

Allergic Rhinitis

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INTRODUCTION

Allergic rhinitis is a global health problem; the second leading cause of chronic diseases in the U.S. , affecting at least 10-25% of the population [1]. Allergic rhinitis has a substantial effect on patient's quality of life, sleep, school performance and productivity. Physicians should also be aware of the association of allergic rhinitis with other conditions such as asthma. Asthma and rhinitis are common comorbidities, suggesting a concept of “one airway, one disease”.

DEFINITION, EPIDEMIOLOGY AND CLASSIFICATION

Allergy is a clinical manifestation of an adverse immune response after repeated contact with usually harmless substances such as pollens, molds, mites, foods. Allergic rhinitis is defined as an inflammation of the nose induced by IgE mediated inflammation due to exposure to foreign substances, referred to as allergens [2]. It is characterized by nasal symptoms of pruritus, sneeze, discharge, and stuffiness additionally the sense of smell also can ben altered.

It is estimated that more than 20% of the world population suffers from IgE mediated allergic diseases. Allergic rhinitis is the most common allergic disease. Overall, allergic rhinitis affects 20 to 40 million people in the U.S [3]. In European countries, the prevalence of allergic rhinitis has been rated from 17 to 29% [4]. It causes a significant decrease in energy, general health perception, and social function; the estimates of the annual cost of allergic rhinitis range from 2 to 5 billion dollars.

The Allergic Rhinitis and Its Impact on Asthma (ARIA) Initiative has developed a document that describes the whole knowledge of allergic rhinitis. Allergic rhinitis has always been subdivided, based on the time of occurrence during the year, into seasonal and perennial disease. But, the new ARIA classification of allergic rhinitis is based on symptoms and quality-of-life parameters. Duration of symptoms is subdivided into “intermittent” or “persistent” disease, while severity is subdivided into “mild” or “moderate-severe”, depending on symptoms and quality of life [2].

PATHOGENESIS

The main characteristic of allergic rhinitis is the involvement of IgE mediated hypersensitivity. The impact of anti-IgE antibody on the symptoms of allergic rhinitis has proven the importance and the role of IgE in the pathophysiology of allergic rhinitis [5]. In an individual with a susceptibility for developing allergic disease, an initial contact with allergen leads to the production of specific IgE molecules. An allergen is recognized by an

antigen-presenting cell then processed and presented to a T helper cell. T helper cells interact with B lymphocytes, leading to their differentiation into IgE producing plasma cells. IgE can then travel via the circulatory system and bind to IgE receptors on basophils and mast cells throughout the body [6].

In a sensitized individual, another exposure with the same allergen initiates the second step of the allergic response process. It mediates the degranulation of basophils and mast cells, and inflammatory mediators such as histamine are released. Histamine binds to their receptors on endothelial cells and vascular smooth muscle causing vasodilation and increased permeability. Early allergic response which is characterized by rhinorrhea, obstruction, sneezing, and pruritus occurred. After the early response if one monitors the response for several hours; symptoms recur and the level of mediators are elevated in approximately in 50% of patients. It is defined as late response [7].

Mediators released during the early phase reaction stimulate the production, maturation, and infiltration of inflammatory cells, including basophils, eosinophils, neutrophils, and mononuclear cells in nasal secretions, as recovered by nasal lavage. Nasal mucosal biopsies, performed 24 hours after topical allergen provocation, also show increases in the number of inflammatory cells, but, in contrast to the nasal secretions, in which eosinophils and neutrophils account for the majority of recovered cells, mononuclear cells predominate [8]. In addition, these mediators produce a

hyperreaction to both specific allergens and nonspecific irritants such as tobacco smoke and chemical fumes, referred to as the priming effect .

Causes

The “hygiene hypothesis” is a controversial theory that may explain the increasing prevalence of allergic disease. It is postulated that exposure to infections early in life decreases the chance of atopy later in life [9]. Genetic susceptibility, environmental factors, exposure to allergens, passive exposure to tobacco may be influence the development of atopy. In childhood food allergy are the major cause of allergic rhinitis and in adolescent period pollen allergy becomes more of a causative factor.

