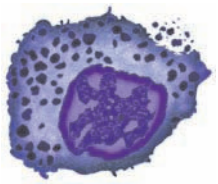

5: Allergy and the skin: eczema and chronic urticaria

Constance H Katelaris and Jane E Peake

ABSTRACT

- Eczema is common, occurring in 15%–20% of infants and young children. For some infants it can be a severe chronic illness with a major impact on the child's general health and on the family. A minority of children will continue to have eczema as adults.
- The exact cause of eczema is not clear, but precipitating or aggravating factors may include food allergens (most commonly, egg) or environmental allergens/irritants, climatic conditions, stress and genetic predisposition.
- Management of eczema consists of education; avoidance of triggers and allergens; liberal use of emollients or topical steroids to control inflammation; use of antihistamines to reduce itch; and treatment of infection if present. Treatment with systemic agents may be required in severe cases, but must be supervised by an immunologist.
- Urticaria ("hives") may affect up to a quarter of people at some time in their lives. Acute urticaria is more common in children, while chronic urticaria is more common in adults. Chronic urticaria is not life-threatening, but the associated pruritus and unsightly weals can cause patients much distress and significantly affect their daily lives.
- Angioedema coexists with urticaria in about 50% of patients. It typically affects the lips, eyelids, palms, soles and genitalia.
- Management of urticaria is through education; avoidance of triggers and allergens (where relevant); use of antihistamines to reduce itch; and short-term use of corticosteroids when antihistamine therapy is ineffective. Referral is indicated for patients with resistant disease.

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The skin is commonly involved in acute allergic reactions. It is also involved in the chronic allergic entities of eczema (common in infancy and childhood) and chronic urticaria (more commonly seen in adults). Here, we outline how these conditions can be recognised and managed in practice and when to refer for specialist advice. We also highlight some current controversies and evolving concepts.

ECZEMA

Eczema is a papulovesicular dermatitis that occurs in 15%–20% of infants and young children. The onset of eczema (also known as atopic dermatitis or atopic eczema/dermatitis syndrome) frequently occurs in the first few months of life and usually within the first year of life. The exact cause of eczema is unknown, but factors that may precipitate or aggravate the condition include food and environmental allergens/irritants, heat or cold, stress, and genetic predisposition. Often dismissed as a trivial disorder, severe eczema can cause significant morbidity and have major social, emotional and financial impacts on children and their families.[1]

Making the diagnosis

The diagnosis of eczema is made clinically, on the basis of the distribution of skin involvement and symptoms. The hallmarks are pruritus and inflammation. In infants, there is usually involvement of the extensor surfaces, face, neck and trunk (Box 1). As the child gets older, eczema more commonly involves the flexural surfaces, but can be widespread and also affect the hands, feet, face and trunk. In acute lesions, there are usually erythematous papules on a background of erythematous skin and pruritus, and sometimes vesiculation and ooze, but, over time, excoriation, scaling, lichenification and thickened plaques may develop (Box 2). The clinical course can be quite varied, often with periods of remission and exacerbation due to a variety of factors.

Eczema should be differentiated from other common forms of dermatitis, such as contact dermatitis and seborrhoeic dermatitis. Distribution often provides the clues. Seborrhoeic dermatitis, which is also common in infants, primarily involves the scalp, axillae and nappy area. Contact dermatitis, more common in older patients, often involves a sudden flare-up of short-lived dermatitis in exposed areas. Apart from history-taking, patch testing can help confirm the cause. Psoriasis should also be considered in the differential diagnosis, especially in older children and adults.

Eczema is not a single entity; rather, it is a group of inflammatory disorders of the skin involving a genetically determined skin barrier defect. Recent data suggest that, as for other diseases such as asthma, there are different forms of eczema. Eczema associated with IgE antibodies is called atopic eczema and eczema without IgE antibodies is called non-atopic eczema.[2,3] Attempts to further delineate the different types of eczema will have important implications for management and prognosis of the disease. Atopic eczema is associated with other atopic diseases such as food allergy, allergic rhinitis and asthma, which may become evident at a later stage.

