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Chapter

Immunological Basis for the Development of Allergic Diseases-Prevalence, Diagnosis and Treatment Strategies

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Abstract

Allergy is an immune disorder due to over responsiveness of immune system to a relatively normal and harmless antigen; derived from environmental and dietary substances commonly referred as allergens. Allergy is an IgE mediated type I hypersensitivity which is characterized by the degranulation of specialized white blood cells known as mast cells and basophils. Majority of characterized allergens are proteinaceous in nature and induce Th2 response. Specific Th2 cytokines elicit the induction of allergen specific IgE antibodies in sensitive individuals. The IgE binds to Fc epsilon receptor on basophil/mast cells and on exposure, allergens cross links the IgE and induce release of hypersensitivity mediators that result in allergic symptoms. The symptoms varies from mild allergies like hay fever, itchiness, rashes, rhinatisis, conjunctivitis to a severe condition such as Asthma and some time life threatening anaphylaxis. At present a various blood based test exist to diagnose allergies which include skin prick, patch test and Specific IgE tests. The best treatment available is to avoid exposure to allergens alternatively use of anti-histamines, steroids or other symptom reducing medications are in practice. Immunotherapy to desensitize the response to allergen and targeted therapy are promising for allergy in future.

Keywords: allergy, Th2 cells, Immunoglobulin E, Basophils, Mast cells, Histamine

1. Introduction

Allergies are among the most common chronic conditions worldwide. Symptoms of allergies range from making miserable to putting at risk for life-threatening reactions. According to the leading experts in allergy, an allergic reaction begins with the hyper sensitization of immune system to a relatively harmless antigen [1, 2]. The function of the immune system is to protect the body from invading pathogens that are responsible for inducing various diseases. In case of an allergic reaction, the immune systems wrongly recognize a common foreign antigen which are otherwise harmless substance as a pathogen. This foreign antigen is referred as an allergen. The immune components hyper react to the allergen and induce adverse immune response by production of Immunoglobulin E (IgE) antibodies [3, 4]. The IgE antibody has affinity to Fc epsilon R1 receptor present on the surface of cells that release inflammatory

mediators on allergen stimulations. The released mediators like histamine and other chemicals cause allergic inflammation that result in allergic hypersensitivity. An inflammatory reaction typically triggers allergic symptoms in the throat and nose with itching and mucous discharge, sinus blockage and irritation in lining of stomach or itching on skin [2, 3]. In certain sensitive population, allergies can obstruct lung function and trigger bronchial hyper responsiveness and can induce asthmatic symptoms. In some people, a life-threatening serious reaction can occur called anaphylaxis [3–5]. A variety of proteins derived from diverse sources from different environment can act as allergens which were responsible for allergic reactions. The most common allergens were derived from plant flower pollens, dust mite, food sources, insect stings, animal hair and dander, mold, drugs, latex and medications.

The concept of "allergy" was originally introduced in 1906 by the Viennese pediatrician Clemens von Pirquet, after he noted that some of his patients were hypersensitive to normally innocuous entities such as dust, pollen, or certain foods [6, 7]. Earlier, all types of inappropriate hyper immune sensitive inflammatory reactions were termed as allergies. It was believed that, most were caused due to an improper increased activation of certain cells of the immune system that induce inflammation. Later, allergic IgE mediated mechanism was established that disproportionately activate certain cells of immune system to induce the release of inflammatory mediators [7]. A new classification system was proposed by Philip Gell and Robin Coombs in 1963 that described Type I to IV hypersensitivity reactions based on the immune mechanism and involvement of immune components [8]. In this system of classification, the allergic reactions or "allergy" was referred and restricted to immediate IgE mediated type I hypersensitivity. This is characterized by rapid onset of developing reactions and appearance of allergic or hypersensitivity symptoms in less than 20 mins after exposure to allergen. The landmark discovery for unrevealing the mechanism of allergy was through isolation and description of the importance of immunoglobulin E (IgE). In 1960, Kimishige Ishizaka and co-workers were first to report the antibody class IgE provided proof that is vital in mediating type I allergic hypersensitivity [9, 10]. The IgE which was now referred as allergic antibody or regenic antibody was primary immune component that can induce atopy or allergy among immune sensitive individuals [10].

2. Epidemiology

Prevalence of allergy or allergic disease fundamentally depends on various factors that govern the susceptibility of population to develop atopic condition. Predominantly genetic and environmental predisposition frames the basis for occurrence of allergy in an individual. Globally 8–10% of the population suffers from one or the other type of allergic disease which range from mild rhinatisis to sever asthma or anaphylaxis. At present a steady increase in the atopy was observed due to change in lifestyle, food habits and environment (**Table 1**). Several hypothesis and study provide evidence of genetic change in the population due to increased immune sensitivity and reduced antigen tolerance. Some report had identified an increase in allergic prevalence due to increase in perennial allergens exposure that happened by housing changes, increase in indoor environment with reduced ventilation and change in hygiene approach that decreased activation of immune regulatory control. The change in dietary habit, increased obesity, reduced physical exercise adds to hyper immune sensitization that increase atopy [11]. The reduced exposure to wild and native environmental antigens and high hygienic living standards expose fewer infections. It is reported that reduced infection at early

Allergy type	Allergic Prevalence and statistics
Allergic rhinatisis	• Worldwide allergic rhinatisis affects 10–30% of the population • Worldwide, sensitization (IgE antibodies) to foreign proteins in the environment is present up to 40% of the population • 7.5% adults and 9% children reported hay fever in an year
Asthma	• About 3 to 9% of the population suffer from allergic asthma. • Incidence had increased from 9.4 to about 18–20% in last five years in some European countries.
Drug allergy	• Worldwide adverse drug reactions may affect upto 10% of the world's population and affect 20% in hospitalized patients • Worldwide drugs may be responsible for up to 20% of fatalities due to anaphylaxis
Food allergy	• Around 8% of the population suffer from various food allergy • 6% at aged 0–2 years, 9% at aged 3–5 years, 8% at 6–18 yrs. and around 3–6% in adults. • 30–38% food allergic children have history of severe reaction and have multiple food allergies.
Insect allergy	• Worldwide, many allergic severe cases were reported with insect bite but lack systemic report. • In upto 50% of individuals who experience fatal reaction there is no documented history of previous systemic reaction.
Skin allergy	• Worldwide urticaria occurs with lifetime prevalence above 20% • Black children in US wwere likely to have had skin allergies (17%) than white (12%) or Asian (10%) children.
General allergy	• Worldwide, the rise in prevalence of allergic disease has continued in the industrialized world for more than 50 years • Worldwide sensitization rates to one or more common allergens among school children are currently approaching 40–50%.

