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Review article

Urticaria and the role of antihistamines in pruritus

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Abstract Urticaria is a group of reactive disorders of heterogeneous etiology. It can be immunologic or non-immunologic in pathogenesis. Amongst the idiopathic group, autoimmunity may be incriminated where anti-FcεIgE IgG are produced. Histamine, kinins, and eicosanoids are the major inflammatory mediators. Urticaria remains a therapeutic challenge for dermatologists. In spite of recent advancements in the etiopathogenesis and pharmacotherapy, antihistamines still remain the pivotal treatment. The review highlights the role of antihistamines in the management of urticaria,

Key words
Urticaria, antihistamines

Introduction

The term urticaria is attributed to Johann Peter Frank of Vienna, and in the English literature, to William Cullen of Scotland.[1] Angio-oedema was recognized by Donato in the sixteenth century but not named by Strubing until the 1880s. Robert Willan first described the association of urticaria with factors such as certain foods.[2] Urticaria, commonly known as 'nettle rash' or 'hives', presents with short-lived, itchy weals that may be pale or pink in the centre, surrounded by a red flare.[3] Deeper swellings of the skin or submucosa are termed 'angio-oedema'. They are usually seen in the mouth, on the eyelids or on the genitalia, but may occur anywhere on the skin.[4]

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Etiopathogenesis

Urticaria is caused by transient leakage of plasma through small blood vessels, usually as a result of release of histamine from skin mast cells. Histamine also causes itching by stimulating nerve receptors, and contributes to the axon reflex flare.[5] Other mediators causing vasopermeability include kinins in hereditary angio-oedema, and leukotrienes in pseudoallergic reactions caused by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).[6,7] Immunologic and non-immunologic causes are recognized, but some cases remain idiopathic even after full evaluation.

Allergic urticaria is caused by type I hypersensitivity reactions. Mast cell degranulation is triggered by the binding of multivalent allergen to specific IgE on high-affinity IgE (FcεRI) membrane receptors.[8] Localized reactions at the site of contact with the allergen cause contact

urticaria. Generalized urticarial reactions can also occur. Anaphylaxis is a severe systemic reaction caused by type I hypersensitivity reactions. It involves difficult breathing, a fall in blood pressure or both, and is usually associated with widespread urticaria and itching.[9]

Idiopathic urticaria comprises up to 70% of cases of chronic duration. Histamine-releasing autoantibodies are present in the blood during disease activity. IgG antibodies are directed against FcεRI on mast cells or IgE bound to it. There is increasing evidence that a good number of this subgroup of idiopathic urticaria patients have an autoimmune disease.[10]

Non-immunological urticaria can be as severe as immunologic disease. Anaphylactoid reactions to radiocontrast may be caused by direct release of mast cell contents without involvement of IgE. Pseudoallergic reactions to aspirin and NSAIDs may occur up to 20 hours after taking the drug, and are thought to involve the release of newly synthesized sulphidopeptide leukotrienes in addition to histamine.[11] Inhibition of kinin breakdown by angiotensin-converting enzyme inhibitors probably explains the rare occurrence of angio-oedema with this class of drugs.[12]

Types of urticaria

Urticaria can be classified into five main groups on the basis of the history, appropriate challenge tests and simple laboratory investigations. However, it must be remembered that these groups are not mutually exclusive and fair amount of overlap exists. The duration of individual weals can be helpful in the history. Weals lasting less than 1 hour usually have a physical cause (the exception is delayed pressure urticaria, which characteristically develops several hours after exposure and lasts up to 24 hours). Contact urticaria usually resolves within 2 hours, conventional urticaria within 24 hours and urticarial vasculitis within 3 days. Angio-oedema may be present for days, but severe contact dermatitis should be suspected if the swelling lasts for several days and resolves with scaling.