Management

Management of eczema principally involves explanation to patients and parents of the chronic nature of the disease, advice on avoiding irritants, and symptom control (Box 1). Irritants such as soaps, perfumes, sand, extreme temperatures and some clothing fabrics should be avoided. As soap strips oils from the skin, adding oils to the bath and using aqueous creams as soap substitutes often works well. Bacterial infection, especially with *Staphylococcus aureus*, can often cause exacerbations of eczema. This can be difficult to diagnose clinically, and empirical treatment with antibiotics may be justified.

Pharmacological therapy

Oral antihistamines: Oral antihistamines may be useful in reducing pruritus in some patients. Older, sedating antihistamines should not

1 Case scenario*

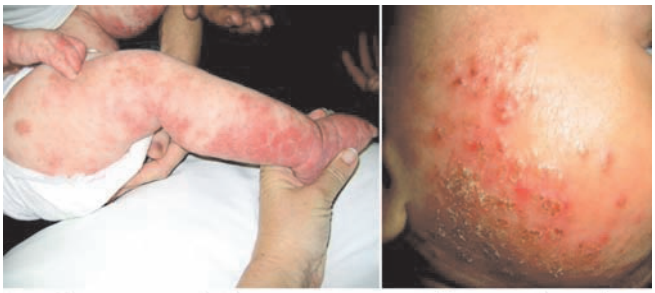
A 12-month-old boy presented with severe eczema. The eczema had started at 6 weeks of age; flare-ups of the condition were common and were becoming more severe. Itch was a major problem, waking him frequently at night.

On examination, widespread generalised eczema was noted. There were some inflammatory plaques, and the skin was excoriated and infected in some areas (see Figures). The baby was otherwise quite well.

The patient's history revealed that various treatments had been applied over the preceding months, with limited success. Oatmeal was regularly added to his bath, and moisturiser was applied twice daily. Methylprednisolone aceponate ointment was used when severe exacerbations occurred, and pimecrolimus cream had been used mainly on his face and legs.

The child was still being breastfed, but had slowly been introduced to solids with a few vegetables, fruits and rice. Goats milk and baby yoghurt had been found to cause welts all over his face. The mother had tried eliminating milk from her diet, but continued eating other dairy products. The father was prone to allergic rhinitis, and members of the extended family were subject to eczema and asthma.

Skin prick testing showed a significant response to egg, cows milk, beef and house dust mite. It was suggested to the mother that she eliminate all dairy products, egg, potato and beef from her diet until weaning and that these foods not be introduced into the child's diet. Cows milk allergy implies allergy to all dairy products and usually also to goats milk. Advice on house dust mite control was also given. Other recommendations were to add cottonseed oil to the bath; wash with aqueous cream and moisturise liberally with soft white paraffin; apply wet wraps twice daily; apply steroid cream twice daily to the limbs and trunk; and continue pimecrolimus cream treatment on the face. Cetirizine and a course of oral cephalosporin were also prescribed. The child was referred to a dietitian to ensure adequate nutrition.



Note that as soon as his leggings were removed he started scratching

On review a few weeks later, the child's skin had improved significantly. He still had some eczema on the limbs, but this was restricted to the cubital and popliteal fossae, hands and feet. He was now sleeping through the night and was considerably less irritable. He had started to be weaned onto soy milk and was eating chicken and lamb without any obvious adverse effect on the skin.

* This is a fictional case scenario based on similar real-life cases. ◆

be used, especially in young children, as there have been reports of severe and even life-threatening side effects.[4]

Emollients: There have been very few randomised controlled trials of the use of emollients in eczema, but those that have been done confirm their usefulness.[5] Moisturising the skin improves its barrier function and reduces itch and irritation. There are a huge number of bathing and moisturising products available for treating eczema, and patients will often try many before finding one that suits. Products should not be continued if they cause burning, stinging or increased itching. Soft white paraffin is one of the more suitable moisturisers and is best applied immediately after getting out of the bath, while the patient is still wet and warm. Wet wraps may be effective in patients with moderate to severe eczema and provide a partial barrier to scratching.

