The allergic scholar

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Abstract

Allergic diseases are on the increase globally. There has been a doubling in the number of scholars suffering from allergy-related disease in the past two decades. This article describes the predisposing factors which contribute to an increased incidence of allergies within the population. These factors include a genetic predisposition, allergen exposure, abnormalities in the bowel flora and infection exposure. Some of these relate to the hygiene hypothesis and the microflora hypothesis, which are discussed in this article. Treatment options for those suffering from allergic disease are also discussed, with an emphasis on asthma, anaphylaxis, allergic rhinitis and atopic dermatitis.

Keywords: atopy, allergy, scholars, corticosteroids, antihistamines

Introduction

One in four paediatric patients seen in paediatricians’ offices suffers from an allergy-related condition.1 Atopic diseases, such as allergic rhinitis and asthma, have increased in prevalence, particularly in industrialised countries over the last two decades.2-4

An allergic response is a hypersensitivity reaction, which is initiated by a humoral immunological response, i.e. an adaptive immune response following primary exposure to an antigen or allergen. This elicits an altered immunological reaction towards such an allergen or antigen, which increases the levels of immunoglobulin E (IgE) which bind to the allergen and stimulate the mast cells to degranulate and release various proinflammatory molecules. These include histamine, lipid mediators, chemokines and various other cytokines.4,5

Atopy refers to the increased sensitivity of IgE to a specific antigen, which, in turn, results in a hypersensitive response upon exposure toward the specific allergen in question.2,4,6,7 However, in practice, the majority of diagnoses are made with a combination of a supportive history and positive allergy tests, facilitated more recently by more distinct diagnostic cut-off points for skin-prick tests and specific IgEs.4

The atopic march

The so-called atopic march refers to the development of different atopic diseases at certain ages during early childhood. It refers to the sequence in which clinical symptoms and atopic diseases manifest themselves as a child grows older.4,7 Atopic dermatitis is the most common starting point, which then usually develops into conditions of the respiratory tract, such as allergic rhinitis and asthma.8

Pathophysiology of atopy

The so-called T-helper cell type 1 (Th1)/T-helper cell type 2 (Th2) paradigm refers to the balance which exists between the Th1 and Th2 subsets of the T lymphocyte. Both Th1 and Th2 subsets differentiate from CD4+-naive T lymphocytes, which means that whenever a raised response towards either the Th1 or the Th2 subset occurs, the other will conversely be reduced.9

A decrease in Th1 subset production results in decreased levels of interferon gamma (IFN-γ), interleukin (IL)-2 and tumour necrosis factor-beta. A decrease in these cytokines leads to an increase in the Th2 effect owing to a decrease in IgG production, which inhibits Th2 formation10 (Figure 1).

Infants who are genetically predisposed have an imbalance towards an elevated Th2 cellular response. Th2 cytokines mediate the release of IL-4, IL-5 and IL-13, as well as IgE production.10 When IgE binds to an allergen, it gains the ability to bind to the high-affinity IgE receptor (FcεR1) that is expressed...
on the mast cell surface. When this receptor is stimulated, mast cell degranulation takes place. This degranulation then leads to the release of potent vasodilators, such as histamine, lipid mediators, chemokines and various other cytokines. Histamine also has the ability to attract other proinflammatory substances. This cascade, created by the excessive release of histamine, then leads to the typical symptoms seen in patients suffering from an atopic disease, such as urticaria, angio-oedema and anaphylaxis.

Platelet-activating factor (PAF) is another endogenous phospholipid mediator of inflammation, which is contained within the alveolar macrophages, eosinophils, mast cells, platelets, basophils and neutrophils. PAF is released upon allergic and inflammatory reactions. The release of PAF is closely associated with increased vascular permeability, bronchoconstriction, eosinophil chemotraction and airway hyperresponsiveness, all of which are involved in the pathophysiology of rhinitis, asthma and anaphylaxis. PAF levels are often elevated in patients with allergic conditions, compared to those in healthy controls.

