

Food allergies and atopic dermatitis

Dr Idris Akinwande 

Locum General Practitioner, Greater Manchester
Email: idrisakinwande@hotmail.com

Dr Kazeem Salako

Consultant in Dermatology and Paediatric Dermatology, Northampton General Hospital

Atopic dermatitis, frequently referred to as atopic eczema, is a common illness that can cause significant psychological and financial burden to patients and their care givers. Therefore, it is not surprising that a cure is often sought. Patients, parents and carers are often concerned about the possibility of food causing or exacerbating the illness. It is not uncommon for patients and care givers to request investigation in the hope of identifying food items that maybe acting as triggers and of effecting improvement or cure with avoidance and dietary changes. This article seeks to review the relationship between atopic dermatitis and food allergies, as well as the relevance of diagnostic tests.

Clinical case scenario

Mrs Williams brings her 13-month-old son Sam to the practice to see you as she is concerned about Sam's skin. He developed red, dry and eczematous patches on his cheeks, arms and legs 3 weeks ago and they are not improving with low-potency steroid creams and emollients. Sam was diagnosed with eczema when he was 6 months old, and his mother informs you that the symptoms were initially well controlled with a short course of low-potency steroid cream and emollients. The skin had been clear of eczema for about 5 months since the initial diagnosis. He does not have any other medical problems. He was exclusively breast fed for the first 6 months. Infant cereal and fruits were added from 6 months and cows' milk introduced to his diet a month ago.

Mrs Williams is concerned that Sam might be allergic to cow's milk, as she has read about a link between food allergies and eczema on the internet. She is thinking about stopping cow's milk, but wants to discuss it with you first. She also wants Sam to be referred for food allergy testing.

Epidemiology of atopic dermatitis

Atopic dermatitis is a chronic relapsing inflammatory skin condition characterised by pruritus and eczematous skin (Dhar and Srinivas, 2016), which manifests as dry, red and itchy skin changes. The cause is still not completely understood. A combination of a genetic predisposition to skin barrier dysfunction and environmental factors, such as irritants, microbes, extremes of temperature, stress and allergens are thought to contribute to its development (Morren et al., 1994).

It commonly starts in childhood, within the first 5 years of age (Baron et al., 2012), with 45% of cases reportedly starting within the first 6 months of life (Nutten, 2015). Children usually outgrow the disease, as around 60% will be disease-free by adolescence (Baron et al., 2012). The prevalence in the United Kingdom is 11–20% in children and 5–10% in adults (Cork et al., 2019). Worldwide prevalence rates are 15–30% for children and 2–10 % for adults (Baron et al., 2012). It may present as the first in a series of atopic diseases. These include food allergy, asthma and

allergic rhinitis; the so-called 'atopic march' (Baron et al., 2012).

Pathophysiology of atopic dermatitis

The pathophysiology of atopic dermatitis is complex and multifactorial. The interplay between barrier dysfunction, immunoglobulin-E (IgE) hypersensitivity, alteration in cell-mediated immune response and environmental factors is considered to be key (David-Boothe et al., 2017). Two main theories have been suggested regarding the cause of atopic dermatitis. One proposes a primary immune dysfunction with a secondary epithelial barrier dysfunction. The other suggests a primary epithelial barrier dysfunction with secondary immunologic dysregulation.

The primary immune dysfunction theory describes T-helper cell dysregulation, resulting in an imbalance in the T-cell subsets with predominance of T-helper 2 cells rather than T-helper 1 cells. This situation results in the increased production of type 2 cytokines, such as interleukins IL-4, IL-5 and IL-13 promoting IgE production, inflammation and subsequent epithelial barrier disturbance (Klonowska et al., 2018). Interleukin IL-17 has also been identified as having raised levels in patients with atopic dermatitis (Koga et al., 2008). The significance of this is uncertain. Eosinophils, mast cells, basophils and a newly identified innate immune cell called group 2 innate lymphoid cell (ILC2s) have also been shown to play a role in the pathogenesis of atopic dermatitis (Mashiko et al., 2017).

The primary epithelial dysfunction theory describes a primary defect in the epithelial barrier. It is thought that this makes the skin permeable to antigens, leading to allergen sensitisation and induction of IgE autoantibodies. Filaggrin is a protein that helps with the conversion of keratinocytes to protein or lipid squames. These make up the outermost barrier of the skin - the stratum corneum. Recent evidence suggests that a mutation in the filaggrin gene is a likely cause of up to 50% of atopic dermatitis. The mutation causes epithelial barrier dysfunction (Nutten, 2015). The consequent dysfunction causes altered pH and trans-epidermal water loss from the skin. This leads to dryness and predisposes to bacterial colonisation and infection and inflammation. It also increases the skin's susceptibility to environmental allergens, leading to sensitisation and induction of IgE autoantibodies (Kubo et al., 2012).

