An evidence-based approach to atopic patients

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Abstract
Patients prone to IgE-mediated allergic reactions are said to be atopic. Historically, atopic dermatitis (eczema), asthma and allergic rhinitis have been termed the “triad of atopy”, although this association has recently come into question. Type I hypersensitivity reactions underlie all atopic and many allergic disorders, and are associated with elevated immunoglobulin E levels. Atopic hypersensitivity disorders exhibit a strong familial or genetic predisposition, although symptoms are induced by exposure to specific allergens. These antigens are typically environmental (e.g. respiratory allergy to pollens, grass or house dust) or foods (e.g. allergy to shellfish). Common clinical manifestations include hay fever, asthma, eczema and urticaria. Many sufferers have immediate reactions to skin tests (injection, patch or scratch) using the offending antigen. Different treatment options are available, including avoidance, antihistamines, corticosteroids, mast cell stabilisers and desensitisation therapy.

Introduction
The term atopy, derived from the Greek atopos, meaning “out of place”, is often used when describing IgE-mediated diseases. Atopic diatheses may manifest in various ways. Historically, atopic dermatitis (eczema, AD), asthma and allergic rhinitis have been termed the “triad of atopy”, although this association has recently come into question. Atopy is characterised by a genetic predisposition to produce immunoglobulin E (IgE) antibodies in response to allergen exposure. Type I hypersensitivity reactions underlie all atopic and many allergic disorders. Although the terms atopy and allergy are often used interchangeably, their meanings are different.

Atopy is defined as a state of hypersensitivity to certain antigens. It is an exaggerated IgE-mediated immune response and all atopic disorders are type I hypersensitivity disorders. There is an inherited or genetic tendency.

Allergy is an exaggerated immune response to a foreign antigen, regardless of mechanism. Therefore, all atopic disorders are considered allergic, but many allergic disorders are not atopic.

Hypersensitivity
The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause detrimental reactions in the host, known as hypersensitivity reactions. The term hypersensitivity denotes a condition in which an immune response results in exaggerated or inappropriate reactions that are harmful to the host. In a given individual, such reactions typically occur after the second contact with a specific antigen (allergen). The first contact is a necessary preliminary event that induces sensitisation to that allergen.

The traditional classification of hypersensitivity reactions distinguishes between four main types of hypersensitivity reactions. Types I, II and III are antibody-mediated, whereas type IV is cell-mediated.

- Type I immediate hypersensitivity (allergy) involves IgE-mediated release of histamine and other mediators from mast cells and basophils.
- Type II hypersensitivity, also known as a cytotoxic hypersensitivity reaction, is mediated by IgG or IgM antibodies bound to cell surface antigens, with subsequent complement fixation.
- Type III immune complex hypersensitivity involves circulating antigen-antibody immune complexes that are deposited in postcapillary venules, with subsequent complement fixation.
- Type IV cell-mediated (delayed) hypersensitivity is mediated by T cells rather than by antibodies.

All atopic disorders are type I hypersensitivity disorders. Type I hypersensitivity manifests as tissue reactions occurring within seconds after the antigen combines with the matching antibody. It may present as systemic anaphylaxis (e.g. after administration of heterologous proteins) or as a local reaction (e.g. hay fever).
The general mechanism of immediate hypersensitivity involves antigen-induced formation of the IgE antibody, which binds firmly by its Fc portion to a receptor on mast cells, basophils and eosinophils. Some time later, a second exposure to the same antigen results in the antigen attaching to cell-bound IgE, cross-linking of IgE molecules, and release of pharmacologically active mediators from cells within seconds to minutes. Cyclic nucleotides and calcium are essential in the release of mediators. There may also be a second “late” phase that lasts for several days and involves infiltration of tissues by leucocytes, particularly eosinophils.

Type I hypersensitivity mediators include:

- **Histamine**: Histamine exists in a preformed state in platelets and in granules of mast cells, basophils and eosinophils. Its release causes vasodilation, increased capillary permeability and smooth muscle contraction (e.g. bronchospasm). Antihistamine drugs block histamine receptor sites and are relatively effective in allergic rhinitis. Histamine is one of the primary mediators of a type I reaction.

- **Prostaglandins and leukotrienes**: Prostaglandins and leukotrienes are derived from arachidonic acid via the cyclooxygenase pathway. Prostaglandins chiefly cause bronchoconstriction. Leukotrienes mainly cause increased permeability of capillaries. These mediators, along with cytokines such as TNF-α and IL-4, are referred to as secondary mediators of a Type I reaction.