**Risk factors for developing atopy**

Table I provides an overview of the risk factors which may contribute to the development of atopy.

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<thead>
<tr>
<th>Risk factors for the development of atopy</th>
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<td>• Infection exposure</td>
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<td>• Genetic predisposition</td>
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<td>• Bowel flora</td>
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<td>• Allergen exposure</td>
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**Genetic trends in allergic disease**

Allergies tend to be familial, with patients who suffer from an allergy tending to have an increased risk of having children with some form of atopy. Various studies have shown that infants born into families who have a history of allergies have an elevated Th1 cytokine and IFN-γ levels, compared to babies from non-atopic families.

Multiple genes are involved which can contribute to the expression of allergies within a patient. When a person expressing these genes is exposed to a variety of environmental factors, he or she is increasingly predisposed to developing an atopic disease.

It has been established that chromosomal regions relating to allergic pathology are inherited by atopic patients. Polymorphisms in skin barrier function and epithelial function have an effect on the risk of the development of atopic disease. Monozygotic twins have a larger correlation between them in terms of their allergies (77%), while dizygotic twins only show a 17% correlation in terms thereof.

**Allergen exposure**

To develop a hypersensitivity reaction toward an allergen, exposure to that allergen is required, and this increases the risk of atopic disease. The level of allergen exposure does not correlate with an increased or decreased risk of sensitisation toward the allergen. Thus, this strengthens the belief that the existence of atopic disease is hereditary. The exposure of a patient to an allergen simply increases the likelihood of an allergy developing.

Conversely, low levels of allergen exposure are not adequate enough to produce a response, while high levels of allergen exposure induce tolerance toward that allergen, i.e. desensitising it.

**Infections and endotoxin exposure**

There is a hypothesis within atopic disease which predicts that the prevalence of atopic diseases is decreased when a child is exposed to more infectious agents. This is called the hygiene hypothesis. It attempts to explain why children who are exposed to animals, viruses, bacteria and various endotoxins are less likely to develop atopic diseases. It was first defined as the decreased risk of developing hay fever in larger households where there was increased exposure to various microbes. It is most likely that this relates to the fact that bacterial, viral and endotoxin factors trigger an immune response of Th1 lymphocytes. Th1 lymphocytes increase the production of IgG antibodies.

Th2 cytokines mediate the release of IL-4, IL-5 and IL-13, as well as IgE production. IgG has the ability to suppress the production of allergy-promoting cytokines, namely IL-4, IL-5, IL-9 and IL-13. (Th1 indirectly suppresses Th2 activity). Interactions between helminths and the immune system have decreased in the post-industrialisation era. The disappearance of these interactions can modulate the immune function.

**Bowel flora**

The microflora hypothesis postulates that a correlation exists between reduced bowel flora exposure in infancy and the increased prevalence of allergic diseases, stating that changes in the microbiological composition within the gastrointestinal tract may lead to a disruption in immune tolerance.

Exposure to microbial flora within the gastrointestinal tract early in life allows for a change in the Th1:Th2 cytokine balance, favouring a Th1 cell response.

The presence of these microbes bundled together within the walls of the intestinal tract, helps to regulate the immune response. When a shift occurs in the balance between these different microbes, the immune system reacts to this change. Mice born to germ-free environments with high dosages of antibiotics exhibited an underdeveloped immune system, with an elevated Th2 cellular response. This elevation in Th2 responsiveness gives rise to increased IgE production. Therefore, there is a strong likelihood that exposure to high dosages of antibiotics in early neonates may alter the composition of the intestinal flora, and have an effect on the normal immune response, leading to elevated Th2 immune responsiveness.
Pollutants