CLINICAL PRESENTATION

History

Clinical history is essential and critical for accurate diagnosis for allergic rhinitis. The primary symptoms of allergic rhinitis are rhinorrhea, sneezing, and nasal obstruction [2]. After the exposure of allergen, itching starts in seconds and sneezing occurs. Rhinorrhea and nasal congestion peaks. Besides nasal symptoms, patients often complain about ocular pruritus, pharyngeal itching, throat clearing, cough. Postnasal drip, lacrimation, red eyes, pressure headaches, loss of smell and taste can be reported also. Patients should be questioned about the onset, duration, type, progression, and severity of their symptoms. A relationship to the seasons is important, with seasonal symptoms usually indicating a pollen allergy; perennial symptoms usually mean an allergy to mites, mold, or animals. An increase in symptoms at night usually suggests an allergy to mites or pet.

The time and location that symptoms occur provide clues to differentiating allergic versus nonallergic rhinitis. If the use of medication, especially antihistamines or intranasal corticosteroids improves symptoms quickly, allergy is probable. Symptoms seen during certain seasons of the year can point the diagnosis toward the seasonal allergic rhinitis especially pollen allergy. Patients sometimes show increased allergic symptoms in certain locations, which may lead to the physician to consider pet, mite or mold allergy. Recent ARIA guidelines recommend intermittent and persistent allergic rhinitis definitions as there are too many exceptions to the old seasonal model. Persistent allergic rhinitis is defined by symptoms present for more than four consecutive days per week or for more than four consecutive weeks [10]. Intermittent is defined as any timeframe less than persistent.

Genetic factors determine the likelihood of an individual becoming sensitized and producing IgE antibodies. A family history of allergies, eczema, or asthma increases this possibility. Food allergy and eczema in childhood can also point toward allergy in older ages. Asking about asthma symptoms is also appropriate. Studies have shown that up to 80% of asthmatics have rhinitis, and that 10% to 40% of rhinitis patients have asthma (2).

The patient should always be questioned about the impact of the symptoms on the quality of his or her life because the correct diagnosis and, ultimately, symptomatic relief from the appropriate treatment will play a large part in the functional impact on the patient's life. Moderate to severe disease is associated with sleep disturbance, impairment of daily activities, or interference with work or school.

Physical Findings

A physical examination should include the evaluation of ear, nose and nasal passages and throat. Anterior rhinoscopy is useful, but findings are often not specific for allergic rhinitis alone. Nasal endoscopy should be performed; it is useful for determination nasal pathologies. Typical findings in the nose for allergic rhinitis include bluish, pale, turbinates; wet, swollen mucosa; and nasal congestion with nasal obstruction. Septal deviation, spurs, concha bullosa, nasal polyps can also be present but it is necessary to discriminate the symptoms associated with allergic rhinitis or other problems.

Swelling of eyelids, venous congestion, scleral thickening, increased vascularity are the common eye findings in allergic rhinitis. Postnasal drip, posterior pharyngeal edema and erythema, cobblestone appearance of pharynx may be observed in pharyngeal examination. Laryngeal edema, wheezing may also be observed due to associated asthma and lower respiratory hyperreactivity.

Allergic shiners, mouth breathing, nasal salute are common findings in children. Serous otitis media can also be diagnosed in children because of the eustachian tube dysfunction besides allergic rhinitis. Malocclusion and high arched palate and maxillofacial dysmorphic face may suggest longstanding disease in children [11].

Special Diagnostic Tests

Allergy testing is performed to establish objective evidence of atopic disease. It also can determine the causative allergens responsible, which would then lead to specific therapeutic recommendations. Identification of hypersensitivity to specific allergens can be clinically useful in the management of the allergic patient. Testing is divided into three main categories: challenge tests, skin tests, in vitro serum assay [12].

Allergen can be placed directly in the nose of the patient or patient respirates the circulating airborne allergen. In challenge tests there is always a risk for anaphylactic reaction and standardization of test for multiple allergens is difficult. These types of challenge tests are useful in diagnosing occupational rhinitis.

Skin testing is an excellent method for demonstrating sensitivity to a given allergen. In skin testing; allergen is placed into the patient's skin. Allergen can be tested with skin prick method or intradermal injection. The allergic reaction is observed in the skin and the response is compared to positive and negative controls. Risk for anaphylaxis is also possible in this method. Great sensitivity, low cost and rapid result are the main advantages of this method however it can not

be performed in patient with dermatologic problems, children because of the multiple pricks and patients who take antihistaminic drugs. It is an easy and simple office procedure with new multitest systems. Intradermal testing, using quantitative 1/5 serial dilutions, is the skin testing method used by most allergists; this type of testing is an excellent quantifier of allergen sensitivity, and, as such, is of benefit in the preparation of safe subcutaneous immunotherapy treatment[13].