Table 1.
Allergic conditions: Statistics and epidemiology [11, 12].

childhood age direct and polarize the developing immune system from Th1 type Th2, that makes the normal harmless antigen to a dangerous hypersensitive allergen that allow an increase in allergic disease.

Decreased rate of exposure to infection is not only increase immune sensitivity it also polarize immune response towards atopic mechanism. The hygienic hypothesis alone was unable to explain the increased prevalence of allergic disease. The recent evidences provide, importance of gastrointestinal microbial environment in development of atopy. Gut health, food and fecal-oral pathogens substantiate greater role to decide the risk for development of atopy. In some studies it was observed that an increased parasitic infection has been shown to associate with decreased prevalence of asthma [12]. This indicates the infection can exert the effect on Th1/Th2 regulation and it speculate that the dominance in Th1 response decrease atopy and Th2 link to IgE induction and elevates allergic diseases.

3. Signs and symptoms

Allergens are proteinaceous molecules that can be found in diverse substances in various forms. These can be inhaled, ingested and can also be exposed through contact to skin. Many allergens present in dust and pollens are airborne particles. These can be easily exposed through air and can induce symptoms in areas that contact

Affected Organ	Symptoms
Nose	Swelling of the nasal mucosa, runny nose and nasal irritation (Allergic rhinitisis)
Sinuses	Allergic sinusitis
Eyes	Redness and itching of the conjunctiva (Allergic conjunctivitis)
Airways	Sneezing, coughing, bronchoconstriction, wheezing and dyspnea. Sometimes outright attack of asthma, in severe cases the airway constructs due to swelling known as laryngeal edema.
Ears	Feeling of fullness, possibly pain and impaired hearing due to the lack of eusta chain tube drainage.
Skin	Rashes such as eczema and hives (Urticaria)
Gastrointestinal tract	Abdominal pain, bloating, vomiting and diarrhea.

Table 2.
Common symptoms of allergic reactions [13].

with allergen such as eyes, nose and lungs. Most common symptoms like hay fever also known as allergic rhinatisis cause runny nose, mucosal irritation and sneezing [13]. Some can also swollen eyes with itching and redness. Inhaled allergic particles can get into lungs and lead to bronchial hyper responsiveness. Particulate allergens inhaled through air can enter the lungs and cause asthmatic symptoms. Narrowing of the airways induce sneezing, coughing and through bronchoconstriction. The increased production of mucus thickens the airways and restricts the airflow to lungs that cause shortness of breath (dyspnea, bronchial hyper responsiveness and wheezing. Apart from these, the allergic reaction can be encounter through contact of allergens, ingestion through food and medications, insect bites and drug administration [13, 14]. Symptoms of contact and food allergy include itchy and swelling of the skin found during hives, gastrointestinal upset, edema, vomiting and diarrhea. Food allergies rarely cause respiratory (asthmatic) reactions, or rhinitis (**Table 2**).

Insect bites, drugs, medications and contact to insect stings with venom produce systemic allergic response affecting multiple organs. The exaggerated hyper immune response which is acute, life threatening and serious is called anaphylaxis and if not attended may induce death. The allergens effect multi organ system including digestive, respiratory, circulatory and cardiac system. Based on the severity and rate of sensitization the allergens can cause cutaneous reactions, edema, hypotension, bronchoconstriction, coma and sometime death [13]. Many allergenic substances such as latex can induce contact dermatitis and angioedema through skin rashes and irritations. The nature and source of allergens are diverse and they cause both cutaneous and systemic symptoms which range from very mild to severe depending on route of exposure and sensitization mechanism.

4. Causes

Causative agents for allergy or hypersensitivity reactions were allergens which present in many diverse sources in the environment. These allergy inducing factors have been placed in two categories (i) host factors and (ii) environmental factors [15]. The human host for the allergic reactions has different immune sensitivity due to various host factors that include gender, race, heredity and age. The genetic makeup and hereditary predisposition forms the basis for the increased incidence of allergic at certain population. However, there is insufficient evidence to explain the increase in allergic disorders with genetic factors alone. The change in food habits,

living style and environmental pollutions and microbial exposure make huge contribution in allergic incidence. There were major environmental factors that alter the immune sensitization to induce atopy. To mention, the exposed inhalant and ingested allergen levels, exposure to infection diseases during early childhood and dietary changes. The alteration in environment certainly induces immune modulation that favors the development of allergic disease in susceptible population. The major class of allergens that predominantly cause allergic reactions belong to one of the following categories.

4.1 Food proteins

- One of the most common food allergies is sensitivity to peanuts. Tree nuts, including pecans, pistachios, pine nuts, and walnuts, are another common allergen.

- Egg allergies affect one to two percent of children. Milk, from cows, goats, or sheep, is another common allergy-causing food. Other foods containing allergenic proteins include soy, wheat, fish, shellfish, fruits, vegetables, spices, synthetic and natural colors, chicken, and chemical additives.

4.2 Non-food proteins

- Pollens, animal dander and dust can trigger an IgE-mediated cutaneous, respiratory, and systemic reaction. There is high prevalence of these allergies in the general population.

- The latex on contact induces delayed type hypersensitivity reaction which appears dry, crusted lesions called contact dermatitis. The delayed allergic response lasts 48 to96 hours. Rubbing the allergic lesions aggravates the reaction and it can lead to ulcerations. For the same latex the anaphylaxis reaction may occur in some sensitive individuals.

