AETIOPATHOGENESIS OF ALLERGIC RHINITIS: CURRENT CONCEPTS

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ABSTRACT

Allergic rhinitis as an IgE mediated inflammatory response of the nasal mucosa to specific allergens has continued to be investigated. The prevalence has been on the increase. This review article is a summary of documented current perspectives on the aetiology and pathogenesis of allergic rhinitis. The aim is to update practitioners on the current concepts and stimulate research in this field in sub Saharan Africa. The role of genetic predisposition and environmental exposure to allergens as documented in many research articles is highlighted. Their interactions in the development of allergic rhinitis have shown that immunological cell modulation is a key factor. These are due to induced molecular changes in the regulation of production of enzymes that influence the expression of immunological cells.

In the pathogenesis of allergic rhinitis, sensitization through antigen presenting cells is an important initial process. This process makes the individual susceptible on re – exposure to the allergen. The roles of the T lymphocyte cells and their different phenotypes are a major factor in the pathogenesis of allergic rhinitis. The complex interactions between these T cell phenotypes through the secretion of different inter leukins are discussed. The contributory role of many mediators in the propagation of cellular mechanisms such as the activation and differentiation of various cell types, prolongation of their survival, the further release of mediators and the neural reflex actions are highlighted.

Studies in Nigeria have documented the allergenic potentials of pollen grains from plants. However, these have not been purified as allergen extracts that can be used for clinical studies. The role of air pollution in the urban cities in Nigeria as adjuvants needs to be investigated. The need for multi-disciplinary collaborative studies among the various stakeholders in Nigeria is advocated.

Keywords: Allergic rhinitis, Aetiology, Pathophysiology, Current concepts

INTRODUCTION

Abnormal skin reactions to foods and insect bites have been noted for centuries. Clemens von Pirquet in 1906 first used the word 'allergy' to describe abnormal reactions to horse serum antitoxin. Earlier in the 19th century, John Bostock provided the first detailed account of hay fever and Charles Blackley was able to prove that pollen was the cause of hay fever[1]. Thus, nasal allergy had been recognized as hay fever which occurs during the pollen season. It has also been noted that although the term hay fever was a misnomer, it still appears to be in use. During the 20th and early 21st centuries, a lot of studies have been done to elucidate the mechanism through which this condition develops. It is now a disease entity known as allergic rhinitis.[2, 3] This review is a synopsis of the current state of knowledge about the aetiology and pathogenesis of allergic rhinitis. Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa induced by an IgE-mediated reaction, following exposure to an allergen. The inflammation of the nasal mucosa may extend into the paranasal sinuses. The concept of Allergic Rhinosinusitis derives from this as the nasal mucosa is in continuity with the mucosa of the paranasal sinuses

Allergic rhinitis (AR) is now recognized as referring to two significant clinical entities:

1. Rhinitis – inflammation of the nasal mucous membranes;
2. Allergy - the specific cause of the rhinitis.

Current research efforts have focused extensively on these two entities. This has resulted in improved knowledge on the aetiology, pathophysiology and clinical aspects the disease. Allergic Rhinitis manifests through nasal symptoms of sneezing, rhinorrhoea (runny nose), nasal itching and nasal congestion or

blockage. There may be accompanying ocular symptoms of itching, watering and red eyes. The diagnosis is made on a good clinical history, physical examination and confirmed by skin prick tests and other investigations. Allergic rhinitis is now regarded as a major chronic respiratory disease because of its prevalence, impact on quality of life, and its link with asthma. A major issue is that this condition has been noted to be under diagnosed, misdiagnosed, undiagnosed and under-estimated.[4, 5, 6] A study in Europe reported that over half of AR sufferers do not seek medical treatment.[7] Another study in France showed that 19% of 230 patients with typical symptoms of allergic rhinitis had never consulted a physician for their nasal problem.[8] These research works provide evidence that the prevalence of the disease is underestimated. The situation in Africa is likely to be worse.

PREVALENCE OF ALLERGIC RHINITIS.

Allergic rhinitis has been shown to pose a global health problem and the prevalence has been noted to be on the increase. Studies have shown that patients from all countries, all ethnic groups and all ages suffer from AR. Bousquet et al in 2001 estimated that 10 – 25% of the world population is affected.[9] In the USA AR is estimated to affect 10 - 30% of adults[10]. In Europe AR is estimated to affect 17 – 29 % of adults.[7] The ISAAC 1998 study report from Ibadan, Nigeria showed an incidence of 39.7 %.[11] There is paucity of population based studies in Nigeria. Most studies have been mainly on a selected group or hospital based and so do not give the true prevalence of allergic rhinitis in Nigeria.[12, 13] Katelaris CH et al in 2012 reported a rising prevalence of about 50%.[14] Thus, it is now estimated that over 400 million people suffer from this disease worldwide.

Time trends in Prevalence of AR

There is evidence that the prevalence of AR is increasing worldwide. There is also direct and very clear evidence that IgE responses against common air borne allergens are also rising.[15] The reasons that have been adduced for the increasing prevalence are changing global climate conditions, improvements in hygiene, changes in diet and changes in environmental exposure in early life. Recent studies have also shown the presence of new adjuvants enhancing sensitization and the progressive absence of factors inducing tolerance.[16]

Clear evidence was shown in the study by Wutrich et al on the prevalence of AR in Switzerland over the period between 1926 and 1995. They noted an increase in the prevalence of AR from 0.82% in 1926 to 8.25% in 1958 which they attributed to the industrial revolution in Europe during the period, increase in the number of specialist Doctors, improved diagnostic ability, and increased awareness. However, it is noteworthy that there was about 40% increase in the prevalence between 1985 (9.6%) and 1995 (14.2%).[17] There are other studies that have clearly shown an increase in the incidence of AR over time.[18]