When a pregnant mother smokes during the embryonic period, her child has an increased risk of developing abnormal IgE responses to food proteins early in life, as well as to developing asthma. This does not necessarily extend to smoking only, and may include living in a heavily polluted area as well. The damaged epidermal surfaces are penetrated by a multitude of exogenous substances, including allergens, irritants, microbes, and pollutants, and even topical drugs. The stratum corneum, which usually acts as a physical barrier that restricts the permeability of most molecules, including pathogenic organisms, becomes compromised when there is an ongoing allergic reaction mediated by IgE. 11

Immunological sensitisation, leading to atopic disease

Foetuses begin producing IgE in the 11th gestational week of pregnancy. Atopy only begins to manifest itself after birth when there is an imbalance in the Th1, Th2 and regulatory T-cell immune responses. 23,24 The balance between these cells is a determining factor in the further development of atopy. 23,24

Infants delivered via Caesarean section are 20% more likely to develop asthma in early childhood than those born via normal vaginal delivery. 4 Breastfeeding has been found to convey a reduced risk of the development of atopic diseases in infants, 23,24 but not as significantly if the child was genetically predisposed to developing atopic conditions. 25,26

Antibiotic use in early infancy is proven to cause severe disturbances in the normal bowel flora. Thus, the use of antibiotics positively correlates with an increased risk of the development of asthma. 27-29

Figure 2 illustrates the most common atopic diseases suffered by children.

Allergic rhinitis

Allergic rhinitis is a condition which occurs due to inflammation of the epithelial lining of the nasal mucosa. This inflammatory process is initiated by the release of histamine owing to the cross-linkage of IgE antibodies with the mast cells. The mast cells then release histamine and other chemokines. 4 The nasal epithelial cells appear to be central in responding directly to exogenous stimuli, such as pollen. 30-38

The most common antigens for allergic rhinitis are inhaled allergens, of which dust mites, animal dander and pollen are the major ones of concern. 30-38 When the patient is sensitised, an antigen comes into contact with the nasal mucosa. This leads to a cross-linking of IgE-mediated receptors on the mast cells. 30-38 In turn, this leads to the degranulation of the mast cells, with a resultant release of histamine and proteases from the preformed granules. In addition, an array of early-phase proinflammatory molecules are synthesised and released, especially prostaglandins, leukotrienes, cytokines, tumour necrosis factor-alpha (TNF-α), and IL-4. The release of these molecules causes oedema and fluid secretion, which may result in congestion and other nasal symptoms. The role of leukotrienes as mediators in allergic rhinitis is well-supported in the literature. 30-38

Cysteinyl leukotrienes are able to facilitate the maturation of eosinophil precursors, and act as eosinophil chemoattractants, promoters of eosinophil adhesion, and inhibitors of eosinophil apoptosis. The leukotrienes and thromboxane A2 (TXA2) are arachidonic acid derivatives. It has been shown in animal models that TXA2 agonists increase nasal airway resistance and vascular permeability. An acute-phase allergic reaction is also characterised by the production of prostaglandin D2 (PGD2), a major proinflammatory prostanoïd, which results is vasodilation and bronchoconstriction, as well as a number of inflammatory biomarkers, such as N-α-tosyl-L-arginine methyl esterase (TAME)-esterase and eosinophil cationic protein (ECP). PGD2 is also believed to be associated with hypertrophic inflammation and acts as a recruiter of eosinophils. 30-38

The late-phase or chronic inflammatory response involves cellular infiltration, which sustains tissue swelling and oedema, and further exacerbates congestion. The ensuing cytokine release results in the nasal mucosa being infiltrated with inflammatory cells. These inflammatory cells, including eosinophils, neutrophils, basophils, mast cells and lymphocytes, sustain and intensify the nasal mucosal inflammatory reaction. The predominant cell type, namely the eosinophil, characterises the chronic inflammatory process which is present during the late-phase allergic response. These eosinophils release a broad range of proinflammatory mediators, including the cysteinyl leukotrienes, ECP, eosinophil peroxidase and major basic protein. These cells are also known to serve as a major source of IL-3, IL-5, granulocyte colony-stimulating factor and IL-13. 30-38 The number of circulating eosinophils is increased in patients with allergic disorders, and the infiltration at the site of aggravation has generally been attributed to the influx of mature cells. In some studies, eosinophil infiltration has been shown to have a significantly negative correlation with nasal airflow in patients with allergic rhinitis.