4.3 Toxins interacting with proteins

- Some food toxins on contact may induce delayed type of hypersensitivity with red rashes, blisters and edema.

- Another non-food protein reaction, urushiol-induced contact dermatitis, originates after contact with poison ivy, poison oak or sumac.

4.4 Genetic basis

- Allergic disease can be hereditary and there is a strong genetic basis for the development of allergic diseases. It has been reported that among homozygous twins, same allergic diseases were find 70% of the time; and in about 40% of non-identical twins same allergy has been reported [16].

- The allergic individuals are reported to have children with similar allergic diseases and with severe symptoms. The immune sensitivity is observed more with allergic lineage compared to non allergic parents. It was observed that the most common allergic disease are familial. It seems that the likelihood of developing allergies is inherited and related to an irregularity in the immune system.

4.5 Hygiene hypothesis

- Allergy is the result of a disproportional activation of immunological response to a relatively non-harmful antigen. An allergen induces the production of regenic IgE antibody through polarization of Th2 mediated immune response from natural Th1 response [17].

- Regular microbial infection elicits Th1 cytokines mediated immune response, which produce neutralizing IgM and IgG against infection agents like bacteria and viruses. This also downregulate Th2 mediated immune response.

- The proposed mechanism of hygienic hypothesis states, insufficient activation of Th1 mediated cytokine can lead to over reactive hyper stimulation of Th2 cytokines which polarize the immune response that leads to allergic diseases.

- This depicts that an individual spending early life in a clean, sterile and hygienic environment had less exposure to true microbial pathogens. The deficit in the development and activation of immune system in early life makes it more sensitive. These create hyper activation and over stimulation of immune components against harmless antigens and turn them into dangerous allergens.

4.6 Other environmental factors

- Geographical variations, climatic conditions, diet habits and lifestyles have considerable association with the incidence of allergic diseases.

- Globally, differences have been exhibited with the number of allergic individuals with in a population that reports allergic diseases [17]. The incidence of allergy is increasing in developed and industrialized countries compared to those which are more traditional or agricultural developing countries. The rate of allergic diseases were higher in urban population versus rural populations which substantiate hygiene hypothesis.

5. Hypersensitivity or inflammatory allergic reactions

The damaging immunologic reactions are called as hypersensitivity reactions. Although, current understanding of allergic diseases has grown vastly since then, this classification system remains useful even today. The 4 types of hypersensitivity reactions are; immediate hypersensitivity (type I) reactions, cytotoxic (type II), Ag-Ab complex mediated (type III), and T cell-mediated (type IV) delayed hypersensitivity [11]. The IgE mediated acute and immediate hypersensitivity reaction is the dominant out of the four types and forms the basis of allergic reactions that trigger and responsible for all allergic symptoms.

5.1 Immediate type IgE-mediated hypersensitivity

IgE mediated hypersensitivity is acute and the inflammation occurs immediately (within 30 mins) after exposure to an antigen (allergen). Allergen specific IgE antibodies binds to the FcεRI receptors present on basophils and mast cells. Exposure to allergen, specifically recognize the FCεRI bound IgE and cross link the adjacent IgEs and activate the signal cascade to trigger mast cell or basophils degranulation. The energy dependent degranulation process releases the non-cytotoxic, preformed

inflammatory mediators that are responsible for induction of allergic symptoms within few minutes [18, 19]. Cellular degranulation releases two types of allergic mediators. Histamine, serotonin and tryptase are preformed mediators that are released by granular exocytosis. Other mediators like prostaglandins, leukotrienes were immediately synthesized de novo and released which act as pro-inflammatory signaling molecules. The two-phase mediators cause effect on glandular secretion, vascular permeability and smooth muscle contraction. These increase the immune cellular infiltration to the site of the inflammation within few minutes to hours and induce allergic reactions and referred as immediate hypersensitivity [20]. The allergic mediators, manifest and cause inflammation in many tissue sand organs (gastrointestinal system, respiratory system or generalized) either locally or systematically based on site of response (**Figure 1**). The symptoms range from mild atopic hay fever, rhinatisis, eczema to a chronic asthma and severe life threatening anaphylaxis.

5.2 Allergic sensitization and reaction

In an allergen sensitized subject with atopy, exposure of skin, nose, or airways to a single dose of allergen produces cutaneous wheal-and-flare reaction, sneezing and runny nose, or wheezing within minutes (**Table 3**), respectively [21, 22]. Depending upon duration and amount of allergen exposure the severity of allergic reaction may occur. Most IgE mediated hypersensitive reactions were immediate and express the clinical symptoms within an hour time. This may reach peak with late phase reactions in about 6 to 9 hours and after subsidizes slowly and resolves. In skin (**Figure 2**), the immediate reaction was characterized by itching and swelling and the late phase reaction by edematous erythoma which is read and forms blisters. In lungs it is noticed with nasal blockage, bronchial hyper responsiveness and further wheezing [22].

The type I hypersensitivity reaction has two stages, the earlier sensitization phase and the later effector phase. During the sensitization, the body encounter the antigen (allergen) for the first time and was recognized by the antigen presenting cells (APCs) as foreign antigen. The cells phagocytosed the antigen and present on the surface through MHC-II molecules. The naïve T helper lymphocyte recognize the presented antigen on MHC II and polarize the response towards Th2 by producing cytokines like interleukin −4 (IL-4) and interleukin −10 (IL-10). These interleukins interact with other type of lymphocytes known as B cells through specific receptors and instruct them through signal transaction that modulate gene transcription resulting in production of Immunoglobulin E (IgE) antibodies [23]. B cell turns into plasma cells and secrete large amount of IgE which circulates in the blood and on reaching basophils and mast cells, they recognize the specific receptors and binds the cell surface. The FcεR1 receptor has high affinity to IgE Fc portion and this referred as allergen sensitization. There was no observed inflammation or appearance of allergic symptoms during the sensitization phase.