AETIOLOGY OF ALLERGIC RHINITIS

Genetic predisposition

Genetic predisposition is a major factor in the aetiology of AR. The clinical evidence include: the fact that a family history of allergic rhinitis is often present and the association of Allergic rhinitis with other atopic diseases that possess a genetic basis, such as allergic asthma or atopic dermatitis.[19] It has been reported that Allergic Rhinitis has a hereditary component but does not exhibit a Mendelian hereditary pattern. The evidence has been demonstrated by studies in twins. It has been reported that in monozygous twins, a 45-60% concordance for AR was observed, while this concordance drops to 25% in dizygous twins. Based on such studies, it has been estimated that AR exhibits an inheritability of 0.33-0.75.[20]

Genetic studies in AR appear to be complex. This is largely due to the finding that the disease derives from the global effect of a series of genes. It was noted that there are interactions among these genes that influence the final outcome. Also noted is the fact that there are interactions between the causal genes and a range of environmental factors. Epigenetic effects which are inheritable changes in gene expression which occur without actual modification in the DNA sequence have also been found.[21-24] Studies have shown associations between allergic rhinitis and certain chromosomes.[21] The main chromosomes implicated are 3 and 4. It has been shown that chromosome 3 has three regions linked to allergic rhinitis, 3q13, 3q13.31, and 3p24 and one region on chromosome 4, 4q24-q27.In addition, Single-nucleotide polymorphism (SNP) of genes encoding for molecules implicated in the pathogenesis of allergic rhinitis have also been established. These molecules include chemokines and their receptors, interleukins and their receptors,

eosinophil peroxidase and leukotrienes.[25]

Environmental allergens

Allergic rhinitis occurs when there is exposure to allergens in the environment in which the individual is present. There are specific allergens that have been found to induce the onset of allergic rhinitis. The types and physicochemical properties of these allergens have been identified. Also other environmental factors have been found to play a role in the antigenicity of the allergens. The commonest forms of allergens that induce AR are aeroallergens.[26, 27] Other allergens include food and drugs. The environments of exposure can be classified as Indoor, Outdoor and Occupational environments.

Indoor Allergens

Indoor allergens have been shown to be the major causes of perennial allergic rhinitis.

The main indoor allergens are:

1. **House dust.**
   House dust is a heterogeneous mixture, which varies according to the environmental location, the region and house. It has been found to consist of various somatic and metabolic substances of mites and allergenic substances derived from particles in the air. These include scales from human skin, domestic insects, fungal spores or mycelia, other products of animal or vegetable origin such as feathers, wool, and natural fibers.[28, 29]

2. **House dust mites**
   House-dust mites (HDM) have been reported as the most common indoor allergens for allergic diseases such as allergic rhinitis and asthma. There are reports that Dermatophagoides pteronyssinus and Dermatophagoides farinae are the most common mite species worldwide.[13, 29, 30] However, others have reported that in some tropical regions, Blomia tropicalis (B. tropicalis), another dust mite species, was found to be the most prevalent.[31, 32] These reports were based on skin prick tests using different allergen extracts. HDM have also been demonstrated to be commonly found in association with house hold beddings, fabrics and carpets. Studies have shown that HDM hypersensitivity causes persistent allergic rhinitis.[33]

3. **Fungal spores**
   The first observation that fungi could cause allergy dates back 300 years. However, for a long time fungi were neglected as an allergen source. Data from many studies have provided evidence for the important role of fungi in nasal allergy in the indoor as well as in the outdoor environment. The common fungi identified are Cladosporium, Aspergillus fumigatus and Alternaria alternate.[34, 35]

4. **Ownership of Pets**
   Mousawi et al in 2004 reported that ownership of animal pets was found to significantly increase the risk of sensitization to pets.[16] Also Bener et al in 2004 reported that the prevalence of asthma, rhinitis, and skin allergy was significantly more common in families with animals than in those without. Cats and dogs were shown to be the main culprits particularly if they are allowed to enter and remain in the indoor. It was found that proteins secreted from these animals contain allergens which were capable of causing hypersensitivity reactions.[36-38] Luczynska et al in 1990 had found that the major cat allergen was a glycoprotein that is transported in the air by particles smaller than 2.5µmand that these particles could remain airborne for long periods.[39]

Outdoor Allergens

Individuals are exposed throughout life to outdoor allergens either outdoors or after the allergen bearing particles penetrate indoors. They are usually responsible for seasonal nasal allergy and sometimes perennial allergies. Outdoor allergens include pollen grains and spores from trees, grasses, weeds and fungi.[40]

Pollen Grains

Pollen grains are the male gametophyte in the sexual reproduction of plants and conifers. Pollination is the mode of transfer of pollen grains from male to female reproductive structures. It can be accomplished through wind, water, or by insects. In wind-pollinated plants, pollen grains are released into the atmosphere to passively find their way onto an appropriate receptive female stigma. Because this is a less efficient method than in insect pollination, wind-pollinated plants produce large amounts of pollen to ensure successful fertilizations. Thus, pollen from these plants is abundant in the atmosphere with a high tendency of human exposure. It has been documented that a pollen grain can be transported for long distances at a high velocity. The pollinating seasons of different plants vary but it is constant from year to year. Thus,

susceptible individuals have seasonal exposures.[41]

Allergens isolated from pollen grains have been identified to be water-soluble low-molecular-weight proteins or glycol proteins. Studies have shown that there are structural and biochemical properties that determine the potency these proteins as allergens. Immunogold labeling experiments have localized allergens of pollen grains in the cytoplasm. A moderate amount of allergen is also found associated with their apertures. Allergenic particles are expelled from the cytoplasm of pollen grains by two proven mechanisms. In the first mechanism, allergens passively diffuse when the pollen grain is in direct contact with the nasal mucosa in an isotonic medium. In the second mechanism a hypotonic medium (such as rain water) allows rapid hydration of the pollen grain to a level that there is spontaneous expulsion of the cytoplasmic allergens into the atmosphere.[42-44] The released allergens are inhalable. In addition, pollen grains have been reported to also release a variety of enzymes, including proteases. These proteases are unique as they are not inactivated by endogenous protease inhibitors and they cause rupture of epithelial junctions, facilitating protein transport.[45] This may explain the reason for the observed rise in allergic rhinitis during the raining season. Behrendt et al. in their studies showed that pollen grains activate the nasal epithelium by the secretioneicosanoid-like substances which cross-react with leukotriene B4 and prostaglandin E2.[46] These are pro-inflammatory mediators.

