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Briefly about Immediate Hypersensitivity

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ABSTRACT

Daily observation of the variations of allergenic pollen presence in the atmosphere holds significant importance for medical professionals and individuals prone to specific pollen allergies. Information regarding daily fluctuations in pollen levels is crucial for evaluating allergen exposure and is shown in the form of an allergy traffic signal and a forecast for pollen over a determined timeframe. An allergy traffic signal serves as a daily update concerning the quantity of pollen grains present in the air of a certain region.

Keywords: Immediate Hypersensitivity, Antigens, Pathophysiology, Allergic Reaction, Health

INTRODUCTION

Almost a hundred years earlier, Portier and Richet reported an unexpected immune response while attempting to increase dogs' resistance to the toxin from sea anemones by administering the toxin to them [1]. Instead of providing the anticipated defense, a number of animals succumbed within moments to respiratory failure after being injected weeks later with tiny doses of the same toxin. To characterize this occurrence, they introduced the term anaphylaxis, which translates to 'against protection'. Further research found that such reactions necessitated prior contact with the foreign agent and required several weeks for the response to appear. They also discovered that sensitivity to anaphylaxis could be transmitted from one animal to another through the injection or infusion of a serum-derived component, which was initially termed reagin. Not long after, studies in humans showed that injecting serum from a person sensitive to anaphylaxis into someone who was not sensitive (passive transfer) led to localized sensitization (inducement of a wheal-and-flare response) at the skin site of the recipient. This passive transfer experiment, initially conducted by Prausnitz and Kustner and now known as the PK test or reaction, first indicated that allergic hypersensitivity was due to a serum protein. This type of reaction was categorized as immediate hypersensitivity because of its quick onset. However, the identity of reagin remained unresolved until the 1960s, when Ishizaka and Ishizaka successfully purified and characterized immunoglobulin E (IgE), confirming that reagin was an antibody molecule. It has since become evident that the presence of specific IgE antibodies is the most crucial factor in determining allergic sensitivity. The production or transfer of IgE antibodies prepares the recipient for both immediate allergic responses and later reactions. Currently, the term allergen is applied to a protein,

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generally a harmless antigen, that triggers the production of IgE antibodies. Allergy encompasses the clinical symptoms caused by IgE-dependent immune reactions, while atopy refers to the hereditary predisposition to produce IgE responses.

Immediate hypersensitivity, also known as Type I hypersensitivity, is defined as a hypersensitivity reaction where exposure to an antigen (allergen) produces an immediate or almost immediate reaction. This reaction is characterized by the rapid release of mediators from mast cells and basophils, leading to symptoms such as itching, hives, and in severe cases, anaphylaxis.

Antigens

For a substance to elicit an immune response, it needs to be introduced to the immune system correctly [1]. The properties of the antigen can influence whether the immune system will produce a specific class of antibodies or if any antibody response will occur at all. For instance, certain antigens that depend on T cells, like polysaccharides, generally do not lead to the creation of IgE antibodies. Therefore, the type of antigen plays a crucial role in determining how the host will respond. Although a thorough understanding of the factors that classify an antigen as an allergen remains elusive, several overarching concepts can be outlined. The most frequent allergens, such as pollen, dust mites, and pet dander, which lead to respiratory issues in people, are proteins weighing between 10 and 20 kDa that are very soluble in water and can function as complete allergens. Repeated exposures at low levels, often in the submicrogram range while diffusing through mucosal surfaces, are particularly effective in triggering an IgE response. Additionally, the characteristics of the host are significant in the formation of IgE responses, as approximately 20% of individuals exposed, particularly those with an atopic disposition, will produce IgE antibodies. Notably, common airborne allergens, like dust mites (specifically Der p 1, a type of cysteine protease), exhibit enzymatic activity in their natural form. Nevertheless, a definitive correlation between the functional characteristics of an allergen and its ability to generate immune responses in susceptible individuals has not been established. Identifying shared structural traits among known allergenic proteins to predict the immunogenicity of new peptides has also posed challenges. However, the ability of a protein to cross-react with pre-existing IgE antibodies against another allergen has been demonstrated to depend on structural congruencies, as seen in the phenomenon of pollen-food allergy syndrome. In this scenario, the consumption of unstable proteins found in raw apples can cross-react with birch pollen-specific IgE present in an individual, resulting in oral mucosal itching. Rapidly cooking the apple deactivates the cross-reactive allergen, thereby alleviating the symptoms.