5.3 Acute response

After the sensitization to allergen, the body had synthesized the IgE antibodies which occupied the surface of granulocytes; mast cell and basophils. The second exposure to the allergen, directly encounters the specific IgE antibodies present on the surface of allergic mast cells and basophils. The cross linking of two adjacent IgE molecules through multivalent allergen initiate the degranulation of these cells by activation of signaling cascade which results in exocytosis of preformed granular contents into the cellular space. The released histamine and other inflammatory chemical mediators (cytokines, interleukins, prostaglandins and leukotrienes)

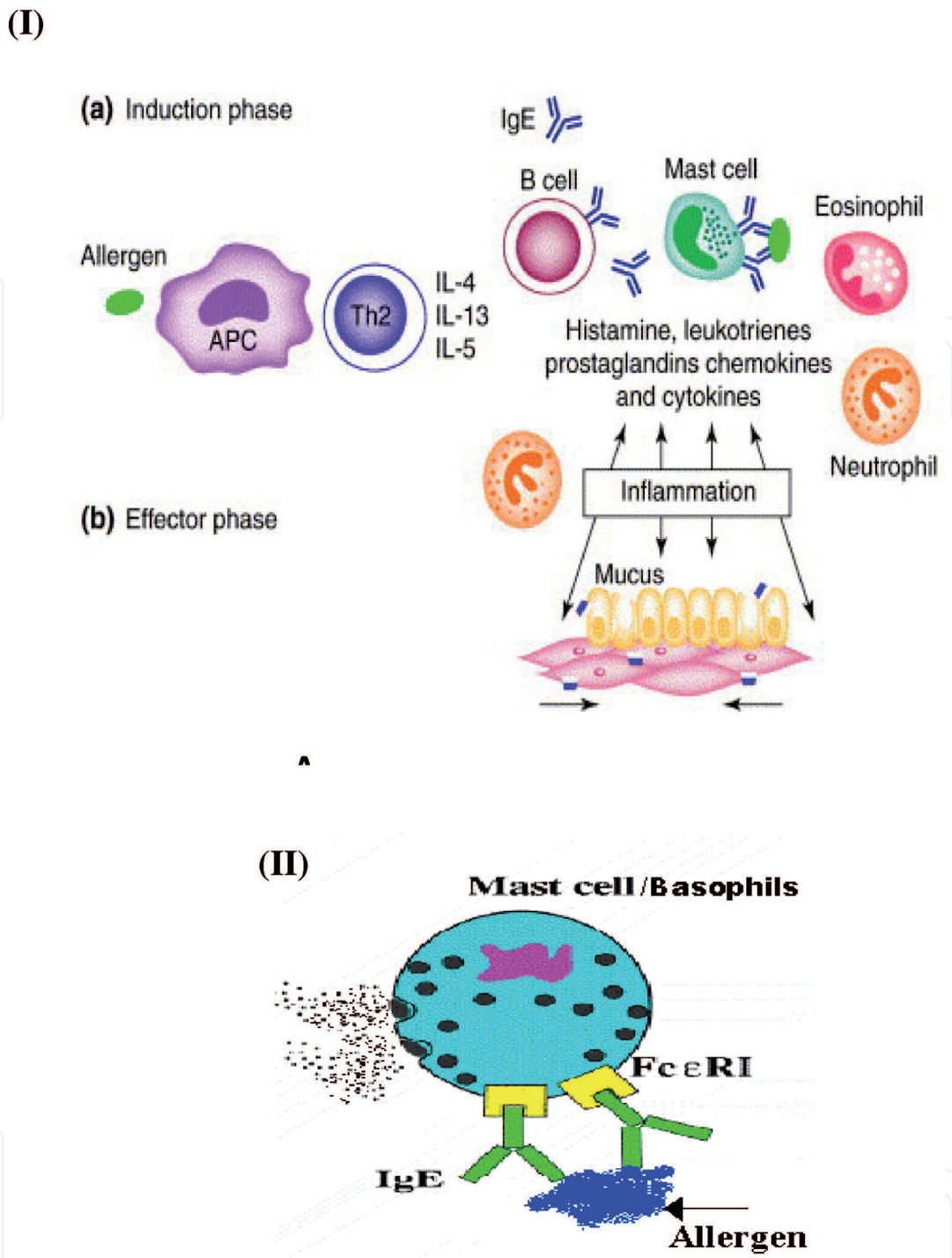


Figure 1.
*(I) Enhanced IgE dependent effector function and potential immunoregulatory function in mast cells or basophils after IgE-dependent upregulation of FcεRI surface expression (***Wedemeyer et al., 2000). (II). Mechanism that triggers the degranulation of mast cell or basophils. Crosslinkage can be mediated by: (A) the allergen that initiated the IgE response.*

induce systemic effects such as mucous secretion, smooth muscle contraction and vasodilatations [24, 25]. This results in the exacerbations of allergic symptoms like rhinorrhea, itchiness, dyspnea and anaphylaxis. Depending on the immune sensitivity of individual and mode and duration of exposure to allergen, the symptoms can be localized (organ or tissue specific); as asthma is localized to respiratory system and eczema to dermis or system-wide (classical anaphylaxis) where the whole body response with systemic effects.

Cell properties	Mast Cells	Basophils
Cell diameter	10–15 μm	5–7 μm
Nucleus	Bilobed or multi-lobed	Round or oval; eccentric
Cell surface contour	Smooth with occasional short, broad projections	Numerous narrow projections
Predominant localization	Connective tissues	Blood
Life span	Weeks or months	Days
Terminally differentiated	No	Yes
Major granule contents	Histamine, chondroitin sulphate, neutral proteinases, tryptase, heparin, TNFα	Histamine, chondroitin sulfate, neutral proteinases, major basic protein, Charcot-leyden protein
Mediators that are synthesized and released after degranulation	TNFα, PAF, LTC_4, PGD_2, IL-4	LTC_4

Abbreviations: TNF-tissue necrosis factor; PAF-platelet activating factor; LTC_4-leukotriene C_4; PGD_2-prostaglandin D_2.