Fungal Spores and Their Allergens

Fungi are saprobic organisms that occupy a kingdom of their own. They are responsible for most of the aerobic decay of plant materials like dead wood, grass, leaves, etc. Fungal spores are dispersed by wind leading to their abundance in the air. Several fungal genera have been associated with allergic respiratory symptoms but few fungal allergens have been characterized to date. The allergens from A. fumigatus, C herbarum, and Alternaria alternata have been the best characterized. It has been reported that Fungal allergens are proteins which are enzymes released from the fungal spore during germination. Thus these allergenic proteins have to be released from the cell before they can be active. Dague et al in 2008 and Aimanianda et al in 2009 noted that a pathway occurs during spore germination which enables the allergens to be released and this makes it imperative for these fungal spores to be alive.[47,48]

The Role of Air pollution

Utell and Samet in their study noted that exposure to high levels of pollutants such as oxides of nitrogen, ozone, sulfur dioxide, black smoke, carbon monoxide, and volatile organic compounds are important contributing factors in both exacerbation and etiology of nasal allergy.[49] Von Mutius et al reported on an epidemiological study of a total of 7653 children in two cities in Germany. The cities were Munich (5030 children) and Leipzig (2623 children). Leipzig had a high degree of air pollution, with sulfur dioxide produced by coal. In Munich, there was a high level of an "automobile type" of pollution. The study showed that the prevalence rates of allergic rhinitis, asthma, and positive skin tests to aeroallergens were significantly lower in Leipzig (2.7%, 3.9%, and 18.2%) than in Munich (8.6%, 5.9%, and 36.7%). This made them conclude that air pollution with smoke from diesel and automobiles was a significant factor in inducing allergic disease.[50] Knox et al. were able to note that carbon particles from diesel engine fumes were capable of concentrating many allergic molecules in a single particle. They concluded that the mechanisms of action of air pollutants were impairment of defense mechanisms in the respiratory mucosa and immunological toxicity.[51] Riedl and Diaz-Sanchez in 2005 reported that air pollutants may also have a direct or indirect role in the pathophysiology of allergic diseases.[52] More work is needed to identify more pollutants that have an impact in the development of nasal allergy, and the mechanism for the disease development. This will need to include the pathways of chemical, molecular, and cellular interactions.

The Hygiene Hypothesis

The hygiene hypothesis of allergy was proposed by David Strachan in 1989. He had noted from his studies that the risk of developing allergies was higher in families with a high number of children. He suggested that the reduced incidence of early childhood infections might be responsible for the increasing risk of developing allergies.[53] This hypothesis is premised on the fact that infections with bacteria, viruses and perhaps other intracellular organisms in early childhood influence the developing immune system. T-cell responses to these infections are believed to generate Th1-like cytokines such as IL-12 and IFN that down-regulate Th2 responses. Thus, the hygiene hypothesis is based on the observations that Th1 responses induced by microbial stimulation down regulate allergen-induced Th2 responses. This is

further supported by the principle of "endotoxin switch", in which a dose-dependent relationship is thought to exist between exposure to bacterial products in early life and the outcome of the immune response. This affects the balance of the Th1/Th2 cytokine levels.

Hygiene Hypothesis and Old Friends (OF) Theory

The "Old Friends" theory was proposed by Rook in 2003. His studies provided evidence that the vital microbial exposures for immune regulation were not the acquired infections in childhood, but are microbes that are normally present in the environment from evolution (which he termed "Old Friends"). These microbes are commensals in the gut, skin and respiratory tracts of humans. These were proposed to activate the immune regulatory mechanisms in childhood. He noted that it was the gradual elimination of these microbial exposures by various means that was responsible.[54] Other studies have shown that the vital period of exposure to these microbes is in early development, during pregnancy, child birth and the neonatal period.[55] A study reviewing epidemiological data in 2008 shows that children delivered through Caesarian sections were more likely to develop allergies.[56]

The Hygiene Hypothesis and The Counter-Regulatory Model.

The reports from studies by Gor et al in 2003 showed that the prevalence of Thl-dependent autoimmune diseases and allergyare increasing. Also parasitic infections which are Th2-associated do not increase the risk of allergy. These were noted to contradict the hygiene hypothesis. They opined that the Thl/Th2 balance model should be re-evaluated. Some recent reviews offer a unifying explanation for the increasing incidence of both allergy and autoimmunity. This is known as the "counter-regulatory" model.[57,58] Anti-inflammatory cytokines, such as IL-10 and transforming growth factor (TGF)-ß, are the key players in the counter-regulatory model. The model proposes that most pathogenic infections have been shown to up-regulate IL-10 production. This is known to suppress allergic and autoimmune disease together. Thus, reduced exposure to pathogenic infections usually leads to decreased levels of anti-inflammatory cytokines.[57 - 59] This is supported by a previous finding of decreased IL-10 production in asthmatic patients by Borish et al in 1996.[60]

PATHOPHYSIOLOGY OF AR

Allergic rhinitis is an IgE-mediated, type 1 hypersensitivity reaction to an inhaled allergen. A series of immunological and biochemical reactions occur to elicit the clinical manifestation of the disease. Studies have shown that Genetic predisposition, allergen exposure, environmental adjuvants and immune response inhibitors are important factors in the pathophysiology.[21]

