An overview of allergy and sinusitis

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Abstract

Allergic diseases affect many people across the globe. They are considered to significantly disturb the quality of life of the people who are affected, creating personal and economic predicaments. Some of the most commonly diagnosed allergic diseases include atopic dermatitis, rhinitis, allergic conjunctivitis and sinusitis. Some conditions, such as eosinophilic esophagitis, are on the rise and are being diagnosed across all continents except for Africa. The use of antihistamines has been the mainstay of therapy for most allergic conditions, except for other conditions that require corticosteroids, or in severe allergic conditions such as anaphylaxis where antihistamines are ineffective as main therapy. It is important to consider first versus second-generation options when treating allergic diseases, also bearing in mind the duration of therapy and any comorbid conditions that a patient might have. This article provides an overview of these conditions and their current management options.

Keywords: allergic disease, antihistamine, anaphylaxis, atopy, atopic march, rhinitis, sinusitis

Introduction

Allergic diseases are complex diseases caused by a combination of genetic and environmental factors. Allergic diseases are on the increase, affecting approximately 30% to 40% of the world’s population. They decrease quality of life and may have an immense influence on personal, social, and economic costs.1

An allergic response is a hypersensitivity reaction mediated by the adaptive immune system. The presence of a trigger, such as an allergen or antigen, induces a humoral immunological response, which in turn initiates a complex immunological reaction. This dysregulation in the immune function elevates the plasma levels of immunoglobulin E (IgE). The release of IgE is followed by binding to the allergen or antigen, which in turn stimulates the mast cells to degranulate and release several pro-inflammatory substances that include histamine, chemokines and numerous cytokines.2

There are many different factors that come into play when searching for the causative agent of allergy. Environmental influences that occur in pregnancy and early childhood can alter the physiologic, immune, structural and behavioral development and thus transform response patterns that influence susceptibility to future diseases.1 Genetics also play a vital role in the susceptibility of an individual to an allergic disease. The most common allergic conditions around the world include, atopic dermatitis, rhinitis, asthma, rhinosinusitis, allergic conjunctivitis and, most recently, allergic oesophagitis.3,4

The atopic march

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.5 ‘Atopic march’ is a term that refers to the development of various atopic diseases that may develop during childhood. The atopic march may also refer to how the sequence of clinical symptoms and atopic disease manifest during childhood growth and development.6 The initial development of atopy has been linked to various predisposing risk factors. These include a genetic predisposition, decreased exposure to infections and endotoxins, postnatal antibiotic use, obesity, tobacco smoke, air pollutants, exposure to allergens, maternal weight gain or obesity, gestational use of antibiotics and maternal stress.7

Pathophysiology of atopy

There is vast evidence that shows that T-lymphocytes play a major role in allergic diseases. The T-helper cell type 1 (Th1)/T-helper cell type 2 (Th2) paradigm has been extensively studied and seems to be the major pathological pathway in allergic diseases. The paradigm explains the relationship between the Th1 and Th2 subsets of the T lymphocyte. Th1 and Th2 subsets tend to differentiate from CD4+-naive T lymphocytes. This means that whenever a raised response towards either the Th1 or the Th2 subset occurs, the other will be reduced.8 When there is a reduction in Th1 production, there is observed decreased levels of interferon gamma (IFN-g), interleukin (IL)-2 and tumour necrosis factor (TNF)-beta. This in turn leads to elevated levels...
of Th2 effect, owing to a decrease in Immunoglobulin G (IgG) production, which inhibits Th2 formation.8,9 Figure 1 shows the imbalance in Th1 and Th2 that leads to atopic diseases.9

The role of histamine in allergy

Histamine is an endogenous substance synthesized from histidine. It has the ability to elicit autacoid effects within peripheral tissues and also act as a neurotransmitter within the central nervous system (CNS).10 The role of histamine in the inflammatory process remains significant in understanding the pathophysiology thereof. The release of histamine in peripheral tissue areas is mediated by mast cell degranulation. This degranulation can be triggered in various ways. In allergic diseases, an interaction between IgE (immunoglobulin E) antibodies and suitable IgE antigens (i.e. the formation of antigen–antibody complexes) that causes allergic reactions (localized histamine release) or anaphylaxis (systemic histamine release), seems to be the major trigger.10