Table 3.
Properties of human mast cells and basophils.

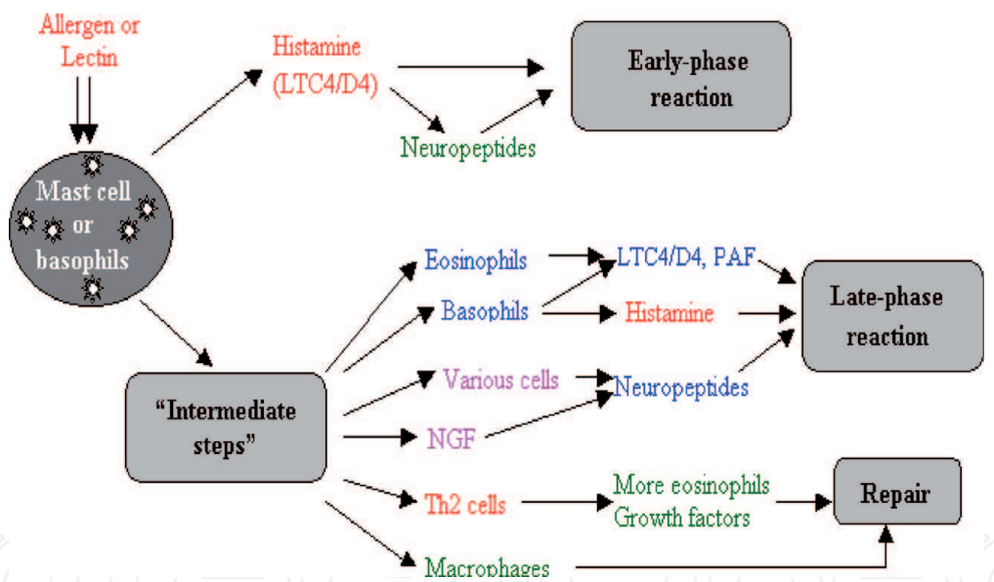


Figure 2.
The progression of allergic inflammation (e.g. in skin on testing), shows the schematic representation and components involved in the development of early-phase and late-phase reactions.

5.4 Late-phase response

Acute chemical mediators induce immediate allergic response. Once these acute response subsidies, often other leukocytes such as neutrophils, eosinophils and macrophages migrate to the site of inflammation to phagocytose and clear the damaged or inflamed tissues and cells. This results in allergic late phase response that usually lapse for 2 to 24 hours depending upon the site of inflammation and kind of allergic reaction [26]. Some time, the cytokines released from the degranulated mast cells play a role in inducing long term late phase allergic reactions that extend the symptoms for long duration. In case of allergic asthma, the late phase response

persist longer that results in bronchoconstriction, impairing the lung function and cause wheezing.

Acute and late phase allergic response and their specific symptomatic disease [25, 26].

a. Immediate (early-phase reaction)

- Gastrointestinal
- Hives, angioedema
- Rhinitis, asthma
- Anaphylaxis

b. Immediate (late-phase reaction)

- Eczema/atopic dermatitis
- Eosinophilic gastroenteritis
- Urticaria

A strict relationship between genetic, skin behavior, immunological factors and trigger events such as environmental, psychological, and infections may be elicited and considered to be involved in the development and severity of allergy.

6. Immune signaling mechanism of IgE-mediated hypersensitivity (allergy)

Mast cells and basophils degranulation process is considered to be a prime signaling event for the development of allergic disease. Cross bridging of mast cell bound IgE molecules by allergen is thought to initiate the activation through Fc epsilon R1 receptor bound G protein coupled GTPase. This in turn causes the activation of phospholipase C and release phosphatidyl inositol bisphosphate (PIP2) and diacyl glycerol (DAG) from membrane lipids. The Inositol triphosphate (IP3) produced induce the release of calcium (Ca^{2+}) from endoplasmic reticulum and increase intracellular calcium levels [27, 28]. Increased Ca^{2+} in cytoplasm activates certain enzymes such as myosin light chain kinase and calmodulin. Calcium combined with DAG activates protein kinase C (PKC), these intracellular events trigger the migration of preformed granules in mast cells and basophils to their periphery. The preformed granules fuse with plasma membrane and release granular contents through exocytosis process [29]. In the same time these events also promote generation of lipid mediators like prostaglandins and leukotrienes resulting in the induction of allergic inflammation (**Figure 3**).

6.1 Modes of activation of mast cells/basophils

Cross linking of adjacent IgE by an allergen induces activation and degranulation of granulocytes (mast cells and basophils). The binding of IgE to cell surface is possible due to the molecule that has ability to bind IgE with high affinity and keeps it attached to cells surface. The Fc epsilon R1 receptor has strong affinity to Fc portion

