

Allergy

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The British Society of Immunology is the largest immunology society in Europe. Our mission is to promote excellence in immunological research, scholarship and clinical practice in order to improve human and animal health. We represent the interests of more than 3,000 immunologists working in academia, clinical medicine, and industry. We have strong international links and collaborate with our European, American and Asian partner societies in order to achieve our aims.

Key points:

- Allergies encompass a wide range of conditions varying in prevalence. They are characterised as an unnecessary immune response to an innocuous substance (such as pollens, latex, or certain foods). When these substances cause an allergic reaction they are considered an allergen.
- The prevalence of allergy in the UK and other developed countries is increasing. The reasons for this are poorly understood but are thought to be linked to changes in human lifestyle that have altered our exposure to the diversity of microbes.
- Commonly used diagnostic methods for identifying allergy include skin prick and/or blood tests combined with a detailed patient history. Component resolved diagnostics is able to provide more detailed and accurate diagnostic information and is becoming more relevant in allergy clinics.
- Allergy immunotherapy or desensitisation can be used in some cases to eliminate a person's allergy by reversing their immune response to the triggering allergen.

Introduction

An allergy is an unnecessary immune response to an innocuous substance (an allergen). Examples of common substances people are allergic to include pollens, dust mites, insect venom and food such as nuts or shellfish.

Allergic reactions can be grouped into two classes. The most common and best understood is mediated by a class of antibody called immunoglobulin E (IgE). Other reactions are non-IgE mediated and typically cause symptoms to appear more slowly, sometimes several hours after exposure. In fact, non-IgE mediated reactions do not

necessarily involve antibodies but instead, cell reactions of the immune system. They are much less common and are generally less well-understood.

The most common way to diagnose an IgE-mediated allergy is through a blood test to identify allergen-specific IgE or a skin prick test which results in a local inflammatory reaction after administration of the trigger allergen.

Allergies can range in severity from symptoms of mild discomfort to the life-threatening systemic reaction seen in anaphylaxis. The type of symptoms depends mainly on how the person is exposed to the allergen. Every year in the UK, the number of allergy cases increases by approximately 5%, and half of those are in children. The 'Hygiene Hypothesis', the idea that increased exposure to microorganisms correlates with a decreased tendency to develop allergy, is one explanation for the rise in prevalence. This has developed into a new hypothesis called The 'Old Friends Mechanism' which links the tendency to develop allergy to an individual's microbiome (collection of microorganisms living in and on a person's body).

What is allergy?

Allergy describes a wide range of conditions, some of which are rare and some very common. In healthy individuals, when the immune system registers a substance as a threat, B cells, a type of white blood cell, produce antibodies. This is a process known as sensitisation and is part of the normal immune response.

In allergic individuals, the immune system misidentifies a harmless substance as a threat. Therefore, an allergy is an unnecessary immune response to an innocuous substance (termed an allergen). Allergens are usually proteins (called antigens) found in a non-infectious allergy-causing substance (for example pollens or dust mites), which ultimately trigger the immune system to respond in a way that can be harmful, causing tissue damage and serious disease. These harmful immune responses are termed hypersensitivities and often cause a number of undesirable reactions which can lead to wheezing, coughing, oedema (swelling), or, in extreme circumstances, anaphylaxis.

IgE-mediated allergy is broadly characterised as a Type 1 hypersensitivity. Other hypersensitivity reactions (II, III and IV) are mediated by other antibody classes, immune cells

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or cellular components. Common IgE-mediated allergies include food allergies, wasp venom and hay fever (see Box 1). Some people may have an inherited tendency towards allergies, a condition known as atopy. Atopic individuals are more prone to asthma, eczema and hay fever (the atopic triad).

Box 1. Common allergies in the UKⁱ

- Food - e.g. nuts, fruit, shellfish, eggs, cow's milk. Affects 6-8% of people in the UK.ⁱⁱ
- Pollen - hay fever affects 25% of the UK.ⁱⁱⁱ
- Dust mites
- Insect bites and stings - wasp venom allergy affects 1 in 150 children and 3 in 100 adults in the UK.ⁱⁱ
- Latex - e.g. gloves

How does an allergy develop?