There are currently four identified histaminergic receptor subtypes (i.e. the H1 to H4 receptors). The H1-receptor is the main active subtype in mediating acute allergic reactions. There are different effects that may be induced by H1-receptor stimulation. Some of these effects lead to allergic conditions, which include allergic rhinitis and conjunctivitis, urticaria, pruritus and angioneurotic oedema.10

Stimulation of these receptors is also responsible for the vasodilatation and the increased vascular (capillary) permeability that accompany allergic reactions and inflammation. Erythema and oedema, including potentially fatal glottis oedema. Understanding histamine regulation assists in the type of treatment to be initiated in various allergic reactions. For instance, histamine is released systemically in anaphylaxis but the use of an antihistamine alone is not effective in treating anaphylaxis.10

Figure 1: The imbalance between Th1 and Th2.
IgG: immunoglobulin G, Th1: T-helper cell type 1, Th2: T-helper cell type 2

**Figure 2: Risk factors of developing atopy.**

Genetic predisposition

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. There is vast evidence that shows that T lymphocytes play a major role in allergic diseases. Several studies have looked at the role of genetics in allergic diseases. Some studies have had mitochondrial RNA (miRNA) as the main focus of such investigations. The earlier studies have shown that several types of miRNA augment the sensitivity of T cells to peptide antigens. Evidence suggests that inhibition of miR-181a expression in immature T cells significantly decreases sensitivity to antigens and enhances the impairment of T-cell selection. T-cell apoptosis is crucial in regulating both the length and strength of T-cell responses. MiR-21 has also been extensively studied, showing significant upregulation during T-cell activation and plays a role in the suppression of apoptosis in activated T cells. It is therefore essential to understand the role of various miRNA in T-cell regulation as the development of polarized TH cells is central to the pathogenesis of allergic inflammation because allergic inflammation is predominately a TH2 response.11

Allergen exposure

Exposure to an allergen in individuals with an atopic disease increases the risk of developing a hypersensitivity reaction, regardless of the level of antigen exposure. The evidence showing that immune sensitization is not dependent on the level of allergen exposure gives credibility towards a belief that the existence of atopic disease is hereditary. On the contrary, some studies suggest that low levels of allergen exposure are not sufficient to produce a response, while high levels of allergen exposure induce tolerance toward that allergen, i.e. desensitizing it.12

Infections and endotoxin exposure

The hygiene hypothesis is applicable to most atopic diseases. It predicts that the prevalence of atopic diseases is decreased when a child is exposed to more infectious agents. It is estimated that the exposure to animals, viruses, bacteria and various endotoxins makes children less likely to develop an atopic disease. The
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Intestinal flora

The presence of microbes in the walls of the intestinal tract helps to regulate an immune response. Exposure to microbial flora, within the gastrointestinal tract, early in life allows for a change in the Th1:Th2 cytokine balance, favoring a Th1 cell response. A shift in the microbial balance initiates a change in immune response. The evidence then suggests that exposure to high dosages of antibiotics in early neonates may alter the composition of intestinal flora, leaning towards an immune response with elevated levels of Th2 which mediates the release of various cytokines including IgE. These Th2 cytokines are common culprits in the development of allergic diseases.

Common allergic diseases across the globe

Several allergic conditions are described in more detail below.

Rhinitis

Rhinitis is an inflammation of the nasal mucosa. According to the Australasian Society of Clinical Immunology and allergy (ASCIA, 2015), there are various causes of rhinitis which include: allergies (hay fever), increased sensitivity to irritants such as smoke, temperature changes or the overuse of decongestant nasal sprays. The most common antigens for allergic rhinitis are inhaled allergens, the most concerning being dust mites, animal dander and pollen.