Atopic dermatitis and food allergy

Studies have identified the prevalence of a food allergy in atopic dermatitis to be around 15% in patients with mild atopic dermatitis (Stokowski, 2011) and 30–40% in patients with moderate-to-severe atopic dermatitis (Boyce et al., 2011). Peanuts, eggs, soy, wheat, seafood and shellfish are common culprits (Katta and Schlichte, 2014).

Although, there is a clearly a higher prevalence of a food allergy in paediatric atopic dermatitis patients (20% in paediatric patients with atopic dermatitis versus 4–5% in the general paediatric population) (Martin et al., 2015), the causal link

between the two conditions remains hypothetical. Also, the mechanism by which they are linked is complex and controversial. In general, IgE and cellular mechanisms are thought to be responsible for acute and delayed food allergies, respectively.

The dual allergen exposure hypothesis suggests that early exposure to a particular food item through the skin primes the immune system to develop an allergy instead of tolerance to the food item, consequent upon early exposure to the food item through the gut (Turcanu et al., 2017). The associated skin dysfunction in atopic dermatitis is thought to promote the entry of food allergens with subsequent mucosa and percutaneous sensitisation. Individuals produce IgE antibodies to one or more food allergens that bind to high-affinity receptors on circulating basophils and tissue mast cells that are present throughout the body (Wasserman et al., 2014). Further allergen exposure binds and crosslinks the IgE antibodies on the cell surface, initiating the production and release of inflammatory markers such as histamines and cytokines that promote allergic inflammation. These mediators cause vasodilation, smooth muscle contraction and mucus secretion, which are responsible for the symptoms observed during acute food allergy (Wasserman et al., 2014).

The mechanism of provoking an allergy after re-exposure to a specific type of allergen is described as a type 1 hypersensitivity reaction and accounts for the acute food allergy symptoms seen in 40–60% of cases (Dhar and Srinivas, 2016). They occur within minutes of food consumption and can involve single or multiple organs. Cutaneous manifestations can include eruptions such as urticated plaques, angioedema-like appearance, excoriations, erythema and morbilliform appearance. Non-dermatological features include vomiting, diarrhoea, abdominal pain, rhinitis, asthma and anaphylaxis. These manifestations are independent of the atopic dermatitis.

Allergen T-cell activation is widely accepted as playing a role in the development of delayed type food allergy. Ingested food allergens are thought to activate antigen-specific T-cells by non-IgE mechanisms. This leads to the production of cytokines that promote the inflammatory process associated with atopic dermatitis. Several studies have investigated the role of food antigen-specific T-cells in atopic dermatitis. For example, Reekers et al. (1999) identified a birch-pollen-specific T-cell response in the skin of a subset of patients with birch-pollen sensitivity and atopic dermatitis. The study further confirmed worsening of eczema by double blind placebo-controlled birch pollen-related food challenge in these patients.

The cellular mechanism that produces the delayed reaction, hours to days after ingesting the trigger food is known as a type IV or delayed hypersensitivity reaction. It often manifests as flare ups of eczema on the areas of pre-existing atopic dermatitis (Bergmann et al., 2013). The prevalence is unknown, although Werfel et al. (2007) argued that it may be underestimated, as delayed reactions are often not included in published studies of food allergy in atopic dermatitis. They can occur in isolation or together with acute food reactions. A combination of the two patterns is said to occur in about 40% of children with positive oral food challenge (Werfel et al., 2007).

Allergy testing

The prevalence of food allergies in patients with atopic dermatitis ranges from 15–30% (Baron et al., 2012). As a result, it is not feasible to screen all patients with atopic dermatitis for food allergy. There is also insufficient evidence to support a specific age for testing response to foods known to cause IgE-mediated food allergies in infants and young children (Boyce et al., 2011).

The Royal College of Paediatrics and Child Health's published guidance on the care pathways for children with eczema and food allergy encourages clinicians to consider and seek to diagnose food allergy in children with atopic dermatitis. This is because of the increased prevalence in this population. The guidance warns that food allergy may manifest as a worsening of atopic dermatitis (Cox et al., 2011; Fox et al., 2011).