Three distinct phases in the pathophysiology of Nasal Allergy / allergic rhinitis are well recognized. These include:

1. Sensitization
2. Early / Immediate reaction
3. Late / delayed reaction

Sensitization

The process of sensitization has been the subject of many research works that have elucidated the complex nature and thrown light on why some individuals have allergy while others do not. It has explained why allergies may develop at some point in people's lives and abates in others. A background of the current state of knowledge of human immunology is necessary before the complex nature of the process of sensitization is further discussed.[61 - 63]

The major cellular components of adaptive and specific immune system are the T cells and B cells. The B cells have been shown to recognize antigens as a whole via their B cell receptors while the T cells recognize only the processed form of antigens. Thus for T cells to recognize an antigen (which are proteins), it has to be broken down into short peptides. These short peptides have the ability to become bound to the proteins of the major histocompatibility complex (MHC) class I or class II. The T cells are of two types, the cytotoxic T cells (Tc) and helper T cells (Th). The former have the proteins of MHC class I on their cell membranes, and function by killing their targets. The helper T cells (Th) have the proteins of MHC class II on their cell membranes. They function by producing cytokines that activate B cells into producing specific antibodies. The antibodies are immunoglobulins (Ig) and there are five major classes which are IgA, IgD, IgE, IgG and IgM. The class of Ig produced is dependent on the cytokines induced which is also dependent on the type of Th cells.[64]

Helper T-cells are divided into 3 broad classes: effect or T-cells, memory T-cells, and regulatory T-cells (Treg).

Effect or T-cells are further divided based on the cytokines they produce as TH1, Th2, and Th17 cells. Th1 cells produce interferon-gamma and interleukin-2 (IL-2) which promote a cell-mediated immune response. Th2 cells produce IL-4 and IL-13, which act on B-cells to promote the production of antigen-specific IgE. Th17 cells produce IL-17, IL-21, and IL-22. They have been shown to have effect on extracellular pathogens, produce antimicrobial peptides and promote neutrophil inflammation which is essential for immunity at the skin and mucosal surfaces. The memory T-cells can rapidly differentiate into effect or T-cells in secondary immune responses. The regulatory T cells are essential in peripheral tolerance by their ability to suppress dysregulated immune responses. They can inhibit Th2 cytokine production through the secretion and action of IL-10 and transforming growth factor-beta(TGF-β). The Treg cells have been shown to be important in the tolerance of allergens.[64-66]

The Process of Sensitization

Inhaled allergens are trapped by the nasal mucus. Antigen-presenting cells (APC) are the dendritic cells and macrophages on the epithelium and submucosa of the nasal cavity. These have the affinity to engulf the allergens which are mainly proteins and glycoproteins. They biochemically break down the proteins into specific peptides. These peptides become immunologically active due to interaction with specific proteins of the major histocompatibility complex class II (MHC class II). Studies have shown that the APCs, especially the dendritic cells have an efficient mechanism of processing allergens after engulfing them.[67] Within the cytoplasm of the APCs, the allergen proteins are endocytosed by phagocytosis and processed through a vesicular pathway consisting of progressively more acidic and proteolytic active compartments known as early endosomes, late endosomes and the lysosomes. Through this pathway the allergenic protein is broken down into immunologically active short peptides that bind to MHC molecules on the cell membrane of the APCs. The APCs are known to have one or more epitopeson their cell wall where an allergen can fit specifically in the groove of MHC class II with good stability. An epitopeis the part on the allergen that is recognizable by the immune system which is the allergenic determinant. Molecular studies have shown that the peptide-binding groove is highly flexible and collapses in the absence of a bound peptide. This makes it an efficient site.[68,69]

The activated APC then migrates to the lymph nodes where they present these allergen peptides to the naïve ('never exposed to antigen') helper T lymphocytes (Th0). The Naive helper T cells (Th0 cells) with appropriate stimulus can differentiate into Th1, Th2 or Th17 phenotypes. The Th2 subset mediates allergy and Interleukin 4 (IL-4) is the required stimulus. The IL-4 is released from innate lymphoid cells (ILC) and is important in the initiation and clonal expansion of a Th2 response. In nasal allergy, Th 2 lymphocytes and memory Tcells production is stimulated. The Th2 lymphocytes further release cytokines (IL-4 and IL-13) and interact with B lymphocytesby isotype switching to induce the synthesis of allergen- specific IgE and development of IgE B cell memory and IgE-secreting plasma cells. Allergen-specific IgE binds to the high affinity receptor for IgE (FcεRI) on the surface of mast cells. This binding results in sensitization.[70,71]

The regulatory T cells (Treg) have been shown to play a role in the regulating the differentiation into Th1, Th2 or Th17 lymphocyte phenotypes. It is at the phase of sensitization that Genetic factors and immunologic change reactions play a role in nasal allergy. It is important to note that recent research works have led to the concepts of polysensitization, co-sensitization, co-recognition, cross-sensitization, and poly allergy.[72,73] These have been shown to affect disease severity.