In addition to the eosinophils, other proinflammatory cells are also known to accumulate within the nasal epithelium during the late-stage response. These include basophils, mast cells, and T cells. The key inflammatory mediator of the late-phase response is TNF-α. TNF-α levels increase dramatically approximately...
an hour after an allergen challenge. This cytokine has been confirmed to activate T cells, endothelial cells, fibroblasts and macrophages. TNF-α is also responsible for an increase in the expression of cell adhesion molecules. Patients with allergic rhinitis also have elevated proinflammatory interleukins (IL-1β, IL-6 and IL-8). All of these events, including IgE synthesis and eosinophil or basophil priming, contribute to the venous engorgement, inflammation, nasal and ocular hyperreactivity, and the symptoms of allergic rhinoconjunctivitis.

**Atopic dermatitis**

Atopic dermatitis is a chronic disease which is easily aggravated by exposure to the predispositioning allergen. These allergens can vary, and include airborne pathogens, e.g. pollen, and various foods. The disease is strongly linked to genetic predispositioning factors, and usually results in skin barrier dysfunction, which then establishes the basis for inflammatory responses, leading to dermatitis.

**Asthma**

Asthma is a chronic inflammatory disease which causes hyperresponsiveness of the bronchial tree, with reversible airflow obstruction. Pathological components of asthma can be described as cellular inflammation, including bronchitis, and remodelling of the structural elements of the airway wall. This includes inflammation of the airway, constriction of the airway via smooth muscle contraction, the hyper-secretion of mucus, bronchial hyperresponsiveness, and additional narrowing of the airway due to mucosal oedema and sloughing of the epithelial cells.

Before implementing the first treatment for asthma, it is important to classify the severity of a patient’s asthma. This assists in reviewing the management of the condition when periodic assessment for asthma control has been established. Making a diagnosis of asthma is based on the identification of both a characteristic pattern of respiratory symptoms and variable expiratory airflow limitation.

The following needs to be considered:

- **Spirometry:** Spirometry should be used in all patients > 5 years of age, to determine whether or not the airway obstruction is at least partially reversible.

**Anaphylaxis**

Anaphylaxis is a severe allergic reaction which evolves rapidly, and may result in anaphylactic shock and the subsequent death of a patient. The exact cause of an anaphylactic attack contributes to the time taken to the onset of anaphylaxis. For example, the intravenous administration of an allergen causes an extremely fast induction into anaphylaxis. The mainstay of therapy for an anaphylactic reaction is adrenaline. Delays or failure to administer adrenaline can result in the death of the patient. The faster the onset of anaphylaxis, the deadlier the reaction. A faster onset of symptoms directly translates into a larger and faster release of histamine.

**Management of the allergic scholar**

Certain behavioural activities have been shown to provide some protection against, or may alleviate some of the symptoms derived from, a current allergic reaction. Other practical interventions include the prevention strategies depicted in Figure 3. These strategies may improve immune tolerance. However, the benefits of probiotics in either preventing or treating allergic disease remain inconclusive.

The prevention strategies identified in Figure 3 should be combined with more specific management principles according to the type of atopy that the patient is experiencing.

**Pharmacological management of the allergic scholar**

Both non-pharmacological and pharmacological strategies can be used in the management of allergic disease. If nonpharmacological strategies do not alleviate the symptoms, then the following pharmacological agents may be used, either topically or systemically, for the prevention and management of allergic disease.