Topical steroids: Inflammation needs to be controlled, and topical steroid creams and ointments are effective for this purpose.[5] A moderate to potent steroid should be applied at the initial signs of inflammation. As the inflammation subsides, steroid use should be tapered off to prevent rebound. This will generally provide better resolution and require a lower total dose of steroid than if a low potency steroid is used alone for a prolonged period. Parental concern about the effects of steroid use, including thinning of the skin, can lead to problems with compliance. However, if steroids are used appropriately for short periods, there is little evidence to support this concern.[6]

Topical calcineurin inhibitors: More recently, the topical calcineurin inhibitors pimecrolimus cream and tacrolimus ointment (the latter currently only available in Australia at certain hospital and compounding pharmacies) have become available as alternatives to topical steroids to suppress inflammation.

Tacrolimus ointment has been found to be safe and effective in patients with moderate to severe eczema.[7] Transient burning and pruritus can occur when the ointment is initially applied. Pimecrolimus is similar in action to tacrolimus but has only been assessed in mild to moderate disease. It can be used to prevent flaring of eczema,[8] and may be useful in body areas where there is concern about applying steroids (eg, on the face, around the eyes and around the groin).

Safety concerns about topical calcineurin inhibitors have been raised with respect to increased risk of skin malignancy (on the basis of animal studies), but a review of the literature suggests that "black box" warnings are not indicated.[9] Nevertheless, calcineurin inhibitors should not be used in clinically infected areas. Further, there are few studies assessing the effectiveness of these newer agents compared with appropriate strength topical steroids.[7]

Treatment-resistant disease

For patients who fail to respond to topical therapy, systemic therapy may be considered. Long-term treatment with oral steroids cannot be justified, because of side effects. Other treatment options — such as narrow-band ultraviolet B therapy, systemic immunosuppressive drugs or intravenous gammaglobulin therapy — are reserved for very severe disease and should only be given under the guidance of a specialist with experience in their use.

When to refer

Referral to a specialist is indicated for any young infant with severe eczema and for those in whom food allergy is suspected of playing a role. A specialist should also be consulted if systemic immunosuppressive drugs are being considered.

Controversies and evolving concepts

Food allergy

The role of food allergy in causing or exacerbating eczema is controversial, perhaps because many studies of food avoidance

have used an unselected population of children with and without sensitisation to foods. Also, foods used in the control group (eg, soy instead of cows milk) may themselves have elicited reactions. Recently, numerous double-blind, placebo-controlled food studies have demonstrated that about 35%–40% of children with moderate to severe eczema have food allergy, and that eliminating the causative food from their diet can bring about significant improvement in the severity and extent of eczema (Box 3).[11-14] However, eczema is often multifactorial, and elimination of allergenic foods does not provide complete resolution in all infants. Food allergy is rare in adult-onset eczema.

Allergy to egg is the most common food allergy associated with eczema. Other commonly associated foods include milk, soy, wheat and peanuts. Thus, food allergy screening tests such as skin prick tests and radioallergosorbent tests should be performed in young infants with severe eczema. False negative tests are uncommon, but false positive tests may occur, particularly in older children.[15] Food challenges are more accurate; reactions may be immediate or delayed. Food allergens from the maternal diet may be excreted in breastmilk and cause eczema in a breastfed infant.[16] A trial of restriction of maternal diet may be useful if an infant is shown to be allergic to a particular food.

Care should always be taken with any recommendations for dietary restriction in young infants. When special diets are used, it is imperative that adequate nutrition be maintained, particularly in young infants, and consultation with a dietitian is advisable.

