The lymphatic system 4: allergies, anaphylaxis and anaphylactic shock

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Abstract
This article, the fourth in a six-part series on the lymphatic system, discusses the nature of allergy, exploring common allergens and the body’s response to them in atopic people, including anaphylaxis. It questions why allergies are becoming increasingly common, particularly in developed countries, exploring a number of theories.

Citation

This article is the fourth in a six-part series about the lymphatic system. This series has previously examined the system’s components, its role in tissue drainage, and the trapping of foreign and potentially pathogenic material. The most recent article highlighted the nature of both non-specific immunity, which is active against a broad range of infectious agents, and specific immunity, which targets single pathogens and usually retains a memory of the encounter to allow a swift response on subsequent re-exposure. A finely tuned immune response is essential to health and survival; however, in some people, immune reactions can be elicited against harmless materials in the environment, leading to allergy. This article explores the nature of allergy and examines how, in some people, allergic responses can become much more serious and potentially lead to life-threatening anaphylaxis and anaphylactic shock.

Allergens and allergy
An allergen can be broadly defined as anything that can trigger an allergic response (Woodfolk et al., 2015). In theory, any foreign (environmental) material can act as an allergen, although some substances are more likely to trigger allergic responses than others: most allergens are proteinaceous in nature (Goodman and Breiteneder, 2019). Common environmental allergens include:

- The various types of tree and flower pollen that cause hayfever;
- House dust, which usually includes the highly allergenic faecal pellets of house dust mites that are responsible for perinatal rhinitis;
- Shellfish and peanut or other nut proteins, which can trigger anaphylactic responses.

Some people seem particularly prone to developing allergies and are referred to as atopic individuals. This susceptibility to allergy is likely to be due to a combination of genetic and environmental factors (Justiz Vaillant et al, 2020). Common environmental allergens include:

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**Keywords**
Lymphatic system/Anaphylaxis/Immunity/Anatomy

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shellfish proteins, insect venom, antibiotics, peanuts (ground nuts) or tree nut proteins. The following description of an IgE-mediated allergic response (illustrated in Fig 1) uses a pollen grain as an example.

To develop an allergy, an initial exposure to the allergen is required; in this example it could be initial exposure to high levels of pollen on a trip to the countryside. Pollen grains are microscopic and easily carried in the air for long distances before being inhaled into the upper respiratory tract through the nose. Many species of plants and trees produce pollen with highly allergenic proteins that can irritate and breach the epithelial mucosal barriers in the respiratory tract (Hosoki et al, 2015). On exposure to pollen allergens (as with most foreign materials), the immune system’s B-lymphocytes mature into plasma cells and generate specific antibodies against the pollen and, in the case of atopic individuals, copious amounts of the allergic antibody IgE. This specific IgE circulates in the blood and binds to tissue-resident mast cells, which are found throughout the body and possess IgE receptors. The mast cells, which are packed with granules of histamine, are now sensitised against that particular type of pollen and the individual will respond quickly to any subsequent re-exposure.

The secondary exposure to the allergen might occur when the pollen count rises. At this point, inhaled pollen grains can quickly react with the specific surface IgE antibodies now coating the mast cells. This causes the mast cells to degranulate, releasing histamine and other inflammatory mediators into the local tissues. Histamine quickly initiates local vasodilation, leading to redness and irritation at the contact site. This triggers the sneezing, runny nose and streaming eyes that are characteristic of hayfever.

Regardless of the allergen, the basic principles of sensitisation and the onset of symptoms following secondary exposure are the same. Allergic (IgE-mediated) responses that have these characteristics are referred to as type 1 or immediate hypersensitivity reactions (Basu and Banik, 2018).