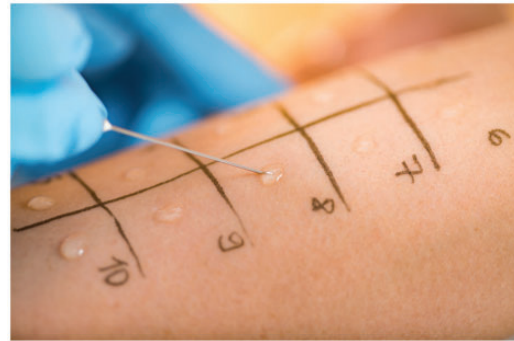
Careful history taking can help to establish a temporal relationship between symptoms and specific foods. It is reasonable to suspect food allergies in patients that present with symptoms (cutaneous, respiratory, gastrointestinal and/or cardiovascular) that occur within minutes to hours of ingesting food, or if the symptoms have occurred following the consumption of particular foods on more than one occasion (Stokowski, 2011). It is also important to consider that food allergies may only present outwardly as skin conditions such as itching and erythema or with features that can overlap those of atopic dermatitis. For example, IgE-mediated cow's milk allergy has been known to present as an acute flare up of pre-existing eczema, whereas non-IgE-mediated cow's milk allergy has been documented to manifest as persistent or severe atopic dermatitis (Venter et al., 2017). The positive predictive value of history is, however, lower with delayed eczematous food reactions. Sampson (2003) reported that only 35–50% of parent-diagnosed food allergies were confirmed by food challenge. There are various environmental factors that play a role in the remitting and relapsing nature of atopic dermatitis that can confuse dietary involvement.

When acute food reaction is suspected, IgE testing can be done either through skin prick tests or specific IgE antibody blood tests to identify sensitisation to the suspected food allergens. The choice of food test should be influenced by the history and the common food allergies in the population, as many patients with atopic dermatitis will be sensitised to several food allergens without any clinical significance.

Skin prick tests

Skin prick tests (Fig. 1) indirectly assesses the reactivity of mast cells on the skin to the presence of specific IgE. It involves pricking the skin with a droplet of allergenic extract. Allergen-specific IgE bind to mast cells, and cross linking by allergens leads to degranulation of the mast cells, producing mediators such as histamine. This results in wheals. The wheal is read 15–20 minutes afterwards and compared with a positive control (histamine) wheal and a negative control. A positive test is a wheal equal to or larger than the histamine control. The test should be performed in clinics with resuscitation facilities and appropriately trained medical staff due to the risk of anaphylaxis.

Figure 1. Skin prick allergy testing.



Microgen Images/Science Photo Library

Serum-specific IgE blood tests

In-vitro testing assesses antigen-specific IgE by analysing the patient's serum. Immunoassays are used to measure interactions between antigens and antigen-specific antibodies. The immunoassays are often referred to as radioallergoabsorbent testing, although the term is outdated because radiation is now rarely used. Enzyme-linked immunosorbent assay, fluorescein enzyme immunoassays and chemiluminescent immunoassays are more commonly used (Diaz et al., 2016).

Serum-specific IgE blood test can be advantageous over the skin prick test, as it can be performed in cases where skin testing is limited by severe dermatitis and does not carry the risk of anaphylaxis. Both tests (skin prick and serum-specific IgE tests) have been reported to have a high negative predictive value but low positive predictive values. Lemon-Mulé et al., (2008) reported that less than 40% of patients with positive skin prick or food-specific IgE tests had oral food challenge-proven food allergy. The high negative predictive values make them useful tools in ruling out specific food allergies.

Patch testing

Patch testing has been found to have a greater sensitivity than skin prick tests and specific IgE measurement in cases of delayed eczematous reactions (Mehl et al., 2006). The allergen is placed on the upper back under occlusive tape and removed in 48 hours. The skin is reassessed at 72 to 96 hours. Papules, erythema and vesicles are observed under the area of contact with positive allergen (Diaz et al., 2016). The lack of standardisation and controversy around reproducibility means that it is not currently recommended in routine clinical practice for assessing delayed food reactions in patients with atopic dermatitis (Bergmann et al., 2013).

Elimination of food

Elimination of suspected foods can be a helpful practical guide in the diagnosis of delayed eczematous food reactions.

Patients can be advised to make food diaries to identify potential trigger foods and a diagnostic elimination of the suspected food followed by gradual reintroduction after 4 to 6 weeks can help evaluate diagnostic relevance. This should be done under the supervision of a trained dietician and only be continued if there is significant clinical improvement. This may, however, not be a fully reliable test, due to its placebo effect. Long-term food elimination in patients without proven food reactions is not advised, due to the risk of nutritional deficiencies (Stokowski, 2011).

