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Review Article

Urticaria: an immunologist's viewpoint

蕁麻疹：免疫病專科醫生的意見

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Urticaria is one of the most commonly encountered chronic conditions in clinical practice. The aetiology of urticaria is diverse, but can be broadly classified into allergic, autoimmune and physical causes. Successful management depends on accurate diagnosis. In allergic urticaria, identification of causative agents and education on avoidance can often ameliorate the problem. Idiopathic or autoimmune urticaria is initially best managed symptomatically, as most of these cases will spontaneously remit, whereas patients with urticarial vasculitis often require immunomodulatory drug treatment.

蕁麻疹是臨床工作中最常遇到的慢性病之一。蕁麻疹的病因多種多樣，概略可分為過敏性，自身免疫性及物理性三類。其治療的成功有賴準確的診斷。對過敏性蕁麻疹，確定其致敏原及教育患者避免接觸，可令病情緩解。至於特發性及自身免疫性蕁麻疹，因其常可自行緩解，故早期以對症處理為佳。蕁麻疹性血管炎則常需免疫調節劑治療。

Keywords: Immunologist, urticaria

關鍵詞：免疫病專科醫生，蕁麻疹

Introduction

Urticaria is a common clinical problem. Lifetime prevalence has been estimated to be 15 to 25% and is more common in middle-aged women.[1-4] The first clinical description was published in the 1800s by Heberden.[5] *Urtica* is the Latin name of the stinging nettle plant that contains histamine.[6]

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Urticaria is characterised by short-lived, itchy, raised wheals due to dermal oedema resulting from plasma leakage. In angio-oedema, the swelling is deeper, resulting in more diffuse and prolonged oedema, particularly affecting the face. Urticaria, in contrast to angio-oedema, is rarely life-threatening but can cause substantial discomfort and frustration. Patients with chronic urticaria report significant deterioration in quality of life. While the symptoms of urticaria and angio-oedema mimic that of an allergic reaction, many cases are autoimmune or idiopathic in nature. The key to successful management of these patients starts with a thorough clinical history and physical examination, as laboratory investigations are rarely helpful.

Allergic urticaria

A careful history can usually identify allergic causes of urticaria. Reactions to food proteins usually occur within two hours of ingestion. The most common food allergens in children include milk, egg, wheat, soy, peanut and fish. In adults, peanuts, nuts and shellfish are most common. Beware of hidden food allergens that are not obvious, such as the use of shellfish in a soap base and peanut butter as a sauce thickener, as well as cross-contamination during food preparation. Other co-factors such as exercise and alcohol can bring out an allergic reaction that would otherwise not occur, and this is especially common in wheat allergy. Food additives can also cause urticaria, usually in patients with pre-existing chronic urticaria. Tartrazine, metabisulphite, sodium nitrite, sodium nitrate, aspartame, BHA, BHT, methylparaben, sodium benzoate and monosodium glutamate have all been implicated. These ingredients can be found in many preserved foods, sauces, drugs and health supplements. It has been estimated that about 5% of chronic urticaria is caused by food additive allergy. Likewise, drugs such as aspirin and other cyclooxygenase 1 inhibitors can also exacerbate preexisting chronic urticaria in a substantial proportion of patients. Similarly, contact urticaria can occur with topical medications, soaps, cosmetics, toiletries, lotions, creams, detergents, fabric softeners, hair dyes, and nail products. Diagnosis can be confirmed with skin prick tests, patch tests or challenge. Treatment is by strict avoidance.

Physical urticaria

Another common cause of urticaria is physical stimuli. Physical urticaria accounts for 20 to 30% of chronic urticaria. It might be the predominant cause of the problem or one of several factors in chronic urticaria. Common types of physical urticaria include dermatographism, cholinergic urticaria, local heat urticaria, cold urticaria, delay-pressure urticaria, vibratory urticaria, solar urticaria, aquagenic urticaria and exercise-induced anaphylaxis.

In symptomatic dermatographism, wheals occur several minutes after the skin is scratched, and might last up to 30 minutes. Irritation from clothes or leaning against hard objects can elicit such a reaction. Sometimes, the reaction might be delayed by several hours, and can last for hours or days. Patients with delay-pressure urticaria frequently complain of pain and burning in addition to itch, and some cases are associated with arthralgia.

Cholinergic urticaria presents as distinctive punctate lesions surrounded by large flares. Symptoms are usually precipitated by a rise in core temperature such as during exercise and hot baths. The lesions are intensely itchy and might coalesce to form large areas of erythema. Systemic symptoms such as bronchospasm and hypotension might occasionally occur. This condition needs to be distinguished from local heat urticaria, in which urticaria is localised to the area where heat is applied. It should also be differentiated from exercise-induced anaphylaxis (EIA), in which exercise, not the rise in body temperature, is the trigger. In EIA, urticaria is an early manifestation, which is usually followed by systemic symptoms of anaphylaxis. It has been estimated that about half of EIA patients might be food-allergic.[7] It is therefore important to ascertain the circumstances surrounding each anaphylactic episode, especially foods that have been ingested prior to these episodes.