Antibody Response

IgE is mainly produced in the perimucosal lymphoid tissues found in the respiratory and gastrointestinal systems [2]. In less developed nations, the primary triggers for IgE production are parasites, particularly nematodes. The amounts of circulating IgE that are considered normal in areas with endemic parasitism are significantly higher, by two to three orders of magnitude, than in Western countries. The large majority of allergens, which are either swallowed or inhaled, activate the same perimucosal cells. In the perimucosal regions, only B lymphocytes featuring membrane-bound IgE are able to transform into IgE-producing plasma cells. This subset of IgE-expressing B cells constitutes only a small portion of the total B cell population in the submucosa but is disproportionately represented in the perimucosal lymphoid tissues in comparison to other lymphoid areas.

During the initial immune response to either an allergen or a parasite, most of the IgE produced

seems to have a weak attraction. The alterations that take place following a subsequent exposure promote the production of IgE with increased affinity, likely due to somatic hypermutations and cell death. The growth of clones that have a higher affinity might explain why allergic responses rarely occur following the initial exposure to an allergen. If an immediate hypersensitivity reaction appears to arise after what appears to be the first contact with a specific allergen, it is important to consider the chance of cross-reactivity between a material that the person was previously allergic to and the substance triggering the allergic response. These cross-reactions generally result from molecular similarities and can be rather unpredictable.

Repeated encounters with parasites or allergens can trigger the development of memory cells, and the amount of high-affinity antigen-targeted IgE in circulation will also rise. In cases of individuals experiencing significant seasonal allergies due to pollen, the amount of antigen-specific IgE may reach as high as 50% of the entire IgE level.

IgE

When a large number of people are subjected to the same antigen via the same method, only a small fraction will produce IgE antibodies, resulting in just a small group being susceptible to allergic reactions during subsequent exposures [1]. Additionally, there is a phenomenon known as asymptomatic sensitization; for instance, while 8% of the population tests positive for a peanut skin test, fewer than 1% experience actual peanut allergy symptoms. The reason why only a small portion of individuals generates antigen-specific

IgE and develops allergies is still unclear. For these reactions to manifest, a specific sequence of immune reactions must occur. Initially, an allergen needs to penetrate an epithelial barrier. The epithelium can relay signals that promote allergic sensitization. Subsequently, the allergen is absorbed by antigen-presenting cells, like dendritic cells, and after undergoing processing, is shown to T lymphocytes. Recent research has revealed that thymic stromal lymphopoietin, a cytokine derived from epithelial cells, plays a crucial role in kickstarting allergic inflammation by influencing dendritic cells to encourage T helper (Th2) cell inflammation. For an IgE antibody response to be triggered, these processes must take place alongside specific cytokines, primarily interleukin (IL)-4, produced by T lymphocytes and other types of cells. IL-4 is essential for both the creation of T lymphocytes (Th2 cells) and for the subsequent activation of B lymphocytes by these Th2 cells. If this activation happens in conjunction with IL-4 and IL-13, B cells undergo immunoglobulin gene class switching, ultimately differentiating fully into plasma cells that generate antigen-specific IgE antibodies. The process of producing IgE-secreting plasma cells is also enhanced by the interaction between the CD40 ligand on the Th2 cell and CD40 on the B cell. Once plasma cells accomplish these processes, they produce identical antigen-specific IgE for their entire lifespan. This IgE release by the plasma cells commonly occurs at mucosal areas, but it is also possible in lymph nodes and various lymphoid tissues. Among the different immunoglobulins, IgE exhibits several distinctive characteristics. For one, unlike IgG, IgE is unable to pass through the placenta and does not interact with complement. Furthermore, IgE has an additional section in its heavy chain that allows it to specifically attach to IgE receptors. IgE is also extensively glycosylated, although the biological significance of this property remains unclear. Lastly, while elevated levels of IgE are associated with allergic conditions, high IgE concentrations can also be present in other illnesses, such as helminth infections; conversely, low serum IgE levels can be found in both allergic and nonallergic individuals.