Conventional urticaria[13]

Recurrent urticaria is termed ‘conventional’ or ‘ordinary’ if there is no predominantly physical cause or underlying small vessel vasculitis. It is the most common pattern. Attacks may occur daily or less frequently. It is considered acute if symptoms last for less than 6 weeks and chronic if for a longer period. Attacks of shorter duration may go on for long periods of time, the so-called ‘acute on chronic urticaria’ (personal observation). Weals are often numerous, and may occur on any part of the skin, including the scalp, palms and soles, where they may be painful rather than itchy. They generally last 2 to 24 hours, vary in size from less than 1 cm to many centimetres across, and may coalesce. Nonspecific symptoms (e.g. lassitude, indigestion) may accompany severe attacks, but wheezing is not a feature. Onset is often abrupt and unexpected, but occasionally there is a history of streptococcal infection, immunization, consuming an unusual food (e.g. fish, eggs, and nuts) or drug therapy (e.g. aspirin, penicillin). Acute conventional urticaria caused by food or drug is often apparent from the history because it occurs within 2 hours of ingestion, but most cases remain unexplained (idiopathic). Blood tests are almost always normal. Tests for specific IgE (fluoroimmunoassay, often misnamed ‘RAST’ because

radioallergosorbent tests were used in the past) may be useful for confirming the cause of allergy. In specialist centres, skin testing with autologous serum is a useful *in vivo* test for histamine-releasing autoantibodies, for which there is no commercially available test. Intradermal skin testing with different antigens proves to be a futile exercise in most cases.

Physical urticaria[14]

Physical urticarias are defined by the triggering stimulus. Immediate dermographism can be elicited by stroking the skin firmly with a blunt instrument, cholinergic urticaria by physical exercise to the point of sweating (sweat glands have cholinergic sympathetic innervations), and cold urticaria by contact with ice or generalized chilling. Cutaneous mast cells degranulate in response to these stimuli; the mechanism is not clear. More than one stimulus may be necessary to elicit urticaria (e.g. cholinergic dermographism). Simple physical challenge tests are useful to confirm the diagnosis.

Contact urticaria[15]

Contact urticaria is not uncommon, but is seldom a reason for referral to the specialist. Immunologic contact urticaria involves binding of percutaneous allergen to specific IgE in previously sensitized individuals. Localized wealing occurs within 10 minutes. Atopic patients are particularly susceptible. Non-immunologic contact urticaria from direct mast cell degranulation or eicosanoid release is probably more common; the mechanism is unclear and difficult to define.[16] Preservatives and fragrances in cosmetics may cause stinging, itching and burning. Food preservatives (e.g. benzoic acid, sorbic acid) and flavourings (e.g. cinnamic aldehyde) may cause contact urticaria around the mouth.

Urticarial vasculitis[17]

Urticarial vasculitis is an uncommon systemic disorder occurring in patients with underlying small-vessel vasculitis caused by immune complex deposition. The skin lesions may be indistinguishable from other forms of urticaria, or may resemble erythema multiforme. They last 2 to 3 days and resolve with a typical violaceous hue. They may burn rather than itch. Patients feel unwell with fever and joint pains, and associated renal, pulmonary or neurological disease must be excluded. The defining feature is venulitis as seen in skin biopsy; erythrocyte sedimentation rate is raised, and some individuals show hypocomplementemia; this could be a sign of poor prognosis and is associated with renal disease.[18]

Angio-oedema[19]

Angio-oedema can occur in conventional, physical and vasculitic urticaria, but may also occur without weals. These cases need to be specially considered to rule out hereditary and acquired C_1 esterase inhibitor deficiency. Measurement of C_4 is a useful screening test. It is reduced in both type I hereditary disease (reduced absolute levels of C_1 inhibitor) and the less common type II hereditary disease (normal quantitative C_1 inhibitor on immunochemical assay but reduced function).

Management

The first step in the management involves the identification and removal of any specific causative factor. The next step is use of antihistamines. Over-the-counter products such as chlorpheniramine and diphenhydramine are usually adequate. Prescription products such as hydroxyzine

and loratadine may be considered when over-the-counter drugs fail. One should initiate therapy with a dose that is within the upper recommended level. This dose can be gradually increased until either improvement occurs or side effects become troublesome. An amount twice the recommended dose should never be exceeded.