**Figure 1**: Factors influencing the development of atopy and atopic allergic disease¹

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th>Environmental factors</th>
<th>Defects in target organs</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presence of specific HLA alleles</td>
<td>• Allergen sensitisation</td>
<td>• Bronchial epithelium</td>
<td>• Viral infections</td>
</tr>
<tr>
<td>• Polymorphisms of FceR1-β</td>
<td>• Having few siblings</td>
<td>• Skin</td>
<td>• Exposure to allergens</td>
</tr>
<tr>
<td>• Polymorphisms of the interleukin-4 family of cytokine genes</td>
<td>• Excessive hygiene</td>
<td>• Gut</td>
<td>• Tobacco smoke</td>
</tr>
<tr>
<td>• Polymorphism of CD14</td>
<td>• Exposure to antibodies in first two years of life</td>
<td></td>
<td>• Indoor and outdoor pollutants</td>
</tr>
<tr>
<td>• Polymorphisms at other loci</td>
<td>• Vaccination and prevention of disease</td>
<td></td>
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**Overview of atopy**

Atopic individuals have a hereditary predisposition to produce IgE antibodies against common environmental allergens, and have clinical manifestations of one or more atopic diseases. Atopic disorders most commonly affect the nose, eyes, skin and lungs, and include AD, contact dermatitis, urticaria and angioedema, latex allergy, allergic lung disorders and allergic reactions to venomous stings. Consideration of the term atopic allergy implies a familial tendency to manifest such conditions as asthma, rhinitis, urticaria and eczematous dermatitis (AD), alone or in combination. However, individuals without an atopic background may also develop hypersensitivity reactions, particularly urticaria and anaphylaxis, associated with the same class of antibody (IgE) found in atopic individuals. Some allergic diseases (e.g. hypersensitivity pneumonitis) operate through IgE-independent mechanisms and in this sense can be considered as nonatopic allergic conditions.²

The allergic inflammatory cascade is often described as having three components, namely sensitisation followed by an early- and late-phase response, which may be thought of in a sequential fashion. Although it sounds simple, it should be recognised that all pathways occur (to a greater or lesser degree) simultaneously, with a complex interaction among a variety of cells, mediators and cytokines.

Atopy is a major risk factor for asthma, and nonatopic individuals have a very low risk of developing asthma.⁴ Patients with asthma commonly suffer from other atopic diseases, particularly...
allergic rhinitis, which may be found in over 80% of asthma and AD. Atopy may be found in 40-50% of the population in affluent countries, with only a proportion of atopic individuals becoming asthmatic. This observation suggests that some other environmental or genetic factor predispose to the development of asthma in atopic individuals. The allergens that lead to sensitisation are proteins that have protease activity, and the most common allergens are derived from house dust mites, cat and dog fur, cockroaches, grass and tree pollens and rodents (in laboratory workers). Many patients have a family history of allergic diseases. Figure 1 shows the factors influencing the development of atopy and atopic allergic disease. The inception of allergic diseases is therefore dependent on interactions between genes and the environment. The induction of atopic allergic disease may require further interaction between target organ defects and/or various environmental triggers.

Symptoms and signs of atopy
Common symptoms of atopy include rhinorrhoea, sneezing and nasal congestion (upper respiratory tract), wheezing and dyspnoea (lower respiratory tract) and itching (eyes and/or skin). Signs may include nasal turbinated oedema, sinus pain on palpation, wheezing, conjunctival hyperaemia and oedema, and skin lichenification. Stridor, wheezing and sometimes hypotension are life-threatening signs of anaphylaxis. In some children, a narrow and high-arched palate, narrow chin and elongated maxilla with overbite (known as “allergic facies”) are thought to be associated with chronic allergy.

Diagnosis of atopy
A thorough history is generally more reliable than testing or screening. History should include questions about frequency and duration of attacks and changes over time, trigger factors if identifiable, relation to seasonal or situational settings (e.g. predictability of occurrence during pollen seasons, after exposure to animals, hay or dust, during exercise or in particular places), family history of similar symptoms or of atopic disorders, and response to attempted treatments. Age at onset may be important in asthma because childhood asthma is likely to be atopic, while asthma starting after the age of 30 years is usually not.