Oral food challenge

An oral food challenge (OFC) is the gold standard for confirming food allergies (Bergmann et al., 2013). They can be performed when a diagnosis remains uncertain from the history, allergy testing or diagnostic elimination of food items. Food challenges are conducted after a period of elimination of the suspected food from the diet. The suspected food is then gradually reintroduced into the diet with concurrent assessment for symptoms. It should be undertaken in an adequately resourced clinic or hospital setting, under close supervision by appropriately trained medical staff with access to facilities for emergency treatment of anaphylaxis and resuscitation.

It can be done either as an open food challenge, patient-blind challenge or a double-blind placebo – controlled challenge (DBPCFC). The DBPCFC method is the most reliable way of confirming food allergy (Bergmann et al., 2013). Here, both the patients and the observer are unaware of the contents of the challenge at the time of consumption to reduce patient and observer biases. It is ideal to observe for symptoms up to 24–48 hours after the challenge, as delayed food reactions can take that long to develop.

Conclusion

Patients with atopic dermatitis have an increased risk of food allergies. This may manifest as either acute IgE-mediated or delayed non-IgE-mediated food reactions. Although universal screening of patients with atopic dermatitis for food allergy is not advised, patients with histories suggestive of food allergies should be evaluated further.

Food-specific serum IgE blood or skin prick tests are useful tools for further evaluation of possible IgE-mediated food allergies. A positive test, together with the history, can help to establish a diagnosis in many cases. A negative test is helpful in excluding IgE-mediated food allergy, due to the high negative predictive value of the test.

Elimination followed by gradual reintroduction of suspected food items can be beneficial in diagnosing delayed food reactions. Long-term food elimination without proven food allergy or reaction is discouraged, due to the risk of nutritional deficiencies. OFC remains the gold standard diagnostic tool for food allergies and can be done when diagnosis remains uncertain after initial tests. This should be done under close supervision by trained personnel in appropriately resourced facilities.

KEY POINTS

- Children with atopic dermatitis are at increased risk of developing food allergies, although the overall risk is small
- A diagnosis of acute food reaction is very likely in a patient with an indicative history and a positive skin prick or raised specific food IgE test
- Raised food-specific IgE levels and positive skin prick tests indicate sensitisation and are not diagnostic of food allergies in isolation
- Measuring total serum IgE level is not helpful, as patients with atopic dermatitis have raised IgE levels independent of food allergies
- OFC is the gold standard for confirmation of food allergy when diagnosis remains uncertain from history, allergy testing or dietary elimination, but should only be undertaken in a suitably equipped hospital setting

ORCID iD

Dr Idris Akinwande  <https://orcid.org/0000-0002-6911-3308>

References and further information

- Baron S, Cohen S and Archer C (2012) Guidance on the diagnosis and clinical management of atopic eczema. *Clinical and Experimental Dermatology* 37(Suppl 1): 7–12. DOI: 10.1111/j.1365-2230.2012.04336.x.
- Bergmann M, Caubet J, Boguniewicz M, et al. (2013) Evaluation of food allergy in patients with atopic dermatitis. *The Journal of Allergy and Clinical Immunology: In Practice* 1(1): 22–28. DOI: 10.1016/j.jaip.2012.11.005.
- Boyce JA, Assa'ad A, Burks AW, et al. (2011) Guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-sponsored expert panel report. *Journal of the American Academy of Dermatology* 64(1): 175–192. DOI:10.1016/j.jaad.2010.11.020.
- Cork M, Danby S and Ogg G (2019) Atopic dermatitis epidemiology and unmet need in the United Kingdom. *Journal of Dermatological Treatment* 1–9. DOI: 10.1080/09546634.2019.1655137.
- Cox H, Lloyd K, Williams H, et al. (2011) Emollients, education and quality of life: The RCPCH care pathway for children with eczema. *Archives of Disease in Childhood* 96(Supplement 2): i19–i24. DOI: 10.1136/archdischild-2011-300695.
- David-Boothe W, Tarbox J and Tarbox M (2017) Atopic dermatitis: Pathophysiology. *Advances in Experimental Medicine and Biology* 1027: 21–37. DOI: 10.1007/978-3-319-64804-0_3.