Environmental allergens

Patients with eczema may have sensitisation to environmental allergens such as house dust mite (HDM) or pet dander. There is strong circumstantial evidence that HDM is an important precipitant for atopic eczema. However, there are relatively few randomised controlled trials looking at the role of HDM eradication in treatment of eczema. The limited studies suggest that there is some benefit if a very low level of HDM can be achieved.[5]

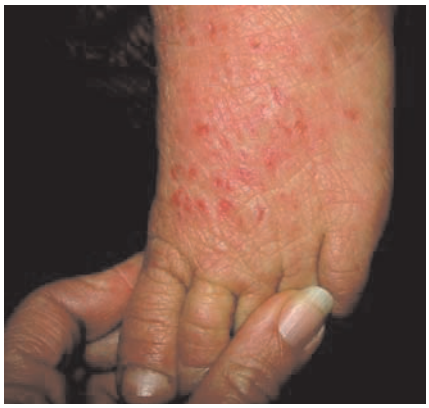
Dietary supplements

Based on the concept that probiotics, which are normal commensal bacteria of the healthy human gut, play a role in the development of normal immune tolerance and may be immunomodulatory, recent studies have looked at probiotics in the treatment and prevention of allergy.[17,18] These studies look promising, but further work is required to clarify whether these agents should be recommended and which is most effective. There is currently no evidence for the use of other dietary supplements such as evening primrose oil, fish oils or omega-3 fatty acids.

Prognosis

For most infants and children, eczema is a mild disease that will resolve during childhood, but for some patients, the condition is severe and may continue into adulthood. The prognosis for eczema has been shown to correlate with its severity and the presence of atopic sensitivity.[19] Patients with chronic, severe eczema and their families need adequate support.

2 Chronic eczema in a 10-year-old child



Over time, with continued inflammation and scratching, the skin becomes very thick. ◆

3 Evidence-based practice tips*

- Patients with atopic eczema have a higher likelihood of developing other atopic diseases such as asthma and allergic rhinitis (Level III-2).
- Removal of an identified allergenic food from the diet can significantly improve eczema in an individual patient (Level III-2).

* Based on National Health and Medical Research Council levels of evidence.[10] ◆

CHRONIC URTICARIA

Urticaria ("hives") is characterised by transient eruptions of pruritic weals or patchy erythema on the skin. It probably affects up to 25% of people at some time in their lives. It affects people of all races and is about twice as common in women as in men. Acute urticaria is more common in children, while chronic urticaria (defined as recurring episodes that last for over 6 weeks) is more common in adults. The incidence of chronic urticaria is unknown, but it is thought to occur in 0.1%–3% of the population.

The significance of chronic urticaria is sometimes trivialised because it is a non-life-threatening disease. However, the unrelenting pruritus and disfiguring, random occurrence of unsightly weals can cause patients great misery. Chronic urticaria has a major impact on quality of life, with impact on activities of daily living similar to that experienced by patients with heart disease.[20]

Making the diagnosis

Urticaria

Urticaria is characterised by transient weals that last less than 24 hours and then disappear without sequelae. It is associated with intense itch. If these two key features are not present, the diagnosis needs to be reconsidered.

The three main types of chronic urticaria are papular urticaria, urticaria with a physical cause, and urticarial vasculitis. They can be distinguished from chronic idiopathic urticaria by weal appearance and characteristic history.

Papular urticaria: Papular urticaria is a reaction to bites from grass mites, fleas and other arthropods. It most commonly occurs in children and during the warmer months. Lesions, typically seen on the extremities, are intensely itchy, leading to marked excoriation and often secondary infection that results in scarring. Lesions often occur in clusters and may last for days.

Urticaria with a physical cause: A physical cause for chronic urticaria is probably present in about 20% of cases (Box 4, Box 5). Dermatographism and cholinergic urticaria are the most common forms of urticaria with a physical cause and have characteristic appearances. Various types of urticaria may coexist in the same patient. However, once the typical history is elicited, no further investigations are required.

Urticarial vasculitis: An atypical appearance, long-lasting lesions or a lack of responsiveness to antihistamine treatment suggests urticarial vasculitis, a rare condition seen in less than 1% of people with chronic urticaria. Patients suspected of having this condition require further investigation (Box 6).