Certain nonspecific tests may suggest, but not confirm, an allergic origin of symptoms. A full blood count should be performed to detect eosinophils in all patients, except those taking corticosteroids (corticosteroids reduce the eosinophil count). Conjunctival or nasal secretions or sputum may be examined for leucocytes. Serum IgE levels are elevated in atopic disorders, but are of little help in diagnosis because they are also elevated in various other disorders (e.g. parasitic infections, infectious mononucleosis, autoimmune and immunodeficiency states).

Specific tests include skin tests that use standardised concentrations of antigen introduced directly into the skin and are indicated when a detailed history and physical examination do not identify the cause and triggers for symptoms. The most commonly used allergens are pollens (tree, grass and weed), moulds, house dust mites, animal dander and sera, insect venom, foods and β-lactam antibiotics. Two techniques may be used: percutaneous (prick) or intradermal. Radioallergosorbent testing (RAST) detects the presence of allergen-specific serum IgE and is indicated when skin testing is contraindicated. Provocative testing involves direct exposure of the mucosae to the allergen and is indicated for patients who must document their reaction (e.g. for occupational or disability claims) or sometimes for diagnosis of food allergy.

Treatment of atopy
Treatment of atopy will depend on the findings of history taking and the trigger factors identified. Generally, the treatment includes one or more of the following:

Environmental control
Removal or avoidance of allergic triggers is the primary treatment of allergy. Strategies include use of synthetic fibre pillows and impermeable mattress covers, frequent washing of bedding in hot water, removal of upholstered furniture, soft toys, carpets and pets, housecleaning and extermination of cockroaches, the use of dehumidifiers in basements and poorly aerated, damp rooms. Other measures include treating homes with heated steam, avoiding food triggers, limiting pets to certain rooms and frequent cleaning of furniture and carpets. Other adjuvant nonallergenic triggers (e.g. cigarette smoke, strong odours, irritating fumes, air pollution, cold temperatures and high humidity) should be avoided or controlled.

Pharmacological therapy
Antihistamines
Antihistamines do not affect histamine production, but block receptors. H1 blockers are a mainstay of treatment in allergic disorders, although H2 blockers may be indicated for certain atopic disorders. Oral H1 blockers provide symptomatic relief in various atopic and allergic disorders (e.g. seasonal hay fever, allergic rhinitis, conjunctivitis, urticaria and other dermatoses). Antihistamines can also be administered via the intranasal or ocular route.

Mast cell stabilisers
Cromolyn and nedocromil block the release of mediators from mast cells, and they are used when antihistamines and topical corticosteroids are ineffective or not well tolerated.

Corticosteroids
Corticosteroids can be given intranasally or orally. Oral corticosteroids are indicated for systemic allergic disorders that are severe but self-limiting (e.g. seasonal asthma flares, severe widespread contact dermatitis), and disorders refractory to other measures.

Calcineurin inhibitors
Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, selectively inhibit the production and release of proinflammatory cytokines and mediators by T cells and mast
cells, and are effective in moderate to severe AD and steroid-resistant AD, provided the skin is not infected.

Other
Leukotriene modifiers are indicated for the treatment of mild persistent asthma and seasonal allergic rhinitis. Anti-IgE antibody (omalizumab) is indicated for moderately persistent or severe asthma refractory to standard treatment, and may also be useful in refractory allergic rhinitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) alone are not useful.

Immunotherapy or desensitisation
Exposure to an allergen in gradually increasing doses (hyposensitisation or desensitisation) via injection, or in high doses sublingually, may induce tolerance and is indicated when allergen exposure cannot be avoided and drug treatment is inadequate. Allergens that typically cannot be avoided include pollens, house dust mites, moulds and the venom of stinging insects.

Hygiene hypothesis
There is increasing support for the hygiene hypothesis as an explanation for the increase in asthma and allergies in recent decades. The hygiene hypothesis states that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (e.g. gut flora or probiotics) and parasites increase susceptibility to allergic diseases by suppressing the natural development of the immune system. Other diseases, such as autoimmune diseases and acute lymphoblastic leukaemia in young people in the developed world, have also been linked to the hygiene hypothesis. There is even some evidence that autism is caused by an immune disease.

The hygiene hypothesis postulates an inverse relationship between AD and an environment that leads to increased pathogen exposure. Flohr et al conducted a review of 64 relevant studies published between 1966 and 2004 to investigate the epidemiological evidence that environmental exposure that leads to an increase in microbial burden reduces the risk of AD. They sought answers to the following questions in particular: whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, the use of antibiotics and AD risk. They also aimed to comment on the new therapeutic approaches in AD that have evolved from the use of antibiotics and AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations, whether any specific infections have been shown to reduce AD risk, and whether there is a link between immunisations.