It is true in most cases that a person cannot have an allergic reaction to a substance that he or she has never come across. Encountering an allergen once is therefore usually necessary to develop an allergy. The process through which a person's body becomes sensitive to a given allergen is known as sensitisation.

Sensitisation

When allergens enter the body, antigen presenting cells (immune cells that capture incoming substances and present them to other immune cells, initiating a cascade of immune responses) at body surfaces, capture and present them to immune cells, particularly T cells (in a similar manner as if the allergen was a foreign invading microbe). Through a number of immune interactions between T cells and B cells, B cells produce allergen-specific IgE antibodies. Once released into the blood, IgE binds to mast cells (the major allergy immune cell), as well as other immune cells such as basophils. Some, but not all, individuals who are sensitised will develop an allergic reaction on re-exposure to the allergen.

Re-exposure to allergen

It is possible for an individual to go their whole life carrying allergen-specific IgE bound mast cells without ever experiencing an allergic reaction or even being aware of the allergy. However, upon re-exposure to the offensive allergen, binding of the allergen to IgE on mast cells can initiate an aggressive and immediate immune response. Mast cells are granular cells, meaning they contain many secretory granules which, when activated, release their contents into the blood stream. In the case of allergy, binding of an allergen to IgE-mast cells results in their rapid degranulation and the release of inflammatory compounds, including histamine, which contribute to local inflammation and the symptoms associated with allergy. In the respiratory tract, for example, inflammation results in mucus secretion and vasodilation in the nose and lungs, which can lead to wheezing and difficulty breathing. In order to offset the immediate symptoms of an allergic reaction, people with allergies can take anti-histamines, a class of drug that limits the action of histamine on the body. In extreme cases of anaphylaxis, patients may require an adrenaline injection (see Box 2).

In addition to early-phase symptoms, a number of symptoms can occur several hours after exposure to the allergen and can even last upwards of weeks. Late-phase reactions can result in similar symptoms, but also tissue destruction and continued immune cell recruitment. Anaphylaxis to foods is more common in young people whereas severe reactions in older people are more commonly triggered by insect venom.

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Box 2. What is anaphylaxis: a clinical case study^v

Case: An otherwise healthy 12-year-old boy was brought into A & E after being stung by a wasp on his forearm. Initially, he complained of localised pain and swelling. Several minutes later he began having difficulty breathing and was apparently wheezing. He soon said he was feeling weak and dizzy. A diagnosis of anaphylactic shock was made and he was given intramuscular adrenaline, which was associated with an improvement of symptoms before he shortly reported feeling back to normal.

Explanation: Globally, up to 2% of people (an increasing rate) will experience anaphylaxis at some point in their lifetime. Anaphylaxis is a systemic response to an allergen. It is the most severe form of allergy. Where other allergies may only involve a single body system, anaphylaxis triggers reactions in several body systems including the respiratory and/or cardiovascular systems, which can result in difficulty breathing, rapid heart rate, drop in blood pressure and cardiac arrest. The primary treatment of anaphylaxis is intramuscular adrenaline injection, which acts quickly to open up airways, stop swelling and raise blood pressure. Carrying an adrenaline injector is recommended for people at risk of this severe form of allergy. Immunologists do not currently understand why some allergic people experience anaphylaxis and others never do; however anyone who has had an anaphylactic reaction before is at higher risk of experiencing it again.

were less likely to develop allergies due to an increased incidence of infection in early childhood, transmitted from older siblings. The 'Hygiene Hypothesis' has since developed into The 'Old Friends Mechanism', a theory which suggests that the likelihood of developing allergies is related to an individual's microbiome, the population of microbes living in and on the human body. Exposure in early life to a diverse range of microbes that have evolved alongside humans for millions of years helps to develop a properly regulated immune system that does not overreact to harmless allergens. Changes to human lifestyles, including less breastfeeding, smaller family size and increased antibiotic use, have affected exposure to a diverse array of microbes and is the most compelling theory for why allergies are increasing in the developed world.

