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A REVIEW ARTICLE ON THE PATHOGENESIS OF URTICARIA

Dermatology

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KEYWORDS

INTRODUCTION

Urticaria is a condition characterized by the development of wheals (hives), angioedema or both. Chronic spontaneous urticaria (CSU) is defined by the Spontaneous appearance of wheals, angioedema, or both for > 6 weeks due to known or unknown causes [1].

CSU is characterized by the degranulation of cutaneous mast cells and the influx of a mixed cellular infiltrate, including neutrophils, lymphocytes, basophils, and eosinophils Basopenia has been linked to severe and refractory forms of CSU. The role of eosinophils is unclear and speculative [2]. Studies on the role of eosinophils as a marker for treatment outcome have yielded mixed results in the few done so far [3]. Chronic urticaria is a disease that has a substantial impact on the quality of life, more so in India where the condition is often under recognized and inadequately treated.

- **Pathogenesis**

Theories of pathogenesis, in history:

Hippocrates, in 16century, described an association between insect bites, nettles, gastrointestinal tract infections and urticaria. Behrens, later by the18th century described idiosyncrasy as a cause [4]. Chemiz proposed the humoral theory as an explanation towards the waxing nature of wheals [5]. Chalmers put forth the Toxin theory, wherein the formation of toxic substances from certain foods, triggers urticaria. Eulenburg stated the nervous theory, that certain contents in food, act on the nervous system to give rise to wheals. Neisser in 1901, described the Angioneurotic theory, which is an extension of nervous theory and states that a secretory neurosis and dilatation results in urticaria. Frank proposed the meteorological theory which states that, the stars under which a person was born and its arrangement, determines his allergic status. The menstrual theory came about in 1864, which stated women are hypersensitive to endogenous hormones and developed urticaria. The micro thrombi theory brought about by Philipson explained that microthrombi were responsible for the migratory nature of the wheals.

Gilchrist and Torak at the onset of the 20th century described the theory of inflammation, which was very well received. Dale and Laidlaw, in 1910 explained that intradermal injection induced smooth muscle contraction, which was responsible for formation of wheals, erythema and pain. When Sir Thomas Lewis in 1927, described the triple response, an important milestone was laid towards a higher understanding of the flare response. Prausnitz & Kustner, added that both allergen and a humoral factor is important to produce wheals and not an allergen by itself. Ishizaka and Johansson discovered these humoral factors, which were found to be a unique class of immunoglobulins called IgE. Further, the discovery of the binding of IgE to the surface of mast cells led to a landmark in understanding the pathogenesis

Current understanding of the pathogenesis of urticaria:

The manifestations of urticaria are best described pathogenetically by mast cell activation and degranulation. This phenomenon can be triggered by both immunological as well as non-immunological stimuli. A type 1 hypersensitivity reaction explains acute urticaria, although IgE dependent mechanisms have been described for chronic urticaria as well. Atopy, which represents an IgE mediated spectrum of allergic diseases that includes bronchial asthma and allergic rhinitis, also explains some forms of allergic urticaria. Numerous mechanisms have thus been proposed for chronic urticaria, the most accepted to date has been the autoimmune hypothesis, which implicates autoantibodies in the pathogenesis of CSU. Functional IgG antibodies targeting IgE or its high affinity receptor on the surface of mast cells and basophils in the skin, have been demonstrated, leading to mast cell activation. Direct mast cell activation can also be brought about by numerous non-immunological stimuli such as beta lactam antibiotics, aspirin, certain food products, radiocontrast agents, Ultra-Violet (UV) radiation etc.

Upon activation of the mast cells, complement fixation via the classical pathway occurs, which facilitates interaction with C3a and C5a molecules, which in turn activates more mast cells, leading to their degranulation and release of inflammatory mediators [6,7].

Numerous mediators with a wide array of functions are released from the mast cells, these are classified as preformed or newly synthesized mediators. Histamine is the most important among the preformed mediators which through its action on histamine receptors (H1-4) causes vasodilatation, increased vasopermeability and itching. Some other preformed mediators involved are proteases like tryptase, chymase, carboxypeptidases, etc. Among the newly synthesized mediator, prostaglandin D2 plays a significant role in the pathogenesis, other mediators in this group are leukotrienes, cytokines, granulocytes macrophage colony stimulating factor, all of which prolongs the inflammation, cytokines perform a wide array of functions in ensuing the inflammatory process.

