

Pathogenesis

Urticaria, angioedema and anaphylaxis are a spectrum of vascular reaction patterns caused by the release of vasoactive and chemotactic pro-inflammatory mediators from mast cells and basophils. In urticaria mast cell degranulation, casuses vasodilatation and leakage of plasma in the superficial dermis; while in angioedema the inflammatory reaction involves deeper vessels located in the subcutaneous or submucosal connective tissue. Anaphylaxis is a similar but more severe systemic vascular reaction presenting with acute, life-threatening, generalized urticaria/angioedema, hypotension and dyspnea[4].

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Activated mast cells release histamine, heparin, acid hydrolases, neutral proteases, eosinophil and neutrophil chemotactic factors stored in their granules. Furthermore, they can also release newly generated lipid-derived mediators such as prostaglandin (PGD_2), leukotrienes (LTB_4, LTC_4, LTD_4), platelet activating factor (PAF) and other cytokines[5]. The predominant mediator of urticaria is histamine. However until now there is no convincing evidence that the newly generated vasoactive products and cytokines from mast cells play any significant or direct role in the pathogenesis of urticaria.

Activation and release of pro-inflammatory mediators from mast cells can be effected by immunological (allergic) or non-immunological (non-allergic) pathogenetic mechanisms[6]. In the classical immediate hypersensitivity reaction activation of mast cells and basophils occurs as a result of cross-linking of two adjacent alpha subunits of high-affinity IgE-receptors on their surfaces by specific antigens or haptens[5,6]. Cross-linking of IgE-receptor can also occur by autoantibodies directed against IgE bound to the mast cell surface or against the alpha subunit of its receptor. The possibility that chronic idiopathic urticaria (CIU) can be an autoimmune disorder was suggested by the frequent association of CIU and autoimmune thyroiditis with thyroglobulin and microsomal (peroxidase) autoantibodies. Furthermore, a histamine releasing factor had been demonstrated in the sera of up to 60% of patients with CIU[7]. The histamine releasing factor is currently recognized as complement activating pathogenetic IgG autoantibodies to the high affinity receptors of IgE. These autoantibodies were mainly of IgG_1 and IgG_3 subtypes and were demonstrated in 30% to 50% of cases of CIU[8]. Complement-fixation and activation is particularly relevant to autoimmune urticaria because the complement fragments C5a and C3a are well-known anaphylatoxins and are potent activators of mast cells and can thus augment the release of histamine by autoantibodies[9]. Complement-mediated acute urticaria/angioedema also occurs in patients with C_1 esterase inhibitor abnormalities, serum sickness and other forms of urticarial vasculitis.

Non-immunological (non-allergic) activation and degranulation of mast cells can be produced with a variety of substances including neuropeptides, drugs (especially antibiotics, non-steroidal anti-inflammatory drugs (NSAIDS), anticonvulsants and opiates), some radiocontrast media, and some foods such as nuts, shell fish and strawberries. These substances produce acute urticarial reactions which are usually similar or indistinguishable from the true allergic variety, and are thus referred to as pseudoallergic or intolerance reactions[10]. The underlying molecular mechanisms of pseudoallergic reactions are often obscure; but have been recognized as non-IgE dependant reactions[11]. Some drugs such as opiates, polymyxin B, dextran and muscle relaxants are known to be specific mast cell degranulating agents and/or direct histamine releasers. The commonest group of drugs causing pseudoallergic urticarial reactions is aspirin and other NSAIDS. Suggested mechanisms for this group of drugs include inborn errors of acetyl salicylic acid metabolism or effects on arachidonic acid metabolism and its cyclooxygenase and lipoxygenase products[12,13].

While it is conceivable that some foods containing vasoactive amines (such as cheese, shell fish, tomatoes and avocados) or histamine releasing substances (such as in

strawberries) can exacerbate or precipitate urticaria, specific food allergies are generally rare[14]. The exact role of food dyes and preservatives in the genesis or continuation of urticaria remains controversial although 20% of chronic urticaria patients had been reported to react to tatrazines and other azodyes[15].

Contact urticaria defined as immediate wealing and itching occurring at sites of contact of the offending agent with the skin or mucous membranes can be caused by allergic or non-allergic mechanisms. Allergic contact urticaria is seen more commonly in atopic individuals, can be caused by foods (e.g. peanut), latex or drugs (e.g. antibiotics and sex hormones). The diagnosis of contact urticaria is usually confirmed by positive patch or scratch tests[16]. Pseudoallergic contact urticaria is mainly caused by chemicals such as ammonium sulphate, menthol and polyethylene glycol which act as direct mast cell degranulating agents. Radiocontrast media commonly cause pseudoallergic urticarial reactions but IgE-mediated reactions can also occur[17].

Angioedema with weals occurs in about 50% of urticaria patients; but angioedema without weals is either caused by hereditary or acquired defects in the inhibitor of the first component of the complement system[18]. Hereditary angioedema is rare, accounting for about 1% of all cases of angioedema and is transmitted as an autosomal dominant trait. Acquired C_1 esterase inhibitor deficiency associated with angioedema is usually of late onset (fifth and sixth decade), with no family history, normal levels of C_1 functional protein and most frequently associated with lymphoproliferative disorders with autoantibodies directed against C_1 inhibitor protein. In patients with angioedema due to C_1 esterase deficiency the suggested mechanisms include coagulation cascade factors, complement system and kallikrein-kinin system; but the most likely primary mediator is bradykinin[19].