Serum-specific IgE levels can also be used to assess the allergic patient. There are several differences between skin testing and specific IgE testing. Specific IgE testing requires only a single venipuncture and does cause local or systemic allergic reactions. Positive skin tests can be suppressed by medication, most commonly antihistamines, while specific IgE testing is unaffected. Skin prick test interpreted subjectively while specific IgE testing is subject to laboratory error. Therefore, both determinations of specific IgE levels and skin testing are useful in the diagnosis of allergic disorders, but their results should always be interpreted in the context of clinical symptoms. Disadvantages in vitro testing include cost, slightly lower sensitivity, and the time delay between drawing blood and obtaining the results [14].

Other diagnostic tests: Peripheral eosinophilia nonspecificly may indicate the presence of atopic diseases. Nasal cytologic examination allows the identification of eosinophils in secretion. In management of children in the differential diagnosis in rhinitis soft tissue radiography is useful for discrimination of allergic diseases and adenoid hypertrophy. Paranasal CT is also useful for evaluation of sinus abnormalities.

TREATMENT

Environmental Control

A logical approach to treat allergic rhinitis is to avoid allergen exposures. Reducing the allergic load may significantly decrease symptoms. Methods of reduced exposure to pollen are to avoid outdoor activities during relevant pollen seasons and to use air conditioning when possible [15]. To control dust, mites and mold; household humidity should be reduced, linens should be washed frequently, carpets and pets should be removed from most used living areas. Hypoallergenic coverages, HEPA filtration and airborne purifiers can also be used [16]. When multiple environmental control techniques are combined, studies have demonstrated moderate success.

Pharmacological Treatment

Pharmacologic management should take into account to the patient's underlying condition, pathophysiology, the dominant symptoms, the patient's age and condition, the coexistence of airway disorders, the patient's preference, and the patient's compliance history.

Antihistamines

There are four receptors for histamine; H1 receptors are found on blood vessels, on sensory nerves, on smooth muscles and in the central nervous system. When histamine binds to H1

receptor; vasodilatation, increased vascular permeability, sneezing, pruritus, glandular secretion are occurred. The contribution of histamine to the early allergic response, largely mediated by the H1 receptor, large number of H1 antagonists now in clinical use.

Antihistamines are frequently used as a first-line therapy; they block H 1 receptor sites and prevent histamine releasing, inhibits increased vascular permeability, smooth muscle contraction, increased mucus production, and pruritus. They also effects the response of skin testing via preventing the 'wheal and flare response' but in vitro test is not effected. Antihistamines are effective in early-phase reaction and therefore reduce sneezing, rhinorrhea, and itching. They have little effect on nasal congestion, a late-phase phenomenon [17].

The first-generation antihistamines are effective in the relief of symptoms of allergic rhinitis. However, first generation antihistamines have some undesirableside effects because of their lack of selectivity and the resulting nonspecific stimulation of other receptors. It causes sedation and impair performance and have been associated with a higher risk of both automobile and work-related accidents, decreased work performance and productivity, and impaired learning performance. Many have anticholinergic effects and cause dry mouth. Chlorpheniramine, clemastine, diphenhydramine, hydroxyzine, ketotifen, mequitazine, oxatomide are the major old generation antihistamines.

Second-generation antihistamines are less lipophilic than first-generation H1 antihistamines and do not penetrate the blood–brain barrier. Receptor selectivity also reduces the incidence of anticholinergic side effects. They have no anticholinergic activity and are well mabsorbed, with a rapid onset of action and symptom relief usually within 1 hour. Acrivastine, azelastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, rupatadine are the major new generation antihistamines.

Azelastine,olopatadine and levocabastine are two local antihistamines. They are quickly effective against nasal or ocular symptoms. They can produce minor local side effects; azelastine has bitter taste. These intranasal antihistamines also tend to decrease nasal congestion more than the oral antihistamines [18].

Topical steroids

Topical steroids are potent medications for the treatment of allergic rhinitis. These agents reduce multiple aspects of the inflammatory response to allergen. They relieve sneezing, itching, and rhinorrhea, and also nasal congestion. Maximal effect may take from 1 to 2 weeks after the onset of their use.

They have minimal systemic absorption with no systemic side effects, and they have been approved for use in children; and do not affect bone growth in children. The most frequent side effect is nasal irritation, is manifested as a nasal burning sensation. Thinning of nasal epithelium, abnormalities in nasal mucosa and septal perforation can be seen after prolonged use. Local side

effects, such as dryness and epistaxis, can be reduced by careful patient instruction on their use, intranasal saline can also be used concomitantly [19]. However, when intranasal antihistamines and intranasal corticosteroids are combined, there is an additive effect.