Allergic rhinitis (AR) affects approximately 20% of the world population and is considered to be the most common chronic disease. AR is a type 1 allergic disease which reduces quality of life depending on the severity. Exposure to nasal allergens stimulate an IgE-mediated type 1 hypersensitivity reaction, resulting in symptomatic reactions to the allergen. The early characteristic symptoms of allergic rhinitis are rhinorrhea, nasal congestion and sneezing. AR can also be associated with various conditions such as bronchial asthma, allergic conjunctivitis, rhinosinusitis and others.

The inhalation of nasal antigens in sensitized individuals causes the antigens to pass through mucosal epithelial cells, binding to IgE antibodies on mast cells distributed over the nasal mucosa. The antigen-antibody complex stimulates an IgE-mast-cell-mediated early-phase response. Chemical mediators, such as histamine and peptide leukotrienes (LTs), are released from mast cells. The release of these mediators cause irritation to the sensory nerve endings and mucosal blood vessels, leading to early phase reaction symptoms (i.e. sneezing, watery rhinorrhea, and nasal mucosal swelling). The early phase symptoms usually appear within 30 minutes after exposure to an allergen. Late-phase response results in tissue damage and remodeling, appearing 24 hours after allergen exposure. The presence of an antigen in the nasal mucosa leads to the stimulation of cytokines, chemical mediators and chemokines which respond by releasing various inflammatory cells, such as activated eosinophil which infiltrate into the nasal mucosa. Leukotrienes, produced by these inflammatory cells, cause nasal mucosal swelling.

Sinusitis

Sinusitis is defined as inflammation of the paranasal sinus mucosa. Sinusitis has been replaced with the more correct term ‘rhinosinusitis’. The term rhinosinusitis is given preference over sinusitis because sinusitis, in most instances, is almost always followed by inflammation of the adjacent nasal mucosa. The classification of rhinosinusitis is usually based on whether it is acute rhinosinusitis (ARS) or chronic rhinosinusitis (CRS). Many scientists concur on the duration of CRS being longer than 12 weeks while ARS still has different duration classifications from different scientists but usually less than 12 weeks.

Acute Rhinosinusitis

Acute rhinosinusitis occurs as a result of inflammation of the nasal mucosa mainly due to bacterial, fungal, or viral infections, as well as allergies or exposure to inhaled irritants. It is essential to properly diagnostically distinguish bacterial ARS from viral ARS, to assist with the treatment plan. Treatment in bacterial ARS involves antibiotics which would be inappropriate if used for viral ARS.

Chronic rhinosinusitis

Chronic rhinosinusitis affects about 10–15% of the adult population in industrialized countries such as Europe and the US, and is one of the most reported chronic conditions. It has been observed over the years that there are multiple variants of CRS which include characterization of the disease by chronic infection, non-eosinophilic inflammation, chronic hyperplastic eosinophilic sinusitis (CHES), aspirin-exacerbated respiratory disease and allergic fungal sinusitis. When there is chronic inflammation in the nasal mucosa, the observed result is mucosal swelling (including polyposis), increased mucus secretion, airway obstruction, and blocked sinus drainage. The inability of the nose to eliminate bacteria, viruses, fungi and allergens create an environment of chronic inflammation which then results in a chronic nasal disease. Some patients with chronic sinusitis present with massive submucosal eosinophilic infiltration. Eosinophilic sinusitis is characterized by multiple nasal polyps, viscous rhinorrhea, and olfactory disorder, and is often complicated by asthma. Eosinophilic sinusitis is extremely intractable and resistant to surgery, resulting in repeated relapses. Oral corticosteroid therapy often results in a complete response.