**House dust mite allergy**

Allergy to house dust mites’ faecal pellets is extremely common, affecting up to 150 million people worldwide (Calderón et al, 2014). House dust mites are found throughout homes, particularly in soft furnishings and bedding, including mattresses and pillows. These small arthropods feed primarily on shed skin cells and other particulate materials and produce large quantities of faecal pellets, which can be inhaled into the respiratory tract. These pellets contain a highly allergenic proteinaceous epitope called Der P1, which has an enzymatic activity and can cleave its way through the tight junctions between the ciliated epithelial cells lining the bronchial tree (Zhang, 2018). When house dust mite allergens enter these subepithelial tissues, they can trigger the production of the allergic antibody IgE in the way described above and in Fig 1.

In the case of house dust mite allergy, the most common feature of the allergic response initiated by secondary exposure is perennial rhinitis, which is characterised by continually streaming eyes and nose. The release of inflammatory mediators (particularly histamine) from degranulating mast cells leads to rapid vasodilation in the ocular and nasal mucosa, causing red eyes and a congested nose. Histamine also binds to receptors on the mucus-producing goblet cells in the upper respiratory tract. This increases mucus production, which contributes to congestion and the continually streaming nose (Fig 2, p56). It is usually easy to recognise perennial rhinitis in a patient because of the red, itchy eyes and so-called ‘allergy salute’ as they are continually wiping their streaming nose.

Sometimes other effects are associated with house dust mite allergy. This can include dermatitis if the faecal pellets are ground into the skin, for example, when the patient rolls over in bed or changes position on the sofa. This can initiate histamine release from the large population of mast cells resident in the skin, leading to a prominent and often itchy skin rash called urticaria. Another major problem associated with house dust mite allergy is that inhaled faecal pellets can provoke asthma attacks in susceptible patients (Gautier and Charpin, 2017). People with a house dust mite allergy can often reduce their symptoms effectively with antihistamines; the frequency of episodes can also be reduced by switching to hypoallergenic bedding and pillows (Portnoy et al, 2013).

**Anaphylaxis and anaphylactic shock**

Most allergic responses are localised to the tissue with which the allergen has made contact; for example, hayfever primarily affects the nose, nasal cavity and eyes, where airborne pollen makes contact. However, some allergens can elicit more widespread and potent effects, known as an anaphylactic response. Common
allergens associated with anaphylaxis include peanut and tree nut proteins, antibiotics, shellfish proteins and insect venoms, such as bee and wasp stings.

Anaphylactic responses are, by definition, severe and life-threatening in nature. They are associated with widespread mast cell degranulation and the release of copious amounts of histamine and other inflammatory mediators, which can elicit systemic effects (Reber et al, 2017). The release of large amounts of histamine can induce widespread vasodilation, which results in a rapid drop in blood pressure. Significant hypotension is a key clinical feature of anaphylactic shock and can lead to weakness, collapse and loss of consciousness (Castells, 2017). Histamine can also have dramatic effects on the airway binding to histamine receptors in the smooth-muscle layers of the bronchial tree, inducing bronchoconstriction and stimulating increased mucus production from goblet cells in the respiratory mucosa (Thangam et al, 2018). During many severe anaphylactic episodes, a lipid mediator called platelet-activating factor (PAF) is released from platelets and a variety of leukocytes (white blood cells), including basophils, neutrophils and monocytes; PAF acts synergistically with histamine to significantly increase vascular permeability (Nakamura and Murata, 2018). This can lead to rapid accumulation of a watery (serous) exudate in soft tissues such as the lips, mouth and tongue, commonly in response to the ingestion of allergens, such as shellfish, tree nut or – more commonly – peanut proteins. In some cases, the swelling can be so severe that the airway becomes completely occluded, necessitating emergency intubation (Bernstein et al, 2017). Other potent mediators of inflammation – including prostaglandin D2 and the slow-reacting substance of anaphylaxis (SRS-A) – exacerbate bronchoconstriction and airway occlusion, resulting in the characteristic wheezing often associated with anaphylactic episodes. SRS-A is estimated to be up to 1,000 times more potent than histamine in inducing bronchoconstriction (Reber et al, 2017).