**Local decongestants**

Local decongestants contain sympathomimetic drugs, like xylometazoline, oxymetazoline and phenylephrine. They produce vasoconstriction via α1-adrenergic receptor stimulation. In turn, this reduces mucosal oedema and local vasodilation. Nevertheless, these effects only last for a limited period. After prolonged use, rebound rhinitis and conjunctivitis (or conjunctivitis medicamentosa) may set in, usually after roughly five days of continuous use. Oxymetazoline and xylometazoline have a long-acting effect on the α1 receptor, whereas phenylephrine...
has a shorter duration of action, lasting up to approximately four hours.\textsuperscript{29,39-41} Systemic decongestants

Many systemic decongestants also contain antihistamines. The antihistamines have an antagonistic effect on the histaminergic H\textsubscript{1} receptors, and will be discussed in the subsequent section. Available systemic decongestants in South Africa include pseudoephedrine, phenylpropanolamine and phenylephrine. These agents produce vasoconstriction through \( \alpha \text{-receptor} \) stimulation, reducing oedema, redness and itching. However, the combination of a systemic decongestant and an older-type H\textsubscript{1} antihistamine can produce drowsiness and a lack of motor coordination. The use of phenylpropanolamine has produced subarachnoid bleeding, with a haemorrhagic stroke in women who used it as an appetite suppressant. The total daily dosage of phenylpropanolamine should not exceed 100 mg.\textsuperscript{45-48}

Local corticosteroids

Glucocorticosteroids modify protein synthesis by regulating transcription, and indirectly by modifying the activity or half-life of transcription factors and mRNA. The following intranasal corticosteroids are currently available: beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. Intranasal administration of the newer agents, namely mometasone, fluticasone, and ciclesonide, results in minimal systemic effects.\textsuperscript{49} The most common local side-effects experienced with the intranasal corticosteroids include dryness, stinging, burning and epistaxis. Chronic use of topical corticosteroids may lead to atrophy of the nasal mucosa.\textsuperscript{35,45,49} Although the use of corticosteroids constitutes the most effective treatment for the inflammation experienced in allergic rhinitis, when these agents are used for seasonal allergic conjunctivitis, pulse dosing should rather be utilised for as short a treatment duration as possible.\textsuperscript{47} The H\textsubscript{1} antihistamines

The H\textsubscript{1}-receptor antagonists or H\textsubscript{1} antihistamines include the older, sedating, multi-potent blockers, or the so-called first-generation H\textsubscript{1} antihistamines, including promethazine, chlorpheniramine, dexchlorpheniramine and cyclizine, and the newer, non-sedating, selective H\textsubscript{1}-receptor blockers, or the so-called second-generation H\textsubscript{1} antihistamines. Examples of these non-sedating antihistamines include cetirizine (and levocetirizine), loratadine, ebastine, fexofenadine and mizolastine. The most compelling difference between the two generations of H\textsubscript{1} antihistamines lies in the fact that the first-generation drugs have the ability to cross the blood-brain barrier, while agents belonging to the second-generation have very limited ability to do so, or none at all. In addition to the aforementioned two generations of systemic (oral and/or parenteral) agents, topical (including intranasal and opthalmic) H\textsubscript{1} antihistamines are available as well.\textsuperscript{29,41,50} Examples of the antihistamines are provided in Figure 4.

• First-generation H\textsubscript{1} antihistamines: These agents have the ability to cross the blood-brain barrier, in addition to being multi-potent blocking agents (meaning that they effectively act as receptor blockers in more than one receptor system). Thus, their chemical structures allow them some degree of non-selective, antagonistic effects of an antimuscarinic or anticholinergic, anti-serotonergic and local anaesthetic nature. Other examples include the tricyclic antidepressants and the phenothiazines. Owing to the multi-potency of their receptor-blocking capabilities, the first-generation H\textsubscript{1} antihistamines have a variety of indications and uses, which range from allergies and rhinoconjunctivitis, to nausea and vomiting, motion sickness and insomnia. However, their anticholinergic side-effects limit their usefulness in a variety of settings, including patients with glaucoma, benign prostatic hyperplasia and in cardiac patients, such as those suffering from ischaemic heart disease, myocardial infarction and congestive heart failure. Of the wide variety of agents belonging to this group, the following examples are particularly noteworthy:29-41,50