- Dhar S and Srinivas S (2016) Food allergy in atopic dermatitis. *Indian Journal of Dermatology* 61(6): 645. DOI: 10.4103/0019-5154.193673.
- Diaz RC, Liang J, Hallet L, et al. (2016) Diagnostic allergy testing: Specific IgE testing. Updated 29 February 2016. Available at: www.medscape.com/viewarticle/738815_2 (accessed 13 December 2019).
- Fox A, Lloyd K, Arkwright P, et al. (2011) The RCPCH care pathway for food allergy in children: An evidence and consensus based national approach. *Archives of Disease in Childhood* 96(Supplement 2): i25–i29. DOI: 10.1136/adc.2011.214502.
- Katta R and Schlichte M (2014) Diet and dermatitis: Food triggers. Available at: <http://jcadonline.com/diet-and-dermatitis-food-triggers/> (accessed 7 December 2019).
- Klonowska J, Gleń J, Nowicki R, et al. (2018) New cytokines in the pathogenesis of atopic dermatitis—New therapeutic targets. *International Journal of Molecular Sciences* 19(10): 3086. DOI: 10.3390/ijms19103086.
- Koga C, Kabashima K, Shiraishi N, et al. (2008) Possible pathogenic role of Th17 cells for atopic dermatitis. *Journal of Investigative Dermatology* 128(11): 2625–2630. DOI: 10.1038/jid.2008.111.
- Kubo A, Nagao K and Amagai M (2012) Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. *Journal of Clinical Investigation* 122(2): 440–447. DOI: 10.1172/JCI57416.
- Lemon-Mulé H, Nowak-Węgrzyn A, Beri C, et al. (2008) Pathophysiology of food-induced anaphylaxis. *Current Allergy and Asthma Reports* 8(3): 201–208. DOI: 10.1007/s11882-008-0034-6.
- Martin P, Eckert J, Koplin J, et al. (2014) Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clinical & Experimental Allergy* 45(1): 255–264. DOI: 10.1111/cea.12406.
- Mashiko S, Mehta H, Bissonnette R, et al. (2017) Increased frequencies of basophils, type 2 innate lymphoid cells and Th2 cells in skin of patients with atopic dermatitis but not psoriasis. *Journal of Dermatological Science* 88(2): 167–174. DOI: 10.1016/j.jdermsci.2017.07.003.
- Mehl A, Rolinckwerninghaus C, Staden U, et al. (2006) The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *Journal of Allergy and Clinical Immunology* 118(4): 923–929. DOI: 10.1016/j.jaci.2006.07.003.
- Morren M, Przybilla B, Bamelis M, et al. (1994) Atopic dermatitis: Triggering factors. *Journal of the American Academy of Dermatology* 31(3): 467–473. DOI: 10.1016/S0190-9622(94)70213-6.
- Nutten S (2015) Atopic dermatitis: Global epidemiology and risk factors. *Annals of Nutrition and Metabolism* 66(1): 8–16. DOI: 10.1159/000370220.
- RCGP. Clinical topic guide: Dermatology. Available at: www.rcgp.org.uk/training-exams/training/gp-curriculum-overview.aspx (accessed 23 June 2020).
- Reekers R, Busche M, Wittmann M, et al. (1999) Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *Journal of Allergy and Clinical Immunology* 104(2): 466–472. DOI: 10.1016/S0091-6749(99)70395-7.
- Sampson H (2003) The evaluation and management of food allergy in atopic dermatitis. *Clinics in Dermatology* 21(3): 183–192. DOI: 10.1016/j.jaip.2012.11.005.
- Stokowski L (2011) Food allergy in dermatology: The patient with atopic dermatitis. Available at: www.medscape.com/viewarticle/738815_2 (accessed 14 December 2019).
- Turcanu V, Brough H, Du Toit G, et al. (2017) Immune mechanisms of food allergy and its prevention by early intervention. *Current Opinion in Immunology* 48: 92–98. DOI: 10.1016/j.coi.2017.08.009.
- Venter C, Brown T, Meyer R, et al. (2017) Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP—An international interpretation of the MAP (Milk Allergy in Primary Care) guideline. *Clinical and Translational Allergy* 7(1): 1–9. DOI: 10.1186/s13601-017-0162-y.
- Waserman S, Bégin P and Watson W (2018) IgE-mediated food allergy. *Allergy, Asthma & Clinical Immunology* 14(S2): 55. DOI: 10.1016/j.jaip.2013.10.001.
- Werfel T, Ballmer-Weber B, Eigenmann P, et al. (2007) Eczematous reactions to food in atopic eczema: Position paper of the EAACI and GA2LEN. *Allergy* 62(7): 723–728. DOI: 10.1111/j.1398-9995.2007.01429.x.

DOI: 10.1177/1755738020952038a

AKT answer relating to medication side effects

Answer C. Antipsychotics

This man has a raised cholesterol level. On questioning, he seems to have a good diet and exercises regularly. Of the medications that he takes that are listed, the antipsychotics group can cause hyperlipidaemia.

InnovAiT article: Intellectual disability and ageing. DOI: 10.1177/1755738020949572.