4 Physical forms of chronic urticaria

Type	Comments
Symptomatic dermatographism	Commonest form of physical urticaria. May accompany other forms. Linear weals with wide flares at site of scratching or stroking. Treatment usually not required.
Cold-induced	Rapid onset of pruritus, erythema and swelling following exposure to cold. Reaction confined to site of exposure. May be life-threatening if whole body exposed (eg, swimming in cold water). Various forms exist: localised cold urticaria, systemic cold urticaria and cold-induced dermatographism.
Cholinergic or heat-induced	Characteristic 1–2 mm weals with marked flare occurring after exercise, sweating, showering, emotional stress or fever.
Exercise-induced anaphylaxis	Large weals often accompanied by angioedema, wheeze and/or hypotension after exercise. Food-dependent and food-independent subtypes have been described.
Pressure-related	Swelling occurs 4–6 hours after pressure applied (typically, swelling of hands after manual work, swelling of feet after standing, or swelling under areas of tight clothing).
Solar	Prompt onset of pruritus followed by weals 1–5 minutes after exposure. Lesions last 1–3 hours. Severity may lessen with tanning.
Aquagenic	Small weals develop on contact with water of any temperature. This is a rare condition.

Angioedema

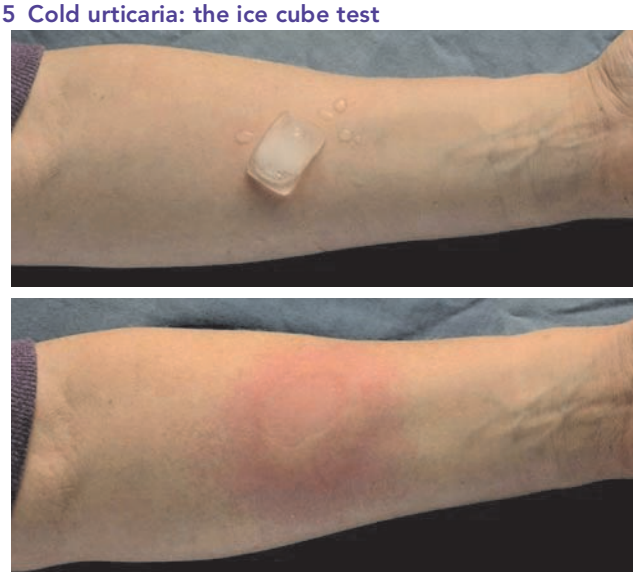
Angioedema (typically affecting the lips, eyelids, palms, soles or genitalia) coexists with urticaria in about 50% of patients. If it occurs as a recurrent condition in isolation, causes other than urticaria should be considered, such as medication (eg, angiotensin-converting enzyme inhibitors) or rare conditions such as hereditary angioedema or acquired deficiency of C1-esterase inhibitor.

Management

The first step in managing urticaria is to try to find a cause, but this is easier said than done. There is little role for extensive laboratory testing, as this rarely helps to identify a cause.

Discussion with patients and parents about minimising bites and trigger factors is useful. Non-specific stimuli that may trigger an episode of urticaria include increasing body heat; alcohol ingestion; and taking certain medications, particularly aspirin and non-steroidal anti-inflammatory drugs, which may exacerbate chronic urticaria in 60% of cases. Some women prone to urticaria note a premenstrual worsening in their condition.

5 Cold urticaria: the ice cube test



The ice cube test is performed by holding ice on the skin for 5 minutes and then removing it. Wealing occurs as the skin rewarms. ◆

Pharmacological therapy

The primary goal of therapy for urticaria is to relieve pruritus, as this is the symptom that impairs the patient's quality of life and causes sleep disturbance. It is important that the patient understand that, despite taking medication, urticarial lesions may still occur.