While theories on mechanisms of mast cell activation have predominated discussions in yesteryears, the role mast cell independent mechanisms of urticaria have gained speed recently. These include the extended role of mixed cellular infiltrates from the blood predominating the dermal space [8,]. Chemotactic factors recruit neutrophils which predominate in early urticarial lesions which in turn releases vasoactive substances and proteases that increase tissue damage. Lymphocytes predominate during the later phase of inflammation. In fact, the ever-evolving role of imbalances between the T lymphocyte subsets, Th1 and Th2 cytokines have been speculated in the pathogenetic mechanisms of chronic urticaria just as in other inflammatory disorders like bronchial asthma and COPD. [9] Th2 type of lymphocytes have been shown to predominate in urticarial lesions, evidence of Th1 and Th17 cells have also been found in some. Eosinopenia and basinopenia have been described in chronic urticarial lesion. Eosinophils increase mast cells and basophil activation, contributing to prolong inflammation. Basophils have granules containing histamine and other mediators which are released upon activation. These changes reverse with treatment. A brief account of the important mediators of inflammation, follows[10].

1. Histamine:

Histamine is the most important preformed mediator of inflammation in urticaria and is stored in mast cells and basophils. Secretagogues stimulate their release, which in turn acts on specific receptors to bring about its action. Activation of H1 to 4 receptors mediates the actions of mast cells. H1 and H2 are the predominant receptors in the skin and are

found in epithelial cells, vascular and perivascular cells mediating itch, vasopermeability and vasodilatation. Activation of H2 receptor alone brings about increased vasopermeability and vasodilation leading to wheal formation. Histamine, in addition, stimulates nerve endings to produce flare, completing the triple response. When compared with healthy controls, greater amounts of histamine are released by mast cells in urticaria and at a lower threshold of receptor activation [11].

2. Proteases:

a. Tryptase:

tryptases are tetrameric cationic protein found abundantly in human mast cells and basophils. They are present in 2 forms, alpha and beta tryptases, respectively. Mast cells release alpha-tryptase whereas mast cell degranulation brings about release of beta-tryptase. Their biologic functions are not completely understood but they increase vasopermeability and airway smooth muscle reactivity. In addition, they act as growth factors for epithelial cells and fibroblast. The total tryptase levels when available serve as potential indirect measures of mast cell activation and mast cell burden.

b. Chymase:

It is a serine esterase which converts angiotensin I to angiotensin II which in turn leads to a brief period of elevated blood pressure in some individuals. They inactivate bradykinin, PAR receptors and neuropeptides and increases mucus production, they are also known to process the packaging of collagen from procollagen.

c. Carboxypeptidase:

these are zinc dependent monomers with exopeptidase activity. Each mast cell contains about 5-16 pg. of carboxypeptidase. They cause the cleavage of the carboxy terminals of histidine, leucine, and phenylalanine[12].

3. Mediators synthesized by stimulation:

a. Prostaglandins & Leukotrienes:

The cyclooxygenase pathway results in the formation of prostaglandins and thromboxane's, due to the action of cytosolic phospholipase on mast cell membranes resulting in activation of arachidonic acid metabolism, similarly activation of lipoxygenase by monohydroxy fatty acids produces leukotrienes. Receptors for PGD2 present in the vascular and perivascular cells are responsible for effects such as bronchospasm, vasodilation, and also inhibition of platelet aggregation [13]. Leukotrienes on the other hand increases vascular permeability and causes bronchoconstriction, they are responsible for the prolonged duration of triple response to antigens.

b. Platelet Activating Factor:

Platelet activating factors are produced by the cell wall of mast cells by acetylating thromboxane's, and other cells such as endothelial cells, neutrophils and macrophages. They are important chemotactic agents, mediate vasodilatation and are also a potent inducer of bronchoconstriction.

c. Cytokines:

Cytokines are a large and diverse family of glycoproteins with many functions. Mast cell derived Th2 cytokines are responsible for allergic immune responses. They may be performed or newly synthesized, tumor necrosis factor alpha (TNF-alpha) and IL-8 are the former type, whereas most other cytokines belong to the latter group and are released hours after stimulation. TNF alpha produces eosinophilic and lymphotactic chemotaxis by activating endothelial cells. IL-8 promotes neutrophilic chemotaxis, whereas IL-4 is involved in synthesis of IgE and also the development of the immunologically distinct Th2 phenotype. IL-5 is responsible for the activation and recruitment of eosinophils. Some of the other cytokines implicated in urticaria are IL 3,4,5,6,9,10,13, MCP-1, lymphotactin and RANTES.

4. Plasma Derived Mediators in Urticaria:

These include the clotting system, complement system, and kinins. Immune complexes formed activate the complement system causing release of C3a and C5a which causes degranulation. Kallikreins cleave kininogens to release vasoactive peptides called kinins, which play a role in urticaria. The role of the clotting pathway in urticaria is not completely defined although they are related to the complement and kinin system.

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