Currently used topical forms of corticosteroids include flunisolide, beclomethasone, triamcinolone, budesonide, ciclesonide, mometasone, and fluticasone.

Systemic steroids

These agents are usually administered to patients during intractable and severe exacerbations of allergic symptoms. They are used successfully in combination with antibiotics for treatment of sinus infections complicating allergic rhinitis. They can be administered either by intramuscular injection or orally. The repeated use of these agents can cause serious side effects [19].

Decongestants

Decongestants show their effect via α_1 and α_2 adrenergic receptors present on blood vessels. They control blood flow and blood volume in capacitance vessels. Increased sympathetic stimulation with adrenergic activity or exercise, nasal mucosa and turbinates are congested. Topical decongestants are effective in reducing nasal congestion. Prolonged use can bring about rhinitis medicamentosa, which is characterized by a reduced duration of action and rebound nasal congestion after cessation of therapy. So; use of these agents should be limited to a few days.

Oral decongestants exert their effects directly and by stimulating release of norepinephrine. Pseudoephedrine and phenylephrine can be used with antihistamines. But in extensive use of oral decongestants hypertensive crisis and cardiovascular problems can be occurred. It should be carefully prescribed in uncontrolled hypertension, severe coronary artery disease, closed angle glaucoma, prostatic hypertrophy, urinary retention [20].

Chromones

Like antihistamines, cromolyn is a mast cell stabilizer; more helpful for sneezing, rhinorrhea, and nasal itching than for nasal congestion. Its safety profile, however, makes it an attractive treatment, especially in children and pregnant women. Intranasal cromolyn must be used before the onset of symptoms to be effective. The recommended dosage is four times daily.

Anticholinergics

Anticholinergic agents inhibit parasympathetic stimulation of glandular secretion by competing for muscarinic receptors on glands. These agents tend to control only rhinorrhea and have no other effects on allergy symptoms. One of the most commonly used intranasal anticholinergics is ipratropium bromide. The side effects of anticholinergics are minor and local, as there is virtually no systemic anticholinergic activity.

Leukotriene inhibitors

Leukotrienes were detected both in the early and late phase of an allergic reaction. Leukotrienes stimulate mucous glands, which results in rhinorrhea, and they also have the ability to increase microvascular permeability and blood flow that result in tissue edema and subsequent congestion. Introduction of leukotriene modifiers increased the therapeutic options for patients who have allergic rhinitis. The drugs in this class include montelukast, pranlukast and zafirlukast, which block cysteinyl leukotriene type receptors. Clinical studies have shown its efficacy to be greater than that of placebo, but less effective than antihistamines and intranasal steroids in the treatment of allergic rhinitis.

IMMUNOTHERAPY

Allergen-specific immunotherapy is a very effective method of treatment in carefully selected patients with allergic rhinitis. It is the only treatment that can lead to a life-long tolerance. Immunotherapy attempts to increase the threshold level of the appearance of symptoms after exposure. Indications for immunotherapy include long-term pharmacotherapy for prolonged periods of time, the inadequacy or intolerability of drug therapy, and significant allergen sensitivities. Before beginning immunotherapy, the physician must first confirm the atopic diagnosis by testing IgE specific to the offending allergen.

Subcutaneous injection immunotherapy (SCIT) begins with low-dose injections of allergen extracts and builds to a maintenance dose. Injections usually begin at weekly intervals and are reduced in frequency when maintenance doses are reached. Allergen injections should be administered under the supervision of a qualified medical practitioner, and patients should be observed for at least 30 minutes after every injection. Proper resuscitative equipment should be present because anaphylactic reactions can occur at any time during treatment.

Sublingual immunotherapy (SLIT) is a new, safe, efficacious and more convenient method for delivering immunotherapy. SLIT tends to be easy and safe to administer at home by the patients themselves, and therefore is likely to be more cost-effective. The allergen is kept under the tongue for one to two minutes and then swallowed. If the vaccine is swallowed immediately, the clinical efficacy decreases substantially [21].

Anti IgE

Omalizumab is a recombinant humanized monoclonal antibody that binds selectively to IgE. It lowers free IgE levels in the circulation. It reduces the free IgE level in serum, inhibits allergen-induced circulating and tissue eosinophils [22].

Surgery

Inferior turbinate hypertrophy appears to be at least partially responsible for nasal congestion seen with allergic rhinitis. Radiofrequency ablation of the inferior turbinate provided decreased nasal resistance and improved congestion.

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