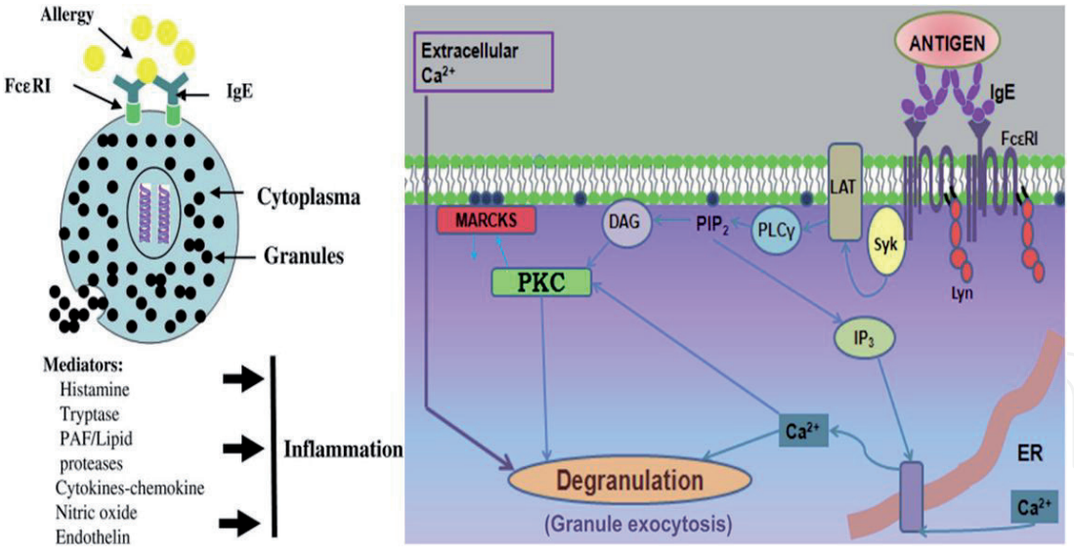


Figure 3.
Biochemical events of mast cell or basophil activation. There is a sequence of biochemical events following the bridging of cell bound IgE by an antigen. The climax of the whole process is the non-cytotoxic secretion of various chemical mediators such as histamine and other pharmacological substances.

of IgE which is made up of epsilon class of constant region. The allergen interacts with specific epitope to fragment of antigen binding (Fab) portion of the IgE. The allergen should be multivalent and with higher size so that it cross-link the two adjacent IgE to induce activation of mast cells for degranulation [30] to induce allergic reaction.

6.2 Cells and components of immune system involved in allergic reactions

The components of immune system are responsible for hyper immune response against allergen. Many cells and antibodies, cytokines are involved in various immune function that results in allergy or atopic reaction. The granulocytes like mast cells, basophils and eosinophils, lymphocytes such as Th2 cells and B cells play a prime role in development of allergic reactions. Inter molecular complex formed between allergen, IgE and FcεRI on the surface of mast cell or basophils are essential for activation of degranulation process to release mediators. That forms the basis for the immune activation to induce allergic diseases.

Atopic allergens: The allergens responsible for atopic diseases are derived principally from natural and airborne organic particles, especially plant pollens, fungal spores, and animal or insect debris, and to lesser extent from ingested food [31]. The ability of different pollens, molds, or foods to sensitize for IgE allergy varies, so that some of these environmental allergens are intrinsically more sensitizing than others, irrespective of the amount of exposure. Some lectins have been identified as allergens peanut agglutinin [32], soybean agglutinin [33] and wheat germ agglutinin [34] and are in general recognized as minor allergens in comparison with other common major allergens.

Mast cells and basophils: Mast cells are mononuclear cells with densely stained metachromatic granules while basophils are polymorphonuclear and are smaller in size (**Table 3**), approximately 5–7 microns versus 10–15 microns [35].

All the circulatory and connective tissues of the human system are susceptible for allergic response. It is due to the distribution of mast cells and basophils almost in all parts of the body. Mast cells are distributed essentially in all connective body parts and are often find adjacent to epidermal and microvasculature. The development, maturation and differentiation of mast cells influenced by cytokines and cellular growth factors like stem cell factor (c-kit ligand). Whereas basophils found

in circulatory system and through hematopoietic cell linage precursor cells which are differentiated and matured from myeloid progenitor cells into specialized granulocytes along with eosinophils [36]. The basophils are circulatory and move through the blood and represent around 1% of the leukocytes. Mast cells are static and are found adhered to connective tissues across the body. These two cells contain preformed allergic pro-inflammatory mediators in the cellular granules which on degranulation cause allergic inflammations.

FcεRI and immunoglobulin E (IgE): The mast cells and basophils have high affinity receptors which has specificity to bind Fc portion of IgE antibody called Fc epsilon R1. This consist of four subunits ($\alpha\beta\gamma_2$) which represent one extracellular alpha (α) domain which is need for IgE binding. The beta (β) subunit is a trans-membrane domain which spans the plasma membrane and the gamma (γ) subunits present as intrinsic membrane protein and are responsible for signal transaction [37]. The FcεRI binds IgE with high affinity (10^9 to 10^{10}/mole) and that is important phenomena for allergic response and development of allergy.

The Immunoglobulin (IgE) is referred as regenic antibody and it play a important role in allergic hypersensitivity reaction. It is a glycoprotein and belongs to one of the class of antibody with molecular weight of 190 kD and has 12% carbohydrate by weight which is present in the heavy chain at Fc portion. The serum concentration of IgE ranges from ng/mL to μg/mL with an atopic serum half-life of 2–3 days [38]. IgE recognizes mast cells and basophils through FcεR1 receptor and gets inactivated by heating at 56°C for at least 30 min. The cytokines IL-4, IL-13 and IL-10 induce synthesis of IgE by plasma cells. The detection allergen-specific IgE antibodies in the individual sera are considered as prominent diagnostic parameter and represent the allergic sensitivity.

Th2 or CD4+ cells: T helper cells are the immune responsive cells that have special interest in humoral immunity through induction of antibody production. The atopic individuals have high circulating allergen specific IgE antibodies. TH cells are circulatory lymphocytes which are characterized as CD4+ cells. There are two subsets of T-helper cells based on the antigen recognition and cytokine secretion. The Th1 cytokines direct the B cell to induce IgM and IgG. In contrast the Th2 type of response produce cytokines IL-4, IL-5, IL-10 and IL-13 [39, 40] these direct the B lymphocytes (B-cells) to produce allergic immunoglobulin IgE. This differentiates the function of Th2 from Th1-type cytokine (IFNγ and IL-2) response. The immunopathological hallmark of allergic disease is the infiltration of affected tissues by cells with a Th2-type cytokine profile [41, 42] that increase IgE production and allergic reactions.

Mediators released by mast cells and basophils: The pathophysiology of allergic reaction is exhibited with the inflammatory symptoms which are initiated by various allergic mediators released through the degranulation of mast cells and basophils. These cells synthesize and prestore granular mediators and instantly generate the lipid mediators [41]. The granular preformed mediators are rapidly released following activation; these represents; histamine, tryptase, serotonin, and other inflammatory cytokines. The others are synthesized de nova following mast cell activation and are release slowly. These include prostaglandin and leukotrienes that are metabolites of membrane lipids [43]. The complete list of mediators from mast cell and basophils are quite extensive and are undoubtedly account for multiple possible pathological consequences of allergic reactions.