Chronic steroid use
It is well known that the administration of systemic corticosteroids produces adverse effects that limit their long-term use. Although corticosteroids are the most frequently used drugs to treat allergic diseases, they may also induce hypersensitivity reactions. From a clinical point of view, hypersensitivity reactions to corticosteroids are classified as immediate (appearing within one hour of drug intake) and characterised by the presence of urticaria and anaphylaxis, and delayed reactions (appearing more than one hour after drug intake), with maculopapular exanthema and delayed urticaria being the most frequently encountered clinical symptoms. This classification is relevant when considering the clinical evaluation and the diagnostic work-up, and is related to the underlying immunological mechanism, with immediate reactions being IgE-mediated and delayed reactions T cell-dependent. Depending on the route of administration, they can also be subdivided into reactions induced by either topical administration or systemic administration.

Topical corticosteroids are the mainstay of treatment of AD. They reduce inflammation and pruritis. They should be applied only to areas of acute exacerbations, whereas emollients should be used over the remainder of the skin. The absorption of topical steroids is much better through hydrated skin. The ideal time for application is therefore in the first three minutes after a bath or shower. However, studies have shown that long-term use of topical steroid cream may worsen AD. Cure may follow total cessation of topical steroid creams, although there is usually an intervening period of severe rebound.

Systemic corticosteroids have been used in severe chronic AD, but their use has been limited in the paediatric population because of the risk of severe adverse effects associated with chronic usage, including growth retardation and immune suppression.

Adverse drug reactions associated with the use of corticosteroids include skin atrophy, striae, telangiectasia, acne, glaucoma, adrenocortical insufficiency and, in extreme cases, Cushing’s syndrome. However, there is no conclusive evidence
that correctly used topical agents cause significant systemic side-effects. When used for the treatment of AD flare-ups for periods of up to four weeks, topical corticosteroids are usually safe and effective. Conversely, it is long-term use or overuse that is associated with adverse effects.

**Contact hypersensitivity**

Contact hypersensitivity is different from an atopic reaction, and is a Type IV (delayed) hypersensitivity reaction. It occurs after sensitisation with simple chemicals (e.g. nickel or formaldehyde), plant materials (e.g. the North American poison ivy, *Toxicodendron radicans*, and poison oak, *T. diversilobum* or *pubescens*), topically applied drugs (e.g. sulphonamides or neomycin), some cosmetics, soaps and other substances. In all cases, small molecules enter the skin and then, acting as hapten, attach to body proteins to serve as complete antigen. Cell-mediated hypersensitivity is induced, particularly in skin. When the skin subsequently comes in contact with the offending agent, the sensitised person develops erythema, itching, vescication, eczema or necrosis of skin within 12-48 hours. Avoidance of the substance will prevent recurrence.

**Hypoallergenic products**

Hypoallergenic cosmetics (creams, lotions and soaps) are claimed by manufacturers to cause fewer allergic reactions than other cosmetic products. Consumers with hypersensitive skin, and even those with "normal" skin, may therefore believe that these products will be gentler than cosmetics without this claim. It is important to note that there are no official standards or definitions that govern the use of the term "hypoallergenic" (the term essentially means whatever a particular company wants it to mean). Manufacturers of cosmetics labelled as hypoallergenic in the USA are not required to submit substantiation of their hypoallergenicity claims to the Food and Drug Administration (FDA). Although the term "hypoallergenic" may have considerable market value in promoting cosmetic products to consumers on a retail basis, it has very little meaning and is primarily used as a marketing tool, since it is not possible to guarantee that a cosmetic or skin-care product will never cause an allergic reaction. Since cosmetic ingredients are in most cases not listed on product labels, consumers who have had allergic reactions or problems with a specific substance will find it hard to avoid products that contain these substances.

**Conclusion**

IgE-mediated atopic allergic diseases are on the increase and are a major socio-economic burden. They are caused by complex interactions between genes and the environment. Future approaches to controlling allergic diseases include improvements in the environment, and safe and effective specific immunotherapy. The role of the pharmacist in atopy is to provide basic supportive care and advice, and to refer the patient for medical opinion when indicated.

**References**