Early Phase (Immediate) Response

After sensitization, there is usually a latency period. When there is a re – exposure of an IgE-sensitized individual to the allergen, the early or immediate phase response is triggered off within minutes. The allergen binds to the Fab portions of two or more IgE antibodies on the mast cells leading to cross - linking. Upon allergen cross-linking of specific IgE bound to the surface high affinity receptors (FcεRI) of mast cells, signaling pathways are induced that lead to degranulation of the mast cell. Mast cell degranulation is the main occurrence in the early phase response. Studies have shown that a crucial process that precedes mast cell degranulation is an increased influx Ca++ into the mast cell cytoplasm. This is supported by studies that have demonstrated that ionophores that increase cytoplasmic Ca++ also promote degranulation, whereas agents that deplete cytoplasmic Ca++ suppress degranulation.[74-76]

Mast cell degranulation results in the release of preformed inflammatory mediators mainly histamine, neutral proteases, and proteoglycans. The proteases

are mainly tryptase, chymase and carboxypeptidase A. The proteoglycans are heparin and chondroitins. Also, the mast cells are activated to secrete newly synthesized lipid mediators such as prostaglandin D2, leukotriene C4, and platelet-activating factor (PAF) as well as numerous pro inflammatory cytokines, chemokines and growth factors, including TNF-a, IL-4, IL-13, and eotaxin. Studies have shown that Mast cells are abundant in the epithelial compartment of the nasal mucosa and can be easily activated upon re-exposure to the allergens.[77-79]

Effects of the Mediators

These mediators are responsible for the early phase allergic reactions and progression to the late phase response. Histamine, the major mediator of AR, stimulates the sensory nerve endings of the trigeminal nerve and induces sneezing and itching. Histamine also directly stimulates the mucous glands to cause secretion of mucous and nasal discharge. It also causes vasodilatation and increased capillary permeability leading to mucosal oedema and nasal congestion.[80, 81] The leukotrienes and prostaglandins act on the blood vessels causing vasodilatation which leads to nasal congestion. The proteases and proteoglycans have been shown to play a major role in mucosal tissue injury that leads to exposure of sensory nerve endings and penetration of more allergen into the nasal mucosa. They also act as chemo attractants thereby stimulating more cell recruitment and other activities that promote the initiation of the late phase reaction.[82-84]

Late Phase Response

The early phase response is usually followed by the late phase response. The late phase response lasts for about 24 hours or more. It is characterized by influx of T lymphocytes, basophils and eosinophils into the nasal submucosa. Several mediators such as leukotrienes, kinins, histamine, chemokines and cytokines, result in the continuation of the symptoms. Released cytokines such as IL-4, IL-5, IL-9 and IL-13 from mast cells, basophils and Th2 cells play major roles in the prolongation of the late phase response. The exact mechanisms of action of these mediators are still areas of continued research efforts.[85]

Recent findings have proven that IL-4 and IL-13 up regulate the action of vascular cell adhesion molecule 1 (VCA-1) on endothelial cells thereby facilitating the infiltration of the nasal mucosa with eosinophils, Th2 lymphocytes and basophils. The chemokines, such as eotaxin, monocyte chemoatractant protein (MCP)-4, and thymus-and activation regulated chemokine (TARC) released from epithelial cells have also been proven to be chemo attractants for eosinophils, basophils and T lymphocytes. Other cytokines like granulocyte macrophage colony-stimulating factor (GM-CSF), released largely by the epithelial cells, and IL-5 from Th2 lymphocytes prolong the survival of the infiltrating eosinophils in the nasal mucosa. Mediators released from the eosinophils such as the eosinophil cationic protein, platelet-activating factor, have additional roles in the late phase response.[85-87] This late phase response is characterized by a prolongation of symptoms of sneezing, rhinorrhea and sustained nasal congestion. Apart from this local inflammation, the mediators can trigger a systemic inflammation which may involve the eyes, the lower airways and the skin.

CONCLUSION

Allergic rhinitis has been established as an IgE mediated inflammatory disease of the nasal mucosa induced by specific allergens. The prevalence has been on the increase and theories have been enunciated to explain this. Genetic predisposition and environmental exposure to allergens have been documented as being causative in research studies. Immunologic cell modulations have been shown to be induced by molecular changes in the regulation of production of enzymes that influence the expression of immunological cells. The pathogenesis of allergic rhinitis has been extensively studied and the immune mechanisms have been identified. Sensitization has been documented as the important initial process. This process makes individuals susceptible to subsequent interactions on re – exposure to the allergen. The complex interactions between T lymphocyte phenotypes namely Th1/Th2 and the regulatory T cells through the secretion of different interleukins have thrown more light in the pathogenesis of allergic rhinitis. High affinity receptors have also been shown to be important determinants of binding sites on various immune cells as these induce signaling pathways for degranulation and release of mediators. Many mediators have been identified that contribute significantly to the propagation of cellular mechanisms such as the activation and differentiation of various cell types and prolongation of their survival. Cytokines, chemokines, neuropeptides and adhesion molecules are the mediators that act on the tissues. This results in the onset of specific and non- specific symptoms of allergic rhinitis. The role of neural reflex actions has also been implicated.

The molecular properties of allergens have been characterized as proteins or glycoproteins that have ability to produce enzymes. Physical and biochemical properties of the inhalant allergens play a role. Buoyant and sticky antigens with low molecular weight (10–50 kDa) may be carried by particles and remain airborne for long periods. The biochemical properties implicated are proteases, lipid-binding ability, actin-binding, Ca++-binding etc. Biochemical properties which enhance the activation of Th2-immune responses are characteristic of allergens. The capacities of an allergen to carry immunologically active substances also increase the allergenicity. The role of air pollution with from automobile fumes has been shown to be contributory.

In Nigeria, palynological studies have shown that there is abundance of pollen grains from plants and spores from fungi that are potential allergens. However, purification of their extracts into standardized forms for clinical trials needs to be done. The role of air pollution in the urban cities of Nigeria in the pathomechanism of allergic rhinitis needs to be studied. Also studies are needed to understand the interplay between epidemiology and moleculargenetics that cause sensitization among Nigerians. This has implications for developing preventive strategies. Thus there is need for multi-disciplinary collaborative study teams involving appropriate stakeholders in Nigeria.