7. *In vivo* and *in vitro* diagnosis of allergic reactions

Allergic disease needs diagnosis and prognosis for constant monitoring and treatment of symptoms. When allergic reaction is suspected in an individual based

on the symptoms, the systemic diagnosis is essential for detection of causative allergen. A detailed case history of exposure and duration for appearance of symptoms with possible repetitive incidence will provide an idea of the type of allergy. The allergy diagnosis varies form case to case and it needs extensive inspection to identify the possible causative agent; the allergen. Based on the case history and information some can be identified rapidly however, the complex, obscure cases need repetitive interceptions to find the allergen. History, physical examination, onset of disease, duration of symptoms, time for resolving symptoms and kind and organ affected are required for initial assessment. This is followed by specific laboratory test which are required for the diagnosis and conformation of the onset of allergic reaction like eosinophils counts, total serum IgE levels, serum histamine levels and related medical examinations (**Figure 4**). It is important to correlate the detailed case history with the laboratory tests and that provide evidence of allergy [44].

Allergic disease is often episodic and that depends on the exposure to allergen to which the individual is sensitive. The case specific objective signs of the allergic symptoms can only be identified during the allergic incidence with proper physical examination. The observed symptoms have to correlate with subjective signs provided in the case history for the proper identification of allergic disease. Allergy diagnosis requires thorough examination to rule out other illness of the subject. A variety of *in vitro* and in vivo laboratory tests are available to supplement the history and physical examinations. There are qualitative and quantitative tests that predict the allergic reaction using sampling fluids and immune cellular responses through immunochemical techniques.

Many of the allergic symptoms shares common pathological behaviors with other illness and that need confirmative cross examination before planning

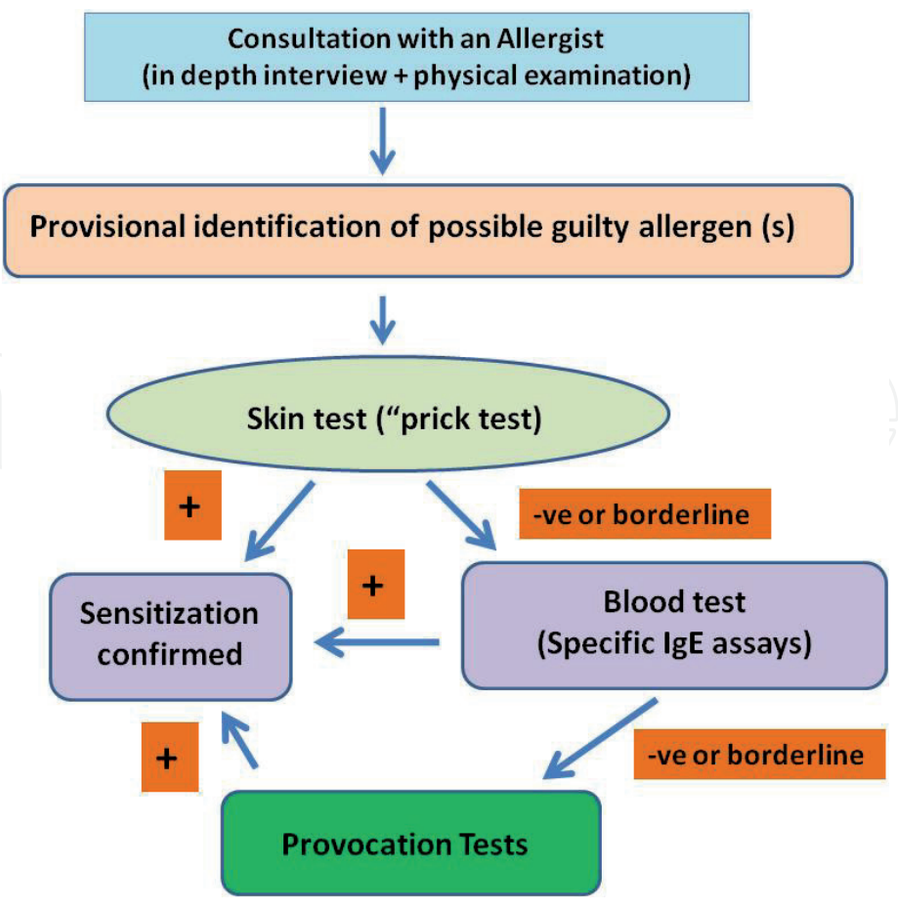


Figure 4.
Schematic diagram showing the identification and assessment of atopic status using clinical history, physical examination and laboratory tests.

treatment regime. For instance, the viral flu induce rhinitis and nasal conjunction which also the same with pollen or dust allergy. The food toxicity or certain diet can cause gastrointestinal upset which is quite same as that of food allergy. The common cold or viral flu airway infections induce bronchoconstriction that results in wheezing which exactly mimics the symptoms of allergic asthma. Henceforth, careful diagnosis is a prerequisite for the identification and treatment of allergic disorders.

7.1 Skin testing

Skin testing is the in vivo mimicking of allergic reaction that demonstrates the allergic sensitivity to specific allergen. The skin testing predict and confirm the presence of allergen specific IgE antibodies in the individual. These were most preferred over the blood testing during allergy diagnosis. Skin testing is also known as prick test and puncture testing. The most two types of allergic tests, which are commonly in use at clinical level for diagnosis are skin prick test (SPT) and prick by prick test (PPT). In the earlier one the suspected allergen sample was placed and was pricked with small needle and allowed for erythoma formation for 30 mins [45]. In later the sample was pricked initially with the needle and then the same was pricked to skin and the pricked area was observed for the development of reaction. The histamine was used as positive control and PBs as negative. The wheel and flare diameter was measured and was compared for the prediction of positive allergic reaction. Some time a similar intradermal test on the skin can also be used for assessment of allergic reaction to certain medication and drugs. The skin testing is widely used in allergic clinic with standard available panel of allergen samples to identify causative allergen and provide proper treatment for allergic symptoms.