Pathophysiology

The primary effects of allergen cross-linking with IgE attached to the membranes of mast cells and basophils include the activation of these cells, their degranulation, and the release of inflammatory mediators [1]. The array of symptoms that occur with immediate hypersensitivity starts shortly after exposure to the allergen and is associated with the discharge of pre-existing and quickly produced mediators from mast cells and basophils. This swift reaction is referred to as the early-phase response. Depending on the location and conditions of allergen contact, the intensity of symptoms can vary, from sneezing and runny nose following pollen inhalation (as observed in allergic rhinitis) to severe anaphylaxis after systemic allergen contact (for instance, due to drugs, insect stings, or foods), which may even result in death. The mediators involved are commonly categorized according to their release mechanism and consist of those that are preformed in granules and liberated through exocytosis (like histamine and tryptase), those that are synthesized swiftly from membrane lipids (such as prostaglandins, leukotrienes, and platelet-activating factor), and finally, cytokines that are produced and released over a span of hours.

A well-known example of immediate hypersensitivity is the wheal-and-flare reaction seen in the skin when exposed to an allergen. The diagnostic approach involving skin testing relies on the capability of IgE-sensitized skin mast cells to react to certain allergens within minutes by releasing vasoactive mediators (like histamine) at the location where the allergen is applied, illustrating the immediate or early-phase response. When histamine is injected into the skin, it initially generates vascular leakage resulting in a swollen area known as a “wheal” due to local edema. This is followed by a nerve reflex that causes increased blood vessel dilation and permeability around the edge of the wheal, producing the redness known as the “flare” response.

After exposure to allergens, acute allergic responses in sensitive individuals can diminish within a few minutes, but they may be succeeded hours later by a secondary inflammatory reaction known as the late-phase response. Around 50% of individuals who experience allergen exposure in the skin, nasal passages, or lungs exhibit a reaction that occurs 4 to 12 hours after the initial exposure. This late-phase response is marked by the return of clinical symptoms along with the local arrival of circulating white blood cells such as eosinophils, lymphocytes, and basophils into the affected area, responding to the substances released during the earlier phase. The mediators released by eosinophils during this late phase play a role in causing tissue damage. In the skin, this response appears as the reemergence of widespread swelling and redness, whereas in the airways, nasal obstruction or bronchial constriction returns. Many characteristics of the late-phase reaction resemble those seen in chronic allergic conditions in humans, including: (i) their reliance on IgE, (ii) the pattern of immune cell presence (particularly eosinophils, basophils, and Th2 lymphocytes), (iii) the link with temporary airway obstruction and elevated airway sensitivity (common features of asthma), (iv) the development of fluid buildup and excessive mucus production, and (v) the types and amounts of inflammatory substances released (e.g., histamine, leukotrienes, cytokines, and chemokines). The late-phase allergic inflammation driven by IgE in humans aids in understanding how ongoing or recurrent exposure to allergens leads to increased

sensitivity ("priming") and the persistent symptoms of allergic rhinitis and asthma.

In allergic conditions, there is a significant accumulation of eosinophils in local tissues. This is likely due to a mix of factors that promote the adhesion of eosinophils, such as IL-4 and IL-13, which stimulate the endothelial adhesion molecule VCAM-1, recognized by the integrin very late activation antigen-4 (VLA-4) on eosinophils. Eosinophils preferentially migrate in response to chemokines from the C-C chemokine family (like eotaxins and MCP-4), produced by tissue-resident cells, including those in the respiratory epithelium. Chemokines bind to specific receptors, for instance, CCR3, a chemokine receptor that selectively attracts eotaxins, which is strongly expressed on eosinophils, basophils, and mast cells. Along with cytokines that enhance eosinophil survival (e.g., IL-5, granulocyte macrophage colony-stimulating factor [GM-CSF]), eosinophilic infiltrates are formed. Each of these molecules presents a potential target for new drug development aimed at treating allergic conditions.