Oral antihistamines: Oral antihistamines remain the mainstay of treatment of chronic urticaria. They are best taken prophylactically, as various stimuli can cause mast cell degranulation, resulting in histamine release. While older antihistamines are cheaper and their sedative effect may be useful for sleeping at night, they are undesirable for long-term use because of other side effects.

Addition of a tricyclic antihistamine such as doxepin may be very effective for night-time discomfort and sleep disturbance due to itch. Doxepin is a potent antihistamine, with H_1- and H_2-histamine blocking activity, as well as having an anti-anxiety effect. However, its sedative side effect is a limitation, especially in older patients.

Some years ago, there were reports that addition of an H_2 antagonist could help control chronic urticaria. The benefit is small, but the treatment may be worth trying, as it may help selected patients.[21] A number of studies have demonstrated benefit from the use of newer, non-sedating antihistamines over that derived from placebo.[22-25]

Leukotriene inhibitors: Theoretically, there may be a use for leukotriene antagonists in the treatment of chronic urticaria. However, randomised controlled trials comparing the use of an antihistamine alone with use of a combined treatment (antihistamine plus montelukast) have shown conflicting evidence of efficacy.[23,26] Currently, montelukast is not listed for use in chronic urticaria and is an expensive treatment.

Oral corticosteroids: Oral corticosteroids are often used for short-term relief of symptoms of chronic urticaria when antihistamine therapy is ineffective. In this circumstance, patients are grateful for temporary relief. But, unfortunately, corticosteroids cannot be a long-term option, as the risk of side effects will outweigh the benefit. Doctors must be responsible for warning their patients of the long-term consequences of corticosteroid use so that the medication is not taken indiscriminately.

6 Urticarial vasculitis*

Suspicious features

- Lesions lasting longer than 24 hours in the one place
- Condition painful rather than itchy
- Bruising or scarring after occurrence of lesions
- Presence of arthralgia or arthritis
- Presence of constitutional symptoms
- Lack of response to antihistamines

Investigations when urticarial vasculitis is suspected

- Skin biopsy to demonstrate vasculitic changes in postcapillary venules (leukocytoclastic vasculitis)
- Full blood count and erythrocyte sedimentation rate
- Urinalysis
- Antinuclear antibodies to extractable nuclear antigens
- Complement studies

* Seen in less than 1% of people with chronic urticaria. ◆

When to refer

In cases of acute severe urticaria and angioedema with no obvious trigger, or where there is a presumed food or drug trigger, specialist evaluation is required to identify the trigger, if at all possible.

Patients with chronic urticaria and/or angioedema who do not respond to the therapies listed above or who are suspected of having an underlying condition should be referred to a specialist.

In cases of recurrent angioedema, specialist evaluation may be appropriate to exclude hereditary or acquired C1-esterase inhibitor deficiency.

Controversies and evolving concepts

Malignancy

There has been concern, based on anecdotal reports, that chronic urticaria may be an indicator of an underlying malignancy, particularly in older patients. A very large Swedish epidemiological study has shown that there is little evidence to support this fear.[27] However, acquired angioedema associated with C1-esterase inhibitor deficiency is associated with malignancy, particularly lymphoma.[27]

Diet

Ingestion of certain foods may produce a generalised acute allergic reaction that includes urticaria. The patient often makes the connection between food ingestion and an acute episode of urticaria, but may fail to consider the possibility of a "hidden ingredient" in the food, such as nuts. In this circumstance, skin prick tests or in-vitro measurement of specific IgE may suggest that a particular food is the likely cause, but food challenges may be the only way to establish a definite relationship. Attributing chronic urticaria to food allergy, rather than some other possible cause, is another common pitfall, with most patients believing a particular food to be the cause of their problem at some stage. Skin prick testing or in-vitro testing for food allergy may relieve the patient from unnecessary avoidance of certain foods.