REFERENCES

1. Kay AB Landmarks in Allergy during the 19th Century. Chem Immunol Allergy. 2014; 100:21-6
2. Sibbald B, Rink E. Labelling of rhinitis and hayfever by doctors. Thorax 1991; 46: 378–381.
3. Charpin D, Sibbald B, Weeke E, Wuthrich B. Epidemiologic identification of allergic rhinitis. Allergy 1996; 51: 293–298.
4. Kuprys I, Elgalal A, Korzycka-Zaborowska B, Gorski P, Kuna P. Underdiagnosis of allergic diseases in the general population of Lodz province. Allergy 2002; 57: Suppl. 73, 185- 90.
5. Richards S, Thornhill D, Roberts H, Harries U. How many people think they have hay fever, and what they do about it. Br J Gen Pract 1992; 42: 284–286.
6. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe, Allergy, 2007; 62(85): 17 – 25
7. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004; 24: 758-64.
8. Demoly P, Didier A, Mathelier-Fusade P, Drouet M, David M, et al. Physician and patient survey of allergic rhinitis in France: perceptions on prevalence, severity of symptoms, care management and specific immunotherapy. Allergy,2008;63:1008–1014
9. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol, 2001; 108: S147-334.
10. Nathan RA, Meltzer EO, Derebery J, Campbell UB, Stang PE, Corrao MA, Allen G, Stanford R. The prevalence of nasal symptoms attributed to allergies in the United States: findings from the burden of rhinitis in an America survey. Allergy Asthma Proc. 2008; 29(6): 600 - 8.
11. Falade AG, Olawuyi F, Osinusi K, Onadeko BO. Prevalence and severity of symptoms of asthma, allergic rhino-conjunctivitis and atopic eczema in secondary school children in Ibadan Nigeria. East Afr. Med J.1998; 75: 695 - 698.
12. Oladeji SM, Nwawolo CC and Akinola OO. Prevalence of Allergic Disorders among University Students in a Tertiary Institution in Nigeria JDMS, 2015; 14(7): 12-16
13. Oladeji S, Nwawolo C, Adewole O. Allergic rhinitis among adult bronchial asthmatic patients in Lagos, Nigeria. J West Afr Coll Surg 2013;3(2):1-14.
14. Katelaris CH, Lee BW, Potter BC, et al. Prevalence and diversity of allergic of allergic rhinitis in regions of the world beyond Europe and North America. Clin Exp Allergy, 2012; 42: 186 - 207.
15. Rossi, R. E., Monasterolo, G. and Monasterolo, S., Detection of specific IgE antibodies in the sera of patients allergic to birch pollen using recombinant allergens Bet v 1, Bet v 2, Bet v 4: evaluation of different IgE reactivity profiles. Allergy;2003; 58(9): 929-932.
16. Al-Mousawi MS, Lovel H, Behbehani N, et al. Asthma and sensitization in a community with low indoor allergen levels and low pet-keeping frequency. J Allergy Clin Immunol, 2004. 114:1389–94.
17. Wüthrich B, Schindler C, Leuenberger P, et al,

Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss Study on Air Pollution and Lung Diseases in Adults. International Archives of Allergy and Immunology, 1995; 106 (2): 149-156.

18. Linneberg A. Changes in atopy over 25 years: allergy epidemic has spread to old age. British Medical Journal, 2005; 331:352-356.
19. Ober C, Yao T-C. The genetics of asthma and allergic disease: a 21st century perspective: genetics of asthma and allergy. Immunol Rev. 2011; 242: 10–30.
20. Hopp RJ, Bewtra AK, Watt GD, et al. Genetic analysis of allergic disease in twins. J Allergy Clin Immunol, 1984; 73: 265–70.
21. Wang DY Risk factors of allergic rhinitis: genetic or environmentalfi Therapeutics and Clinical Risk Management 2005; 1(2): 115– 123.
22. North ML, Ellis AK. The role of epigenetics in the developmental origins of allergic disease. Ann Allergy Asthma Immunol., 2011; 106: 355-61.
23. Zhang J, Noguchi E, Migita O, Yokouchi Y, Nakayama J, Shibasaki M, Arinami T. Association of a haplotype block spanning SDAD1 gene and CXC chemokine genes with allergic rhinitis. J Allergy Clin Immunol 2005;115: 548-554
24. Eskandari HG, Unal M, Ozturk OG, Vayisoglu Y, Muslu N. Leukotriene C4 synthase A-444C gene polymorphism in patients with allergic rhinitis. Otolaryngol Head Neck Surg 2006; 134: 997-1000.
25. Li CS, Chae SC, Lee JH, Zhang Q, Chung HT. Identification of single nucleotide polymorphisms in FOXJ1 and their association with allergic rhinitis. J Hum Genet 2006; 51(4): 292-297.
26. Scheurer S, Toda M, Vieths S. What makes an allergenfiClinExp Allergy 2015; 45: 1150-61.
27. Platts-Mills TA, Woodfolk JA. Allergens and their role in the allergic immune response. Immunol Rev 2011; 242: 51 - 68.
28. Zhang L, Chew FT, Soh SY, et al. Prevalence and distribution of indoor allergens in Singapore. Clin Exp Allergy, 1997; 27: 876–85.
29. Mbatchou N, Diane N, Nganda M, Yacouba M N and Njock L R. Sensitization to common aeroallergens in a population of young adults in a sub-Saharan Africa setting: a cross-sectional study.Allergy Asthma Clin Immunol, 2016; 12:1-6
30. Pawankar R, Mori S, Ozu C, and Kimura S. Overview on the Pathomechanisms of allergic rhinitis Asia Pac Allergy. 2011; 1: 157-167
31. Wang DY, Goh DYT, Ho AKL, et al. The upper and lower airway responses to nasal challenge with house dust mite Blomia tropicalis. Allergy, 2003; 58: 78–82.
32. Fernandez-Caldas E, Lockey RF. Blomia tropicalis, a mite whose time has come. Allergy, 2004; 59: 1161–4.
33. Custovic A, Simpson A. The role of inhalant allergens in allergic airways disease. J Investig Allergol Clin Immunol. 2012; 22: 393-401.
34. Esch RE, Hartsell CJ, Crenshaw R and Jacobson RS. Common Allergenic Pollens, Fungi, Animals, and Arthropods. Clinical Reviews in Allergy and Immunology. 2001; 21: 261 – 292
35. Essien BC and Aina DO. The role of Airborne Pollen grains of some Angiosperms and FungalSpores in Allergic and Pathogenic Infections in Anyigba, Kogi State, Nigeria. Int. J. Adv. Med. Sci. Biotechnol. 2014; 2(3): 23-28
36. Bener A, Mobayed H, Sattar HA, et al. Pets ownership: its effect on allergy and respiratory symptoms. Allerg Immunol, 2004; 36: 306–10.
37. Lodrup Carlsen KC, Roll S, Carlsen KH, et al. Does pet ownership in infancy lead to asthma or allergy at school agefi Pooled analysis of individual participant data for 11 European birth cohorts. 2012; 7(8): 43214 - 22.
38. Custovic A, Simpson BM, Simpson A, Hallam CL, Marolia H, Walsh D, et al. Current mite, cat, and dog allergen exposure, pet ownership, and sensitization to inhalant allergens in adults. J Allergy Clin Immunol. 2003; 111: 402-407.
39. Luczynska CM, Li Y, Chapman MD, et al. Airborne concentrations and particle size distribution of allergen derived from domestic cats (Felis domesticus). Measurements using cascade impactor, liquid impinger, and a two-site monoclonal antibody assay for Fel d I. AmRev Respir Dis, 1990; 141:361–7.
40. Burge HA and Rogers CA. Outdoor Allergens. Environ Health Perspect. 2000; 108(4):653-659.
41. Njokuocha RC, Osayi EE (2005). Airborne Pollen Survey in relations to Allergy and Plant pathogens in Nsukka, Nigeria. Nig. J. Biol. Res. Biotechnol., 2005; (1):77-84.
42. Sowunmi MA (1995). Pollen Grains of Nigerian Plants. Grana. 34:120- 141.
43. Adeonipekun A. P. & Olowokudejo J. D.Pollen Grain at Offshore Locations in the Eastern Niger Delta: Implications on Geologic Sedimentation,