Allergic Reaction

Hypersensitivity reactions are immune responses triggered by allergens, which typically do not provoke adverse reactions in most people [3]. Those classified as "atopic" develop immune responses to these allergens, resulting in symptoms such as hay fever or wheezing from pollen, or nausea and lip swelling after consuming specific foods. Such reactions arise from initial sensitizing exposures and subsequent reexposure to the allergen, and are generally categorized into immediate or delayed hypersensitivity reactions. Below are two mechanisms that describe immediate hypersensitivity reactions involved in allergies, including the severe and potentially life-threatening systemic allergic responses that occur rapidly, known as anaphylaxis.

Common reactions following vaccination can include both local and generalized symptoms such as fever [4]. These responses do not prevent individuals from receiving future vaccinations. Reactions at the injection site are usually mild and may involve swelling, redness, and tenderness. A delayed hypersensitivity reaction to a vaccine ingredient, like neomycin, thimerosal, or aluminum, might result in a temporary small lump at the site of injection. Individuals with allergic contact dermatitis regarding neomycin can still receive vaccines containing neomycin; however, they may experience a brief, small bump at the injection site. Likewise, people allergic to thimerosal could have substantial local reactions to vaccines that include thimerosal, although most individuals will not show any symptoms. Vaccines with aluminum may rarely cause lasting nodules at the injection area. Instances of severe allergic reactions to vaccines are extremely uncommon. The evaluated risk of an allergic reaction is approximately 1.31 cases per million vaccine doses. Reactions attributed to vaccines are seldom due to the vaccine itself but are typically the result of ingredients and additives. Components in vaccines may include inactive ingredients like gelatin, egg protein, formaldehyde, thimerosal, or neomycin, which can trigger specific IgE-mediated responses. Excipients are included in vaccines to enhance factors like stability, solubility, absorption, and to minimize microbial growth. Common excipients found in vaccines and injectable medications, such as polyethylene glycol and polysorbate, aid in improving water solubility. Excipients are a significant contributor to specific IgE-mediated and immediate reactions from vaccines.

Gelatin is included in a variety of vaccines as a stabilizing agent. Vaccines like MMR, varicella, and Japanese encephalitis contain gelatin. It has often been identified as the cause of anaphylactic reactions linked to these vaccines. If a patient has a history of allergies to gelatin-containing foods, such as gummy candies or jelly, further assessment should be conducted before administering vaccines with gelatin. A lack of gelatin consumption in the past does not eliminate the possibility of a gelatin allergy regarding vaccines, as they are administered through different routes. The gelatin utilized in vaccines is sourced either from bovine or porcine origins, leading to significant cross-reactivity. Individuals with sensitivities to beef or pork may also develop sensitivity to gelatin, which may increase their risk of having reactions to these vaccines. Egg protein can be found in MMR and influenza vaccines; however, having an allergy to eggs does not prohibit individuals from receiving these vaccines. The HepB vaccine and the quadrivalent human papillomavirus vaccine (HPV4) contain trace amounts of yeast protein, but adverse reactions are quite rare. Patients with latex allergies face risks when receiving vaccines with vial stoppers made from dry natural rubber latex, although the potential risk is minimal. Even though such reactions are infrequent, those with a history of immediate hypersensitivity reactions to substances like gelatin, yeast, latex, thimerosal, or neomycin should undergo skin testing before vaccination.

Airway Obstruction

Airway obstruction in asthma sufferers who are sensitive to allergens develops gradually over several hours following exposure to the allergen and occurs in two separate phases [5]. The initial phase is characterized by airway narrowing, peaking roughly 30 minutes after encountering the allergen, with full relief typically occurring around 2 hours later. Roughly half of individuals with asthma exhibit a secondary phase of obstruction, re-emerging 4 to 6 hours post allergen exposure. This late-phase reaction is associated with the infiltration of the airways by Th2 cells and eosinophils.

The resulting bronchoconstriction can be reversed with bronchodilators.

Airway hyperresponsiveness is influenced by the nervous system, specifically through the parasympathetic pathways like the vagus nerve, and can be completely reversed by bronchodilators that either block muscarinic parasympathetic signals directly (e.g., ipratropium bromide) or activate β2-adrenergic receptors that oppose muscarinic bronchoconstrictive actions. Airway hyperresponsiveness is identified as intermittent bronchoconstriction that is alleviated by bronchodilators. Thus, late-phase responses following exposure to an antigen indicate a specific type of airway hyperresponsiveness.