Anaphylactic shock is a medical emergency and requires rapid assessment and treatment to ensure the best chance of survival. The standard treatment is adrenaline. If a patient has previously had an anaphylactic episode, they may have been given an auto-injection device such as an EpiPen. Two devices are usually provided in case more than one dose of adrenaline is required. These devices are designed to auto-inject a fixed dose of adrenaline (usually 0.3mg) into the anterolateral aspect of the thigh and can be injected through clothing if necessary (EpiPen, 2020). Because adrenaline is a natural fight-or-flight hormone it dilates the airway, allowing the patient to breathe more easily, while simultaneously inducing peripheral vasoconstriction and increasing the heart rate to help restore blood pressure (Knight et al, 2020). Most patients begin to feel better quickly following the dose of adrenaline; however, sometimes other medications are also used, including antihistamines and asthma inhalers, such as salbutamol (a beta-agonist that mimics adrenaline to promote bronchodilation). For severe anaphylactic episodes, novel drugs that block the biosynthesis of the more potent inflammatory mediators are available, such as SRS-A (Haeggström, 2018).

Anaphylaxis and peanut allergy
Peanut allergy appears to be particularly common in children: up to 2% are affected in the UK and, worryingly, many of them experience severe anaphylactic responses when exposed to peanut products (Allergy UK, 2020). Peanuts are not, strictly speaking, nuts, but are legumes more closely related to lentils and peas. They are unusual in that they have multiple allergenic proteinaceous epitopes associated with them: currently 16 have been identified, which are denoted as Ara h1 to Ara h16 (Palladino and Breiteneder, 2018). Peanut allergies have become progressively more common over the last few decades, although the reasons for this are still poorly understood.

Certainly exposure to peanut products has increased over the years. It has also been demonstrated that peanut allergens can appear in breast milk within minutes of being consumed by the mother (Bernard et al, 2014). Initially it was thought that avoiding peanut products during pregnancy and while breastfeeding would reduce the incidence of peanut allergy in children, but this does not appear to be the case. The current advice in the UK is that peanuts and peanut products should be consumed during pregnancy and when breastfeeding and eaten in early childhood (from the age of six months) to allow tolerance to peanut proteins to naturally develop (Allergy UK, 2020; NHS, 2017).

In China, where peanut consumption is much higher than the UK, the incidence of peanut allergy is much lower. It has been hypothesised that this may be due to the way peanuts are consumed in the UK: grinding peanuts into pastes to make peanut butter and roasting them to make peanut oil (also referred to as groundnut oil) may expose more of the allergenic epitopes or denature and change the configuration of the peanut proteins, potentially making them more allergenic (Iqbal et al, 2016).

Non-IgE-mediated anaphylaxis
Most episodes of allergy and anaphylaxis are reliant on IgE sensitisation of mast cells. Rarely, however, anaphylaxis can be initiated without the involvement of IgE or any other antibodies. One of the most frequently encountered examples of this is following the use of contrast mediums...
involved in coronary and cerebral angiography. To visualise blood vessels to look for occlusion or blood vessel malformation or defects, radiopaque dyes, such as gadolinium (Omniscan), are injected and circulate throughout the body. In around 1 in 10,000 patients, gadolinium-based contrast mediums can trigger severe anaphylactic responses (Rosado et al, 2020). The exact mechanism causing these responses is not fully understood, but it is thought that the contrast medium directly irritates and initiates the release of histamine and other inflammatory mediators from tissue-resident mast cells (Kun and Jakubowski, 2012). Although such reactions are relatively rare, it is important that health professionals who work with gadolinium-based contrast mediums are trained and equipped to deal with anaphylactic reactions when they arise.