Diagnosis of physical urticaria is by challenge. A well-defined amount of pressure can be applied to the skin by a dermographometer to diagnose dermatographism and delay-pressure urticaria.[8] An intradermal methacholine skin test can be used to confirm cholinergic urticaria but is only positive in 30% of such patients.[9] In exercise-induced anaphylaxis, skin prick test to foods can be used to identify possible food allergies. Diagnosis can be confirmed by exercise challenge.

Autoimmune urticaria

The first indication that a substantial proportion (about 40%) of chronic idiopathic urticaria cases are autoimmune in nature came from an observation that autologous serum that was re-injected into normal-appearing skin could cause a localised wheal-and-flare response during disease activity but not during remission.[10] Subsequently, antibodies against the high affinity IgE receptor FcεRI were found in 38% of patients with chronic urticaria, and these antibodies can cause complement-dependent histamine release from mast cells and basophils.[11,12] There is a strong genetic predisposition for autoimmune urticaria, with a strikingly increased frequency of HLA-DRB1*04 (DR4) and its associated allele DQB1*0302 (DQ8) in patients with chronic idiopathic urticaria compared with a healthy control population.[13] Chronic urticaria is also significantly associated with autoimmune thyroid diseases and other autoimmune diseases.[14,15] In the author's series of 89 consecutive patients with chronic urticaria, 21 (23.6%) had anti-thyroid microsomal antibodies, of which eight also had anti-thyroglobulin antibodies. Three of these 21 patients was subsequently found to have subclinical hyperthyroidism. Two received radioiodine and the urticaria has also resolved afterwards. Twelve patients (13.5%) had antinuclear antibody (ANA) titre >1:40, of which two also had antibodies against extractable nuclear antigens (ENA) and one had antibody against double-stranded DNA (dsDNA). None of these patients have exhibited other symptoms of connective tissue disease so far.

Urticarial vasculitis

Another form of urticaria that must be considered is urticarial vasculitis (UV). As a variant of leucocytoclastic vasculitis, UV can be a localised or systemic process, and if extensive might lead to hypocomplementemic urticarial vasculitis (HUV). Many patients with UV have features of systemic autoimmune diseases such as SLE. The prevalence of this disorder in patients with chronic urticaria is about 5%.[16] UV is suspected if the urticarial lesions last for longer than 24 hours and resolve with purpura or hyperpigmentation. The urticaria might be painful or tender in addition to being pruritic. The diagnosis is confirmed by skin biopsy, which often shows leukocytoclasia and fibrinoid deposits within the venules. Immunohistochemistry reveals the presence of immunoglobulin and C3 deposition in the vessels of 70% of cases.[17] In severe cases where hypocomplementemia is present, patients might also present with angio-oedema, glomerulonephritis, arthralgia, uveitis, episcleritis, abdominal pain, obstructive lung disease and neurological symptoms. As opposed to SLE, patients with HUV do not have antibodies against dsDNA or ENA, although 50% have ANA.[18] The levels of complement components C3 and C4 might range from normal to undetectable, but C1q is always severely depressed. UV is most likely caused by immune complex deposition, and hepatitis B and hepatitis C viruses can cause the formation of such immune complexes.

Management

When dealing with patients with urticaria, the value of a careful history cannot be overemphasised. The temporal relationship between the onset of urticaria and the introduction of new foods, medications and skin care products should be noted. Immediate-type allergic reactions to food and drugs usually occur within two hours of ingestion, and often within minutes. Hidden food and drug ingredients might be difficult to elucidate; a drug tablet often contains dozens of "inactive ingredients" including colouring, binders, stabilisers and preservatives. Patients with severe respiratory allergies can also develop urticaria and angio-oedema when exposed to a heavy allergen load. Many patients with hay fever develop urticaria at the height of the pollen season. If the history is suggestive of an allergic cause, skin prick tests or serum specific

IgE tests are indicated. These tests have excellent negative predictive value, but a positive reaction does not necessarily mean that the allergen is to blame. The panel of test allergens should be chosen judiciously based on the history, and the results should ideally be confirmed by challenge unless there is a strong risk of anaphylaxis. Indiscriminate use of "screening panels" will result in numerous false positive reactions and introduce confusion. Patients with active urticaria, dermatographism and those taking antihistamines cannot undergo skin prick testing and would therefore require blood testing. First line treatment of allergic urticaria is avoidance, and patients should be taught how to look out for hidden allergens. In patients with respiratory allergies, especially to unavoidable allergens, desensitisation should be considered.