Vegetation Reconstruction and Allergy – A Preliminary Study. Global Journal of Science Frontier Research Biological Sciences. 2012; 12 (5): 27 – 33

44. Adekanmbi, O., Ogundipe, O. Aeropalynological studies of the University of Lagos campus, Nigeria. Notulae Scientia Biologicae. 2010; 2(4): 34-39.
45. Taketomi EA, Sopelete MC, Moreira PF and Vieira FAM Pollen allergic disease: pollens and its major allergens.Rev Bras Otorhinolaryngol. 2006; 72(4): 562 - 7.
46. Behrendt H, Kasche A, Ebner Von Eschenbach C, Risse U, Huss-Marp J, Ring J. Secretion of proinflammatory eicosanoid-like substances precedes allergen release from pollen grains in the initiation of allergic sensitization. Int Arch Allergy Immunol 2001; 124(1-3): 121 - 5.
47. Dague E, Alsteens D, Latgé JP, Dufrene YF. High-resolution cell surface dynamics of germinating Aspergillus fumigatus conidia. Biophys J. 2008; 94(2): 656-60.
48. Aimanianda V, Bayry J, Bozza S, Kniemeyer O, Perruccio K, Elluru SR, et al. Surface hydrophobin prevents immune recognition of airborne fungal spores. Nature. 2009; 460(7259): 1117-21.
49. Utell MJ, Samet JM. Particulate air pollution and health: new evidence on an old problem. Am Rev Respir Dis, 1993. 147:1334–5.
50. Von Mutius E, Martinez FD, Fritzsch C, et al. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir CritCare Med, 1994b; 149: 358–64.
51. Knox RB, Suphioglu C, Taylor P, Desai R, Watson HC, Peng JL, Bursill LA. Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. Clin Exp Allergy 1997; 27(3): 246-51.
52. Riedl M and Diaz-Sanchez D. Biology of diesel exhaust effects on respiratory function. J Allergy Clin Immunol, 2005. 115: 221–8.
53. Strachan DP. Hay fever, hygiene and household size. BMJ. 1989. 299: 1259–60.
54. Rook GAW. 99th Dahlem conference on infection, inflammation and chronic inflammatorydisorders: Darwinian medicine and the 'hygiene' or 'old friends' hypothesis. Clinical and Experimental Immunology,2010; 160: 70–9.
55. Rook GAW, Raison CL, Lowry CA. Microbial 'old friends', immune regulation and socioeconomic status. Clinical andExperimental Immunology,2014; 177: 1–12.
56. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clinical andExperimental Allergy,2008; 38: 629–33.
57. Gor, D. O., Rose, N. R., & Greenspan, N. S. (2003). TH1-TH2: a procrustean paradigm. Nat Immunol, 2003; 4, 503- 505.
58. Moore, K. W., de Waal Malefyt, R., Coffman, R. L. &O'Gara, A. Interleukin-10 and the interleukin-10 receptor. Annu. Rev. Immunol. 2001; 19, 683–765 (2001).
59. Van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, Yazdanbakhsh M: Role for parasite-induced interluekine-10 in children infected by Schistosoma haematobium.Lancet. 2000; 356:1723-27.
60. Borish L, Aarons A, Rumbyrt J, Cvietusa P, Negri J, Wenzel S. Interleukin -10 regulation in normal subjects and patients with asthma. J Allergy Clin Immunol, 1996; 97(6): 1288 – 1296.
61. Deraz TE. Immunopathogenesis of allergic rhinitis,Egypt J Pediatr Allergy Immunol 2010; 8(1): 3-7.
62. Bousquet PJ, Castelli C, Daures JP, Heinrich J, Hooper R, Sunyer J, Wist M, Jarvis D, Burney P: Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). Ann Epidemiol. 2010; 20:797–803.
63. de Jong AB, Dikkeschei LD, Brand PL: Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized and polysensitized children. Pediatr Allergy Immunol 2011; 22: 166–171.
64. Pawankar RU, Okuda M, Okubo K, Ra C. Lymphocyte subsets of the nasal mucosa in perennial allergic rhinitis. Am J Respir Crit Care Med 1995; 152: 2049-58.
65. Ying S, Durham SR, Barkans J, Masuyama K, Jacobson M, Rak S, Lowhagen O, Moqbel R, Kay AB, Hamid QA. T cells are the principal source of interleukin-5 mRNA in allergen-induced rhinitis. Am J Respir Cell Mol Biol 1993; 9: 356-60.
66. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, Kay AB, Hamid QA. Cytokine messenger RNA expression for IL-3,