Some individuals can experience prominent skin reactions when exposed to sudden changes in ambient temperature, for example, when leaving a hot, centrally heated house to go outside on a freezing winter morning. These so-called heat or cold urticarial reactions typically cause a prickling sensation and prominent skin rash. However, more rarely, such responses may develop into more severe reactions that resemble anaphylaxis, resulting in significantly reduced blood pressure and wheezing. As with reactions to contrast mediums, these types of response are thought to be initiated by direct stimulation of the tissue-resident mast cells, which degranulate in response to the sudden changes in temperature experienced at the skin’s surface (Simmons, 2010).

Non-allergic histamine reactions
Histamine is synthesised in basophils and mast cells from the amino acid L-histidine. Both cell types produce an enzyme called L-histidine decarboxylase, which rapidly converts L-histidine into histamine that is then stockpiled in the cells in the form of granules. Dark-fleshed species of fish, such as anchovies and tuna, have high concentrations of L-histidine in their muscle tissue. Many groups of bacteria synthesise the enzyme L-histidine decarboxylase and, if freshly caught fish are not stored correctly, these bacteria can colonise and grow on the flesh of the fish and rapidly convert the L-histidine into biologically active histamine. When this spoilt fish is eaten, large amounts of preformed histamine are consumed and can elicit symptoms very similar to anaphylactic shock; this is known as Scombroid poisoning. Histamine is a powerful vasodilator and can also act with other mediators to increase vascular permeability, resulting in redness and severe swelling of the lips and oral tissues, as well as gastrointestinal symptoms, including vomiting and diarrhoea. Scombroid poisoning is usually self-limiting and can be treated effectively with antihistamines (Stratta and Badino, 2012).

Why are allergies becoming more common?
Some people appear to be highly susceptible to developing allergies compared with the general population. The exact reason for this increased susceptibility to allergic responses in atopic individuals is poorly understood; however, many factors are thought to be involved, including the inheritance of certain genes and the environment people are exposed to while growing up.

The hygiene hypothesis
In the 1980s it was noted that allergies were more prevalent in developed western
Antibody class switching

The previous article in this series (Nigam and Knight, 2020) examined the role played by different leukocytes in the immune infection, these cells produce chemical signals called cytokines that facilitate normal antibody production to resolve the infection. Helper T-cells exist as two major populations of cells: Th1 cells and Th2 cells. We appear to be born with a large population of Th2 cells and subsequently acquire greater populations of Th1 cells when we suffer repeated infections in early childhood (Fig 3, p27). People with a balanced population of Th1 and Th2 cells appear less likely to be atopic and show reduced susceptibility to allergic disease (Fig 3a).

When a person with a balanced population of Th1 and Th2 cells encounters a pathogen such as a bacterium, their B-lymphocytes in the immune system is less able to mount an effective antibody-mediated immune response (Zaghouani et al, 2009). We appear to be born with a large population of IgE instead of the usual IgG; as described above, this results in the IgE circulating throughout the body in the blood and sensitising mast cells following the initial exposure to the allergen. This phenomenon is referred to as antibody class switching and is a key feature of allergy (Junttila, 2018).

Gut microbiota

It has been noted that many regions of the world with low incidences of allergic disease also have endemic worm infestations, which have been largely eliminated in most developed countries. It is now known that having certain resident worm parasites in the gastrointestinal tract can lead to the production of anti-inflammatory cytokines – such as interleukin 10 (IL10) – that downregulate the immune system, making allergic responses less likely (Scudellari, 2017).

The healthy human gut is usually colonised by a diverse variety of micro-organisms in early infancy, including multiple species of bacteria, viruses and fungi, which collectively form the gut microbiota (Knight et al, 2019). However, it has been suggested that the use of antibiotics, smaller family sizes, reducing sharing of toys and food and increased use of surface-cleaning products have led to an impoverished gut microbiota, with a less diverse population of microbes.

It is known that the gut microbiota produces a multitude of chemical signals that can modulate the immune system: the gut microbiota has even been referred to as a virtual endocrine organ (Valdes et al, 2018). However, a lack of exposure to a diverse spectrum of micro-organisms in early life is thought to contribute to atopy and increase the subsequent risk of allergies. NT

References


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