In the absence of clues pointing to an allergic aetiology, acute urticaria and angio-oedema is often the result of a viral infection. Such infections are often asymptomatic, but can result in very severe urticaria that proves difficult to treat. Such rashes are often unresponsive to antihistamines, and systemic steroid might be needed. It is my practice to start at 0.5 mg/kg/day of prednisolone, and slowly taper over the course of two to three weeks depending on the response. Too rapid a taper often results in rebound. Milder cases can be treated with antihistamines alone, and the rash usually resolves spontaneously after six to twelve weeks. It is not necessary to launch an intensive investigation effort unless the rash persists beyond this period of time.

Patients with daily outbreak of urticaria for more than six weeks have chronic urticaria, and many of these cases are autoimmune in nature. A positive autologous serum skin test (ASST) will give strong support to this diagnosis. However, not all patients with positive ASST have anti-FcεRI antibodies. Baseline blood tests for complete blood count, routine blood chemistry, antinuclear antibodies, anti-thyroid antibodies, total IgE, ESR and C3/C4 level should be done. In patients with anti-thyroid antibodies who have clinical hyperthyroidism, the urticaria often resolves once the condition is treated with radioiodine or carbimazole. In those patients who are euthyroid or hypothyroid, the use of thyroxine is associated with improvement in the rash, although a dose that suppresses TSH to subnormal levels while maintaining the free T4 within the normal range is often needed.

In patients without anti-thyroid antibodies or other signs and symptoms of systemic autoimmunity, antihistamines remain the first line of treatment. The older sedating type of antihistamines often work better in these patients, and the sedation can be an advantage to help them sleep at night. If the patient has daily outbreaks, the drug should be taken every night, and a newer non-sedating antihistamine is taken during the day on an as needed basis. If there is inadequate response to conventional doses, the dose can be doubled; e.g. hydroxyzine 50 mg nocte plus fexofenadine 360 mg mane, as long as the side effects are tolerable. The addition of the anti-allergic compound ketotifen, or an H_2-blocker such as famotidine might also be helpful. Patients with severe symptoms not controlled by antihistamines might benefit from immunomodulatory drugs. Cyclosporin A is the only such drug to have been proven effective by a double-blind placebo-controlled study.[19] The recommended dose is 4 mg/kg/day in two divided doses, and treatment should be continued for 16 weeks. Anecdotal evidence suggests that hydroxychloroquine, azathioprine, tacrolimus and intravenous immunoglobulins might also be useful. Up to 70% of chronic idiopathic urticaria might remit within one year, but some patients might have the disease for ten years or more.[20,21] Patients suspected of having UV, and patients who respond poorly to standard treatment should have their diagnosis confirmed by skin biopsy and immunofluorescence. UV patients with mild symptoms can be treatment with antihistamines alone, but those with more severe symptoms often require systemic steroid. Patients with hepatitis C infection should consider

interferon-α treatment. Other agents found to be useful include dapsone and colchicine, both of which affect neutrophil function. Patients must be screened for G6PD deficiency before starting dapsone, and there is a risk of severe hypersensitivity syndrome. Colchicine is teratogenic and also has significant gastroinstestinal side effects. Hydroxychloroquine is often useful in those patients with limited cutaneous disease. Azathioprine is a useful steroid-sparing agent, allowing the dose of steroid to be reduced to lessen the adverse effects of chronic use. In patients with HUV, cyclophosphamide, cycosporin A and mycophenolate have been shown to be beneficial, alone or in combination with steroid. Patients with normocomplementemic UV tend to have a good prognosis, with an average duration of three to four years before remission. However, the outcome of patients with HUV seems to be more variable, especially when systemic involvement is present.

Conclusion

It is important to bear in mind that urticaria is a symptom with a variety of different aetiologies. Successful treatment requires the correct identification of the cause of disease. As patients with allergic urticaria run the risk of severe anaphylaxis, the responsible allergen(s) must be identified and avoided. Symptomatic treatment is often sufficient in the majority of chronic urticaria cases; however, if the disease becomes persistent or uncontrollable, immunomodulatory drug treatment might be required.

Urticaria is a common condition attributed to different aetiological factors. Successful treatment requires their identification and if possible avoidance or elimination. Patients with allergic urticaria run the risk of severe anaphylaxis; the responsible allergen(s) must be identified and avoided. Symptomatic treatment is often sufficient in the majority of chronic urticaria cases; however, if the disease becomes persistent or uncontrollable, immunomodulatory drug treatment might be required.

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