Many medications especially aspirin, NSAIDS, pencillins may cause urticaria with angioedema. However the angiotensin converting enzyme inhibitors (ACE) are the only known drugs that produce angioedema without weals, and they act by potentiation and/or prolongation of the effects of bradykinin[20].

Urticarial vasculitis is a rare from of chronic urticaria in which histological evidence of vascular damage can be identified by a skin biopsy. It is characterized by painful erythematous or edematous lesions which persists for more than 24 hours and usually resolve without residua or with purpura, bruising and hyperpigmentation. It is a clinical manifestation of cutaneous necrotizing venalitis due to a type III hypersensitivity reaction with activation of the complement system and deposition of immune complexes[21]. Approximately 70% of the afflicted individuals with urticarial vasculitis are women, but the prevalence of this disorder remains unknown. The archetypal form of urticarial vasculitis is serum sickness which follows parenteral injections of therapeutic sera; but other causes include connective tissue disorders, drugs, (especially pencillins), radiocontrast media, infections (e.g. hepatitis B and C), physical urticarias and colon carcinoma[22]. The onset of the serum sickness episode usually occurs 1-3 weeks after exposure and is often associated with systemic symptoms such as fever, arthralgia and gastrointestinal upset.

Management of urticaria/angioedema

The ideal treatment of urticaria/angioedema is identification and removal of its cause. Careful history taking by a knowledgeable physician or a detailed questionnaire is the most appropriate method for diagnosis and evaluation of urticaria. In acute urticaria a causative factor can be found in about 50% of patients, if a detailed history is taken. In chronic urticaria significant findings in the history and physical examination should dictate the laboratory investigations Therefore, autoimmune, vasculitic, physical and contact forms of chronic urticaria should be considered before a diagnosis of idiopathic urticaria can be suggested. Histamine releasing autoantibodies can be detected by the autologus serum skin test (ASST) which raises a weal on re-injection of the patient serum[23]. Furthermore, physical urticarias are subsets of chronic urticaria and it is worth noting that they comprise 20% to 30% of CIU cases[24]. The physical triggers include mechanical, thermal, exercise, solar and aquatic exposures. The diagnosis of each type of physical urticaria can easily be confirmed by its specific clinical test(s).

The first-line of therapy in urticaria is directed at blocking the effects of histamine through its H_1 receptor activity. The second generation H_1 antihistamines such as loratadine, cetrizine and acrivastine or their newly introduced derivatives such as desoloratidine, fexofenadine and levocetirizine are now the treatment of choice for urticaria and has replaced the old traditional antihistamines[25]. The use of the old traditional antihistamines is limited by their side effects, including sedation, anticholinergic effects and some excitation in children. However they can still be useful if night-sedation is needed or in combination with second generation H_1 or H_2 antihistamine in some patients. The tricyclic antidepressant doxepin has potent H_1 and H2 antihistaminic activity and has been effective at low doses in the treatment of chronic urticaria[26].

The second-line therapy is generally used to control severe or refractory urticaria/angioedema with or without impending anaphylaxis using glucocorticoids, epinephrine and antihistamines. Systemic steroids are often required as short oral courses at standard dosage (0.5- 1mg/kg/d) to control severe generalized urticaria or urticarial vasculitis. Their use in chronic and less severe forms of urticaria is not recommended[27]. The attenuated androgens danazol and stanozolol, antifibrinolytics, purified or recombinant C_1 protein and frozen plasma are the treatment options currently available for management of hereditary angioedema. The emergency treatment for acute non-hereditary angioedema with impending anaphylaxis is parenteral corticosteroids, antihistamines and epinephrine given by S.C., I.M. or I.V. injection every 10-15 minutes until recovery from an attack.

The treatments reported to be beneficial in some chronic urticaria patients include H_2 antihistamines, doxepin, the beta-adrenergic agonist terbutaline and the calcium-channel blocker nifedipine. In a selected group of chronic urticaria patients the new leukotriene receptor antagonists montelukast and cetrizine were found to be effective, however, in a

recent randomized placebo-controlled trial there was no difference between the groups treated with montelukast and placebo[28,29].

In small uncontrolled trials immunomodulation by plasmaphresesis, intravenous immunoglobulines or cyclosporine A have been successfully used in patients with severe, unremitting or recalcitrant chronic urticaria[30]. Isolated reports exist for the treatment of urticarial vasculitis and other forms of chronic urticaria with indomethacin, colchicine, sulfasalazine, dapsone, hydroxychloroquine, methotrexate and cyclophophosamide.

The development of new therapeutic agents for urticarial reactions include anti-IgE monoclonal antibodies, specific targeting of autoantibodies to IgE receptors and phosphodiesterase antagonists which can down-regulate immune and inflammatory cells[31]. Some of these new agents may turn out to be more effective and safer options in the treatment of chronic urticaria.

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