Allergic rhinosinusitis

The presence of an allergen can cause inflammation of the sinus mucosa which may be acute or even chronic. This inflammation prevents the usual clearance of bacteria from the sinus cavity, increasing the chances of developing secondary bacterial...
Asthma

Asthma is one of the most common chronic inflammatory diseases that affect both children and adults. The inflammatory process causes hyper-responsiveness in the bronchial tree, with reversible airflow obstruction. Inflammation of the bronchial tree may result in airway constriction through smooth muscle contraction, the hyper-secretion of mucus, bronchial hyper-responsiveness, and additional narrowing of the airway due to mucosal oedema and sloughing of the epithelial cells.11

Allergic asthma is observed to be the most common type, caused mainly by inhaled allergens inducing an immune system response.11 The implementation of therapy must be done after accurate classification of asthma severity. This assists in reviewing the management of the condition when periodic assessment for asthma control has been established. Diagnosing asthma is based on two tools which are: identification of a characteristic pattern of respiratory symptoms and expiratory airflow limitation which vary according to each patient.29

Management of allergic diseases

Allergic diseases can be strategically managed both non-pharmacologically and pharmacologically.28 The use of pharmacological preparations is usually preferred for use when non-pharmacological methods prove ineffective or insufficient in alleviating the allergic symptoms. Different pharmaceutical preparations (systemic, intranasal, topical, etc.) are used depending on the symptoms and type of allergic disease.28,30

Local decongestants

Local decongestants are mainly sympathomimetic drugs that stimulate α1-adrenergic receptors producing vasoconstriction. This in turn decreases mucosal oedema and local vasodilation.20 Examples of the most commonly used drugs include xylometazoline, phenylephrine and oxymetazoline.31 Local decongestants are usually indicated to reduce acute symptoms as prolonged use can produce undesirable effects to the user.20 After persistent use (usually more than 5 days), rebound rhinitis and conjunctivitis medicamentosa start to appear. 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.32

Systemic decongestants

These agents stimulate α1-receptors producing vasoconstriction, reducing oedema, redness and itching. Their preparations usually contain an antihistamine. It is important to note that combination therapy of a systemic decongestant and an older-type H1-antihistamine can produce drowsiness and a lack of motor coordination. Systemic decongestants available in South Africa include pseudoephedrine, phenylephrine and phenylpropanolamine. The use of phenylpropanolamine has produced sub-arachnoid bleeding with a haemorrhagic stroke in women using it as an appetite suppressant. The total daily dosage of phenylpropanolamine should not exceed a 100 mg.30

Corticosteroids

Glucocorticosteroids can be used for various allergic conditions such as asthma, allergic rhinitis and minimal use in allergic conjunctivitis. They exert their pharmacological action by modifying protein synthesis through regulating
transcription, and indirectly by modifying the activity or half-life of transcription factors and mRNA. The currently available intranasal corticosteroids include: beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. The newer agents, namely mometasone, fluticasone, and ciclesonide, are also administered intranasally and result in minimal systemic effects. The most common local side-effects experienced with the intranasal corticosteroids may lead to atrophy of the nasal mucosa. It is therefore advisable to use these agents for the shortest time possible to prevent unpleasant adverse effects associated with long term use. Systemic corticosteroids such as hydrocortisone and prednisone can be used in chronic dermatitis to reduce frequency of allergic flares.

**The H1-antihistamines**

H1-antihistamines based on pharmacological classification are grouped into different generations. This system of classification is based on their target receptors as well as side-effect profile. The H1-antihistamines are classified into first generation (older, sedating multi-potent blockers) and second generation (non-sedating, newer) antihistamines. First generation antihistamines include promethazine, chlorpheniramine, dexchlorpheniramine and cyclizine, whilst the second-generation antihistamines include cetirizine (and levocetirizine), loratadine, ebastine, fexofenadine and mizolastine. The most significant difference between the two classes is that first generation H1-antihistamines have the ability to cross the blood brain barrier and the second generation non-sedating H1-antihistamines have very limited ability, if none at all to cross the blood brain barrier. It is also important to note that two generations of systemic (oral and/or parenteral) agents, topical (including intranasal and ophthalmic) H1-antihistamines are available as well.