✓ The options include hydroxyzine, promethazine and diphenhydramine or sedation. However, more suitable agents may be used in the management of insomnia
✓ Cyclizine (syn. meclizine), diphenhydramine, hydroxyzine or promethazine, are examples of antiemetic agents. First-generation H\textsubscript{1} antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo

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\caption{Examples of currently-available H\textsubscript{1}-antihistamines\textsuperscript{29,41,50}}
\end{figure}
✓ Chlorpheniramine displays lower levels of sedation than many of the other examples in this group, and may therefore be better suited to the management of allergic reactions.

It should be noted that these “older” drugs have never been optimally investigated and profiled from a clinical pharmacology perspective.50

- Second-generation H₁-antihistamines: In addition to not being able to penetrate the central nervous system (CNS) to any significant degree, the second-generation H₁ antihistamines are also devoid of any antiemetic activity or anticholinergic side-effects. Of the various agents belonging to this group (including a few examples of the active enantiomers of racemic drugs), the following examples are of particular interest:39-41,50

✓ Fexofenadine has the shortest half-life of the systemic agents. Therefore, it should be taken twice daily. (The others only require once-daily dosing intervals). Furthermore, it also happens to be the one that does not display any H₁-receptor occupancy inside the CNS at therapeutic dosages (Figure 5)

✓ Cetirizine has the greatest likelihood of displaying some degree of H₁-receptor occupancy inside the CNS, which may result in some level of sedation, albeit in higher-than-recommended dosages

✓ The first two examples of the so-called second-generation H₁ antihistamines, namely terfenadine and astemizole, were withdrawn from the market owing to unacceptable levels of cardiac toxicity.

Note that the H₁ antihistamines do not form the mainstay of treatment in cases of severe angio-oedema or anaphylaxis, but may be used as effective adjunctive therapy to adrenaline (and other emergency drugs and resuscitative interventions) in such instances.30-41

Ophthalmic (eyedrop) preparations include levocabastine, epinastine, olopatadine and ketotifen. (The latter also acts as a mast cell stabiliser). Levocabastine, in addition to azelastine, is also available as a nasal spray for use in patients who suffer from allergic rhinitis.

Rupatadine fumarate is a newly launched, second-generation, non-sedating, long-acting histamine antagonist (H₁-receptor antagonist) and PAF receptor inhibitor. Rupatadine fumarate is approved for the treatment of allergic rhinitis and chronic urticaria in adults and children aged 12 years and older. The approved dosage is 10 mg daily. It inhibits the degranulation of mast cells and the subsequent release of cytokines, more specifically of TNF-α present in both the mast cells and monocytes.51

The leukotriene receptor antagonists

Examples of leukotriene receptor antagonists include zafirlukast and montelukast. They are competitive antagonists of the cysteinyl leukotriene receptor 1. They have the advantage of oral administration. Montelukast is even available as a sprinkle and in a chewable tablet form for paediatric use. Montelukast presents an additional option in the management of seasonal allergic rhinitis in children with asthma (Figure 5).52

Conclusion

Allergy-related illness is a commonly encountered health problem in paediatric practice. The atopic march underlies the pathophysiological manifestations of atopy-related conditions, such as atopic dermatitis, allergic rhinitis, asthma and anaphylaxis. The principles which underlie the management of the allergic scholar include pharmacotherapeutical interventions, such as topical decongestants and corticosteroids, as well as systemic H₁ antihistamines. The older first-generation antihistamines are more suited to the management of acute allergic reactions, but their tendency to cause drowsiness and impaired motor coordination makes them less appropriate in the ongoing management of allergy-related conditions in schoolchildren. The second-generation H₁-receptor antagonists are preferred treatment option in this setting.

References


Figure 5: An approximation of the degree of central nervous system penetration and the resultant central nervous system side-effects of the first-generation H₁ antihistamines versus the second-generation H₁ antihistamines.50


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