Research across various species has shown that airway hyperresponsiveness associated with allergic inflammation fundamentally relies on Th2 cells and specialized type 2 innate lymphoid cells (ILC2) that have been specifically attracted to the lungs. Additionally, it is well understood now that IL-13 is the primary cytokine from Th2 cells and ILC2 that facilitates airway hyperresponsiveness by targeting airway cells, such as smooth muscle cells, that possess the IL-13 receptor. However, IL-13 itself does not directly cause bronchoconstriction. In individuals with asthma, bronchoconstriction can be triggered by multiple external factors apart from allergens, including changes in temperature and humidity, strong odors, and irritating aerosols, as well as internal triggers like intense emotions, showing little direct relation to immune mechanisms. Therefore, rather than being the direct cause of airway obstruction, IL-13 lays the groundwork for a broad response to various agents leading to bronchoconstriction mediated by the nervous system.

A different and more deceptive type of airway blockage is the physical obstruction caused by the buildup of mucus and fibrin clots in the airways, forming stubborn plugs, a condition referred to as plastic bronchitis. Airway blockages resulting from plastic bronchitis do not respond quickly to bronchodilators or other medications and are therefore a leading cause of fatal asthma attacks due to suffocation.

IL-4 and IL-13 also facilitate the recruitment and maintenance of allergic effector cells within the airway epithelium and submucosal layers, which allow for swift reactions to inhaled allergens. By engaging with a receptor that includes the alpha subunit of the IL-4 receptor (IL-4Rα), both IL-4 and IL-13 signal fundamental airway cells, such as epithelial cells, to produce a limited range of attractants that encourage the movement of allergic cells with specific binding receptors from the lung and airway blood supply.

Diagnostic Test

The total IgE levels, even in those with allergies, tend to be very low and usually go undetected by most standard tests measuring IgG, IgA, and IgM [2]. The amount of specific IgE against any particular allergen constitutes only a tiny portion of the total IgE. Measuring these minimal concentrations became feasible due to advancements in highly sensitive immunoassays.

The paper disc radioimmunosorbent assay was among the initial solid-phase radioimmunoassays introduced for use in diagnostic medicine. This test quantifies total serum immunoglobulin E (IgE). In summary, a serum specimen is introduced onto a small segment of adsorbent paper that features covalently attached anti-IgE antibodies. The bound antibodies trap IgE, and subsequently, 125I-labeled anti-IgE antibodies are introduced, which interact with the IgE anchored on the paper. The radioactivity measured in this solid form correlates directly with the IgE concentration present in the sampled serum. Later advancements resulted in sensitive enzyme immunoassays and quantitative fluorescence assays that can also accurately measure total IgE concentrations without utilizing radiolabeled substances.

IgE assay outcomes are reported in nanograms per milliliter (ng/mL, where 1 ng equals 10-6 mg) or in International Units (where 1 IU equals 2.5 ng/mL); a level of 180 IU/mL is thought to be the maximum normal limit for healthy adults. Those suffering from allergies typically exhibit higher IgE levels. However, some individuals without symptoms may also show increased IgE concentrations. Consequently, diagnosing immediate hypersensitivity should not rely solely on elevated IgE levels.

CONCLUSION

Allergic conditions rank among the most prevalent illnesses today. Allergy, or hypersensitivity, represents an atypical and exaggerated response of the immune system to various generally non-harmful environmental agents. Various biological particles carried through the air are the primary contributors to respiratory ailments. Pollen is classified as the strongest natural aeroallergen and the most frequent cause of respiratory allergic disorders, particularly in developed nations. Although pollen grains are too large to enter the deeper parts of the respiratory system, they can impact the eyes, nose, and nasal passages. Worldwide epidemiological research indicates that 25% of the global population suffers from allergies, with a rising trend that crosses age, race, and social divides. Different allergenic plants are typical to specific regions, influenced by geographical climate and vegetation, while meteorological factors significantly

affect the airborne concentration of pollen. Fewer than one hundred plant species worldwide produce allergenic pollen, with urban areas primarily receiving allergenic pollen from woody plant species.

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CONFLICT OF INTEREST

The author declares no conflicts of interest.

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