Idiosyncratic reactions to food additives have been suggested as an important cause of chronic urticaria, but this area suffers from a lack of rigorous placebo-controlled studies and also from the inherent problem of challenging patients with chronic urticaria and then trying to interpret the results. Early studies reporting reactions to tartrazine and benzoates in patients with chronic urticaria were not placebo-controlled.[28] Other complicating factors include whether or not an elimination diet was used before challenging, which food additives were included in the challenge battery, the dosages of food additives used, and whether medication was ceased before challenging (and if so, for how long). Based on the few rigorous studies that have been performed, food additives appear to be a distinctly uncommon cause of chronic urticaria.[29]

Helicobacter pylori

The question of whether *Helicobacter pylori* infection is a cause of chronic urticaria remains controversial. A link between the two, first described in the European literature, has not been confirmed by other studies.[30] Reports of improvement in chronic urticaria after eradication of *H. pylori* infection have added to the debate.[31] Although *H. pylori* seropositivity is not higher in patients with chronic urticaria than in other patients, eradication of the infection where it coexists appears worthwhile. Patients presenting with a history of reflux and urticaria may be considered for investigation for *H. pylori* and appropriate treatment if found.

Thyroid autoimmunity

A link between chronic urticaria and thyroid autoimmunity has been known of for more than 20 years.[32] Kikuchi et al[33] reported that patients with chronic urticaria had an increased prevalence of IgG antithyroid antibodies (usually antithyroid peroxidase) compared with controls (10%–13% v 3%–5%). They demonstrated that antithyroid antibodies are definitely associated with the presence of antibodies to the IgE receptor, and concluded that antithyroid antibodies and antibodies to the IgE receptor are associated immune abnormalities, rather than one being the cause of the other.

The use of thyroxine to treat patients with chronic urticaria and thyroid autoimmunity in the absence of thyroid disease remains controversial. Some investigators have reported improvement in chronic urticaria symptoms with thryoxine treatment.[34] In a recent study that included both euthyroid and hypothyroid women, 16 of 20 women with chronic urticaria who were given thyroxine to suppress thyroid-stimulating hormone showed improvement in chronic urticarial symptoms after 12 weeks.[35]

Is chronic urticaria an autoimmune disease?

In the past decade, 35%–45% of patients with chronic urticaria have been found to have an autoimmune basis for their condition. An IgG antibody directed to the alpha subunit of the IgE receptor has been demonstrated in 35% of patients, and a functional anti-IgE antibody has been found in a further 5%–10%.[36] Measurement of these antibodies is confined to research laboratories. However, an intradermal skin test with autologous sera can induce a delayed weal with a macroscopic and microscopic appearance similar to that seen in chronic urticaria. The stimulus for this autoantibody production is unknown.

The notion that chronic urticaria may be an autoimmune disease opens up the possibility of using immunomodulatory treatment when antihistamines have failed to control the condition. There is one controlled trial demonstrating a positive effect from the use of hydroxychloroquine.[37] Cyclosporin A has been shown to be an effective treatment, but its use should be restricted and requires careful monitoring because of its potential to cause renal and other side effects.[38] Plasmapheresis or administration of intravenous gammaglobulin or low-dose tacrolimus have also been tried, with some benefit, in small numbers of patients with autoimmune chronic urticaria.

Fact or fiction — true or false?

1. All eczema is allergy-based (T/F)
2. Food allergy plays no role in eczema (T/F)
3. Food allergy is an important cause of chronic urticaria (T/F)
4. Five per cent of the population suffers from dermatographism (T/F)

1. False. About 20% of people with eczema are not atopic and allergy does not play a role in their disease.
2. False. 35%–40% of children with moderate to severe eczema have food allergy.
3. False. Approximately 5% of patients with chronic urticaria may have food intolerance. Food allergy is more likely to be associated with acute urticaria.
4. True. This does not require treatment, but antihistamines are useful if the condition causes embarrassment. ◆

Prognosis

Fifty per cent of patients who experience chronic urticaria will be symptom free at the end of 1 year, but 20% will continue to have problems for many years. Approaches based on the concept of chronic urticaria as an autoimmune disease offer promise to patients who have severe long-term disease.

Competing interests

None identified.

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