There are several mechanisms suggested to be responsible for inducing protection from various immunological disorders, including allergy. One of these is the skewing towards an immune profile of T helper 2 cells (Th2 cells) over T helper 1 cells (Th1 cells). T helper cells are a class of immune cells, which produce inflammatory mediators called cytokines. Th1 cells produce cytokines predominantly for fighting off bacterial and viral infections, where Th2 cells produce cytokines that fight off parasitic infections and contribute to IgE production and allergic responses. In a more 'hygienic' environment where there is less contact with infectious agents, an immune profile is skewed towards the latter, due to the lack of need to fight against as many invading microbes. Similarly, there is evidence of decreased allergy prevalence in developing countries, where children may not have access to safe sanitation systems, clean water, exposure to parasitic organisms and generally spend more time outside, compared to developed countries.

Why are allergies increasing?

Allergy is widespread in the UK and worldwide and the number of people affected and experiencing severe allergic symptoms continues to increase, particularly in the developed world. For example, in the UK, cases of food allergies have doubled in the last decade and the number of hospitalisations caused by severe allergic reactions have increased 7-fold. Indeed, in 2014/2015, there were approximately 80,000 A & E attendances for allergies in England. This was an increase of almost 9,000 from the year before^{vi}.

The idea that exposure to infectious agents may decrease the risk of allergy was first introduced in 1989. This concept, termed The 'Hygiene Hypothesis' came from the observation that children in families with older siblings

Diagnostic tests

The two most commonly used diagnostic tests are the skin prick test and a blood test to measure levels of specific IgE.

Skin prick test – a doctor will add a liquid containing a small amount of the suspected allergen to a patient's forearm and then will prick the skin using a sterile lancet. If the area begins to swell or itch, that is considered a positive reaction.

Specific IgE test – a blood test to look for the presence of specific IgE targeted against the suspected allergen(s).

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Component resolved diagnostics (CRD) –diagnostic test for IgE-mediated allergy, which detects IgE specific to pieces of an allergen. CRD may be able to provide more detailed and accurate diagnostic information about an IgE allergy in terms of clinical relevance, prognosis and management.

Test results must be combined with a detailed allergy-focused patient history to accurately give a diagnosis. In cases where patient history and IgE tests do not match, a doctor may consider provocation challenge test under specialist supervision with gradually increasing amounts of the suspected allergen. This is particularly useful to rule out false-positive results, which can be a barrier in allergy diagnosis.

Desensitisation/Immunotherapy

The best way to prevent an allergic reaction is to avoid contact with the offensive allergen. However, in many cases, this is impractical and can sometimes be impossible, for example when the allergen is dust mite. Allergy research has established a way to reverse a person's allergy development in some cases. Allergy immunotherapy (AIT), or desensitisation involves administration of a particular allergen, given in gradually increasing doses, eventually developing immunity or tolerance to the allergen. In practice, the treatment can be administered as drops, as a dissolvable tablet under the tongue, or as an injection into the arm. AIT is a long-lasting treatment and has been effective for treating people with hay fever, house dust mite, animal dander, and wasp and bee venom allergy. Despite the advances made in allergy treatment, more strategies are needed to treat other allergies. Clinical trials for food allergy desensitisation are ongoing and there are currently no products available for clinical use. This treatment should only be given under the supervision of a qualified clinician.

During AIT, the immune system's responses change. These changes may include producing less IgE, producing 'blocking' IgG antibodies, and producing more regulatory T cells, promoting tolerance and a less active immune response. However, the exact mechanism behind desensitisation is not yet known and it is likely that different patients exhibit different immune profiles following the treatment.

ⁱ NHS choices 2016 Allergies.

ⁱⁱ Allergy UK Allergy statistics.

ⁱⁱⁱ Pawankar *et al.* 2011 World Allergy Organisation. White Book on Allergy.

^{iv} Takase *et al.* 2013. University of Hawaii Department of Pediatrics. Anaphylaxis and other acute allergic reactions.

^v Simons *et al.* 2011. The World Allergy Organisation Journal. **4** (2)13-37.

^{vi} NHS Digital 2015 Accident and Emergency Attendances in England 2014-2015.

^{vii} Strachan 1989. British Medical Journal. **299** (6710) 1259-60.

^{viii} Okada *et al.* 2010. Clinical & Experimental Immunology. **160** (1) 1-9.