7.2 Blood testing

Blood is the primary biological sample for diagnosis of illness in clinics. The blood sample contains various immune components that are related to allergic reactions [46]. Various blood allergy testing parameters and methods are available which can detect and diagnose allergy and identify allergens. The most often used are serum total IgE level; that estimate the IgE content in the subject serum per mL. The other is allergen specific IgE level which predicts the confirmative diagnosis of elicitor. Both are measured through radiometric (RAST) or colorimetric (ELISA) immune assays.

7.3 Other methods of testing

Allergen challenge testing: During allergen challenge test, the subject was monitored and the whole procedure was done in the presence of a expert clinician. In this, a small amount of suspected allergen was introduced to subject through oral or other routes and appearance of allergic reactions were monitored. This test provides confirmative evidence and identifies the causative allergen.

Elimination/Challenge tests: In this procedure, subject was instructed to avid coming in contact with allergen prior to test. During asymptomatic time, few suspected allergens were added with food or medicines and were given to subject and the appearance of allergic symptoms was recorded. Based on this a true allergen can be identified for planning treatment.

Patch testing: Patch testing is much in practice for identifying the contact dermatisis or delayed type of allergic reactions. In this case an allergen is placed on the patch and that is stick to the back of the subject. The symptoms will be observed after 24 hrs for the appearance of symptoms.

Unreliable tests: There are some allergic tests which are not considered for practice by International allergy council and those does not provide proper scientific evidence to identify allergy or allergens. Some of them are cytotoxicity testing, provocative tests, subcutaneous or sublingual testing. In future with substantiate research and technical improvement can be used for diagnosis of some of the allergic diseases.

8. Treatments

Advancement in allergy research had made enormous contribution for the treatment of mild to severe allergic diseases. There are many treatments available to treat various symptoms of allergic diseases and several medications are available and are effectively treat and manage atopic conditions. For anaphylaxis epinephrine shots are available which can be carried with the patients and for others, anti histamines and anti inflammatory drugs are routinely recommended to cope up with the symptoms [46, 47]. Depending on the source of allergens various diagnosis methods have been devised and based on those therapeutic methods have evolved to address problems associated with allergic reactions. The following are some commonly followed approaches to treat allergic diseases.

8.1 Avoidance

Avoiding exposure to allergen is the best and valid recommendation for limiting allergic reactions in sensitized individuals. It is one of the simple and traditional approach for treatment of allergy. However, it becomes difficult to avoid certain environmental allergen which are dispersed in the air and can be easily inhaled without any notice or have any control. In such cases the avoidance becomes difficult and need alternative therapeutic methods to address problems.

8.2 Pharmacotherapy

When allergen tracking and avoidance is not possible and exposure to allergen becomes inevitable then the pharmacotherapy can provide protection to ease of allergen induced symptoms. Many drugs have been designed which act as antagonistic to the allergic mediators and block their actions. Some common drug targets are anti histamines and anti leukotrienes which prevent the action of inflammatory mediators and block the appearance of allergic symptoms [46]. The FDA approve drugs that include antihistamines, adrenaline (epinephrine), theophylline and Glucocorticosteroids which acts primarily as anti inflammatory molecules. The anti-leukotrienes such as Montelukast (Singulair) or Zafirlukast (Accolate) are in common use along with mast cell stabilizer, decongestants and eosinophil chemotoxins are used as drugs to prevent and monitor acute and chronic allergic disorders [47].

8.3 Immunotherapy

In case the allergen has been identified and sensitization process is well established with the subject, in that case the desensitization or hyposensitization is adopted as treatment to vaccinate the allergic subject with small doses of allergen over a long period. During this the subject tolerates the allergen dose and reduces its sensitivity and increase IgG production over IgE that avoid allergic reactions. Studies have demonstrated the efficiency of this type of immune therapy and the long term practice had shown preventive effect of immunotherapy in reducing the development of atopy. A second form of immunotherapy involves the intravenous

injection of monoclonal anti-IgE antibodies. These bind to free and B-cell associated IgE; signaling and induce their destruction [48]. A third type, Sublingual immunotherapy, is an orally-administered therapy that takes advantage of oral immune tolerance to non-pathogenic antigens such as foods and resident bacteria [49]. Allergen shot treatment may appear as future closest therapy to cure for allergy. This therapy requires close monitoring and long-term commitment for the efficient treatment by the subject.

8.4 Unproven and ineffective treatments

In some of the recent studies, an enzyme potentiated desensitization (EPD), experimental treatment has been tried and had not produced any promising results. Many hypoallergic food preparation now follow the same strategy. The treatment approach but failed to convince and had not accepted as effective [50]. EPD uses dilutions of allergen with an enzyme, beta-glucuronidase, that changes the allergen nature and polarize T-regulatory lymphocytes which favor desensitization, or down-regulate IgE induction and prevent allergic reactions.

9. Conclusion

Allergies may cause symptoms ranging from mild abdominal discomfort to life-threatening anaphylaxis. Avoiding offending allergen exposure may not be easy if the causative is uncommon or not identified. However, successful avoidance of exposure to allergens may reduce the symptoms in the allergic individuals. Presently most of the treatment and diagnosis methods available are only to reduce the symptoms but the medications methods will not provide any permanent relief from the allergic diseases. New studies and investigations are in progress from the researcher to provide solutions for the allergy treatment. New invention in the field of immunology provides methods and techniques to find new horizons to understand allergic disorders. Since allergies are associated with disorder of immune function, scientists working to find therapy will benefit from new developments in immunology research. Understanding the regulatory mechanism of Allergic disease and designing suitable method for rapid allergen detection and revisiting for the success of immunotherapy and pharmacotherapy will advance the allergy research and provide suitable bench to treat and prevent allergies. The advances in molecular biology that lead to understanding of immune molecular networks will certainly provide promising hope for the preventive and therapeutic solution to allergies in near future.

Conflict of interest

The author declare no conflict of interest.

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