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<tr>
<th>Table I: The differences between first- and second-generation histamine 1 antihistamines</th>
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First-generation H1-antihistamines

These older H1-receptor blockers have shown to have sedative and multi-potent receptor blocking abilities. Their ability to cross the blood brain barrier distinguishes them from the newer generation H1-antihistamines. The chemical structure of the first-generation antihistamines permits them to have a certain degree of non-selectivity, exerting antagonistic effects of an antimuscarinic or anticholinergic, antihistaminergic, α1-adrenergic blocking, anti-serotonergic and local anaesthetic nature. Because of their wide range of receptor blocking, the first-generation H1-antihistamines have a variety of indications and uses, which range from allergies and rhino-conjunctivitis, to nausea and vomiting, motion sickness and insomnia. Their effects on multiple receptors on the other hand also has undesirable effects and are not recommended to be used in patients who suffer from glaucoma, benign prostatic hyperplasia and in cardiac patients (i.e. ischemic heart disease, myocardial infarction and congestive heart failure).35

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<th>Table II: The adverse effects of first-generation histamine 1 antihistamines, as reflected by receptor activity.36</th>
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<td>Muscarinic receptor</td>
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<td>α-adrenergic receptor</td>
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<td>Serotonergic receptor</td>
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The following drugs in this group are of note:

- The options include hydroxyzine, promethazine and diphenhydramine. These drugs are used in the management of insomnia but there are more suitable agents that may be used.

- Cyclizine (syn. meclizine), diphenhydramine, hydroxyzine or promethazine are examples of antiemetic agents. First-generation H1-antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo.

- Chlorpheniramine is better suited for use in allergic reactions due to its relatively lower sedation levels than the other first generation antihistamines.

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

Second-generation H1-antihistamines

Second generation H1-antihistamines are relatively newer antihistamines that do not possess the ability to cross the blood brain barrier. They also have no antiemetic, anticholinergic and central nervous system effects unlike the first-generation antihistamines. Drugs like fexofenadine are actively transported into the lumen of the gut, kidney and brain by p-glycoproteins, which restrict their ability to accumulate and cause unwanted side-effects. However, agents such as rifampicin, which induce p-glycoprotein, may increase the clearance of fexofenadine and reduce its efficacy.37 Second generation H1-antihistamines are mostly dosed once daily with minimal risk of developing tolerance. The long-term safety of the second-generation H1-antihistamines, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, has been documented in randomised controlled trials lasting 6–18 months in adults, and in children as young as 1–2 years old.38

Ophthalmic (eye-drop) 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.39

Rupatadine fumarate is a newly launched, second-generation, long-acting histamine antagonist (H1-receptor antagonist) and platelet-activating factor receptor inhibitor. Rupatadine fumarate is approved for the treatment of allergic rhinitis and chronic urticaria in adults and children aged 12 years and older. It inhibits the degranulation of mast cells and the subsequent release of cytokines, more specifically of tissue necrotising factor which is available in mast cells and monocytes.40

The leukotriene-receptor antagonists

Examples of leukotriene receptor antagonists include zafirlukast and montelukast. They are competitive antagonists of the cysteinyl leukotriene receptor-1 (cysLT-1). They have the advantage of oral administration. Montelukast is also available as a sprinkle and in a chewable tablet form for the convenient use in pediatrics. Montelukast presents an additional option in the management of seasonal allergic rhinitis in children with asthma.41

Conclusion

Allergic conditions seem to be on a constant rise. Evidence suggests that with inadequate management of an acute allergic disease, a development of a chronic allergic disease in highly probable. Conditions such as rhinitis and sinusitis are examples of conditions that become chronic when acute symptoms are not adequately managed. The use of antihistamines provides symptomatic relief in patients with allergic conditions. The use of first generation antihistamines should be limited to patients who have chronic allergic conditions, have cardiac problems or suffer from benign prostatic hyperplasia due to their stimulation of multiple receptors and tendencies to cause drowsiness. The use of second-generation antihistamines remains the best alternative to chronic allergic conditions except for conditions such as atopic dermatitis and asthma which usually require corticosteroids as long-term therapy.
References