IL-4, IL-5, and granulocyte/macrophage-colony-stimulating factor in the nasal mucosa after local allergen provocation: relationship totissue eosinophilia. J Immunol 1992; 148: 2390-4.

67. Godthelp T, Fokkens WJ, Kleinjan A, Holm AF, Mulder PG, Prens EP, Rijntes E. Antigen presenting cells in the nasal mucosa of patients with allergic rhinitis during allergen provocation. Clin Exp Allergy, 1996; 26: 677-88.
68. Dague E, Delcorte A, Latge JP, Dufrene YF. Combined use of atomic force microscopy, X-ray photoelectron spectroscopy and secondary ion mass spectrometry for cell surface analysis. Langmuir, 2008; 24(7): 2955-2959.
69. von Bubnoff, D., Geiger, E., and Bieber, T. Antigen-presenting cells in allergy. J Allergy Clin. Immunol. 2001; 705: 329-339.
70. Turner, H., and Kinet, J. P. Signalling through the high-affinity IgE receptor Fc epsilonRI. Nature, 1999; 402: 24-30.
71. Vercelli, D., Jabara, H. H., Arai, K., and Geha, R. S. Induction of human IgEsynthesis requires interleukin 4 and T/B cell interactions involving the T cell receptor/CD3complex and MHC class II antigens. J Exp Med, 1989; 169: 1295-1307.
72. Ciprandi G, Cirillo I: Monosensitization and polysensitization in allergic rhinitis. Eur J Intern Med, 2011; 22: 75–79.
73. Bousquet J, Anto JM, Bachert C, Bousquet PJ, Colombo P, Crameri R, Daeron M, Fokkens W, Leynaert B, Lahoz C, Maurer M, Passalacqua G, Valenta R, Van Hage M, Van Ree R: Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA2LEN project. Allergy, 2006; 61:671–680.
74. Holowka, D., Sil, D., Torigoe, C. & Baird, B. Insights into immunoglobulin E receptor signalling from structurally defined ligands. Immunol. Rev, 2007; 217: 269–279.
75. Pawankar R. Mast cells as orchestrators of the allergic reaction: the IgE-IgE receptor mast cell network. Curr Opin Allergy Clin Immunol., 2001; 1: 3 - 6.
76. Salib RJ, Kumar S, Wilson SJ, Howar th PH. Nasal mucosal immune expression of the mast cell chemoattractants TGF-beta, eotaxin, and stem cell factor and their receptors in allergic rhinitis. J Allergy Clin Immunol, 2004; 114: 799 - 806.
77. Pawankar R, Yamagishi S, Yagi T. Revisiting the roles of mast cells in allergic rhinitis and its relation to local IgE synthesis. Am J Rhinol., 2000; 14: 309-17.
78. Pawankar R, Yamagishi S, Takizawa R, Yagi T. Mast cell-IgE-and mast cell-structural cell interactions in allergic airway disease. Curr Drug Targets Inflamm Allergy 2003; 2: 303-12.
79. Dai H and Korthuis RJ. Mast Cell Proteases and Inflammation,Drug Discov Today Dis Models. 2011; 8(1): 47–55.
80. Parikh SA, Cho SH, Oh CK. Preformed enzymes in mast cell granules and their potential role in allergic rhinitis. Curr Allergy Asthma Rep. 2003; 3: 266–272.
81. Taylor-Clark T, Foreman J. Histamine-mediated mechanisms in the human nasal airway. Curr Opin Pharmacol 2005; 5:214–220.
82. Kojima T, Shirasaki H, Asakura K, Kataura A, Shimamoto K, Iimura O: Release of kinin and other chemical mediators after antigenic stimulation in allergic rhinitis patients. Adv Exp Med Biol. 1989; 247A: 379-383.
83. Stevens RL, Austen KF. Recent advances in the cellular and molecular biology of mast cellsImmunol Today, 1989; 10: 381-386
84. P. Bradding. Human mast cell cytokines. Clin Exp Allergy, 1996; 26: 13-19
85. Varga EM, Jacobson MR, Till SJ, Masuyama K, O'Brien F, Rak S, Lund V, Scadding GK, Hamid QA, Durham SR. Cellular infiltration and cytokine mRNA expression in perennial allergic rhinitis. Allergy, 1999; 54: 338-45.
86. Baggiolini M, Dahinden CA. CC chemokines in allergic inflammation. Immunol Today, 1994; 15: 127-33.
87. Garcia-Zepeda EA, Rothenberg ME, Ownbey RT, Celestin J, Leder P, Luster AD. Human eotaxin is a specific chemoattractant for eosinophil cells and provides a new mechanism to explain tissue eosinophilia. Nat Med, 1996;2:449-56.