General measures[20]

Detailed history-taking, careful explanation, written information and cooling lotions (e.g. Calamine lotion) can help patients cope with their disease, particularly when drug treatment is disappointing. Identifying the causes of physical or contact urticarias may help patients avoid them. Drugs that may aggravate the urticaria nonspecifically (e.g. aspirin) should be avoided. Stress, alcohol and overheating should be minimized. Exclusion diets (e.g. food colourings, preservatives, natural salicylates) may be useful when indicated by the history, but are difficult to follow and are usually reserved until after first-line drug therapies have been tried.[21]

First-line treatment[22]

Antihistamines are the treatment of choice in all urticarias except C_1 esterase inhibitor deficiency. Most patients prefer a low dose and non-sedating antihistamine by day (e.g. levo-cetrizine, 5 mg/day). Addition of a sedating antihistamine (e.g. hydroxyzine, 10 mg/day) in the night can help the patient sleep and relieve the pruritus. Caution is required while combining certain antihistamines with drugs like erythromycin and ketoconazole, for risk of cardiac arrhythmias (torsade de pointes).[23] The tricyclic antidepressant doxepin, 10 mg thrice daily or as a single dose of 30 mg at night, has potent H_1 and H_2 antagonistic properties and is preferred by some patients.[24] Alternatively, an H_2 antagonist (e.g. ranitidine, 150 mg twice daily) or a mast cell stabilizer (e.g. nifedipine, 5 mg) can be added, but the results may be disappointing.[25] H_2 antagonists should never be used alone in urticaria, as there may be overreaction of H_1 receptors resulting in worsening of lesions.

Second-line treatment[26]

Prednisolone, usually 0.5 mg/Kg body weight stat followed by a tapering dosage schedule over a period of 1 to 2 weeks may be necessary in severe acute urticaria or angio-oedema. Prolonged treatment of chronic urticaria with oral corticosteroids should be avoided except in disabling delayed-pressure urticaria and urticarial vasculitis, which are usually unresponsive to antihistamines. Subcutaneous administration of 0.5 to 1.0 ml of 1:1000 adrenaline is useful in severe angio-oedema of the mouth, and can be life-saving in anaphylaxis.

Third-line treatment[27]

Studies on immunosuppressive therapies in disabling chronic autoimmune urticaria, using plasmapheresis or intravenous immunoglobulins, have been encouraging. The efficacy of cyclosporin A in such cases has recently been confirmed.[28]

Hereditary angio-oedema

Hereditary angio-oedema can often be prevented by low-dose anabolic steroids (e.g. stanozolol, 2.5 to 5 mg/day), which increase functional inhibitor levels.[29] Virilizing effects are a disadvantage in women. Tranexamic acid, an antifibrinolytic agent is used for acute episodes, but is contraindicated in thromboembolic disease.[30] Antihistamines are of no use.

Points to remember

- About 20% of the population experience episodes of urticaria at least once in their lifetime.
- Type I hypersensitivity reactions may be involved in acute conventional and contact urticaria, but uncommonly in chronic urticaria.
- The diagnosis of urticaria can often be made only from the history. Patients may not present with skin lesions.
- Ask for history of drug intake and search for an infective focus.
- Nearly 50% of chronic idiopathic urticaria is associated with histamine-releasing auto-antibodies.
- Episodes of urticaria lasting for more than 24 hours need to be evaluated for vasculitis and systemic disease.
- Antihistamines are the mainstay of treatment.
- Caution is to be taken while combining antihistamines with drugs like erythromycin and ketoconazole, for risk of cardiac arrhythmia (torsade de pointes).

Antihistamines and pruritus

No aspect of pruritus has evoked more debate than the use of antihistamines to relieve itching. To many non-dermatologists the presence of a patient with a dermatological disorder evokes a reflex desire to prescribe antihistamines.

The anesthetic effect of topical antihistamines may be used to benefit the patient with pruritus. Topical antihistamines carry a significant risk of sensitization and hence must be used with caution. For the short term (up to 7 days) management of pruritus, 5% doxepin hydrochloride cream is effective. However, its systemic absorption causes sedation. Visible discontinuity on the skin is a definite contraindication.

Systemic therapy with antihistamines is used as a panacea for all itchy dermatoses. Where histamine plays the major role in causing itching, as in urticaria, antihistamines are absolutely indicated. But in the vast majority of itchy disorders where histamine is not the mediator, antihistamines at best work by virtue of their sedative action. In such cases, the newer nonsedating antihistamines are never effective.

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