DIAGNOSIS OF RESPIRATORY ALLERGIC DISEASES

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ABSTRACT

Objective: While the majority of allergic diseases, such as allergic rhinitis, are not life-threatening, they do affect the patient’s quality of life and often weigh heavily on the economic stability of the family. For these reasons, it is an absolute necessity to correctly diagnose allergy. To do so, it is essential to compile a detailed patient history, after which a progressive management program can be developed. The effectiveness of this program mainly depends on how accurately the causes of allergy are identified, although environmental controls, pharmacotherapy and immunotherapy also play an important role.

Key words: Allergic rhinitis, allergic asthma, skin prick test, serum specific IgE, serum total IgE, eosinophil count in nasal fluid, environmental control, pharmacotherapy, allergen-specific immunotherapy.

Introduction

The prevalence of allergic diseases is increasing worldwide and particularly in western countries[1]. Up to 40% of individuals are prone to allergic diseases, including food allergy, allergic rhinitis (hay fever), asthma, drug allergy and insect venom allergy[2]. The nature of the allergic response can vary from bothersome symptoms (e.g. irritation of the nose and eyes and cough) to life-threatening events (c.f. drug allergy and insect venom allergy).

This article focuses on the epidemiology, diagnosis and treatment of allergic respiratory diseases, in particular allergic rhinitis, which is the most prevalent allergic disease in the world.

Definition and genetics of respiratory allergic diseases

Asthma and allergic rhinitis were clinically defined in 1998 and 2001, respectively[3,4]. A common characteristic of both these disorders is that the chest and nose symptoms are induced after allergen exposure by an IgE-mediated inflammation[5]. Patients with asthma and/or allergic rhinitis have a genetic predisposition to produce a specific inflammatory response to allergens, which are normally harmless. Allergic responses are initiated by exposure to allergens in susceptible or atopic subjects[5,6]. The term atopic is derived from a Greek word meaning “strange or out of place” and was first introduced by Coca and Cooke in 1923[7]. It refers to a personal and/or familial tendency to produce IgE antibodies and sensitization in response to ordinary exposure. The clinical expressions of atopy are food allergy, atopic dermatitis, allergic rhinitis and allergic asthma; however, IgE hypersensitivity reactions can also be non-atopic, for example drug allergy and insect venom allergy[8].

Atopic diseases are characterized by an inflammation that involves the surface of the mucosa exposure. Another characteristic is that an atopic subject with one allergic condition tends to be at risk for other allergic conditions[9,8].

While a characteristic of non-atopic IgE allergic diseases (i.e. drug allergy and insect venoms...
Epidemiology of atopic allergic diseases

Atopic allergic diseases are a common condition in the western world and are increasing in the developed countries. Four relevant concepts to bear in mind in the epidemiology of atopic allergic diseases are:

- Prevalence
- Costs
- The “allergic march”
- The “hygiene hypothesis”

Prevalence

Asher et al. obtained worldwide comparable population estimates of the direction and size of change in the prevalence of symptoms of asthma, allergic rhino-conjunctivitis and eczema, using identical instruments. The study demonstrated a clear pattern for the change in prevalence. Most centers showed a change, with increases more common than decreases and occurring more commonly in the younger than the older age groups. The changes were greatest for eczema in the younger age group, followed by allergic rhinoconjunctivitis in both age groups. The only regions where increases in prevalence of all three disorders in both age groups occurred more often than decreases were Pacific Asia and India.

Allergic rhinitis (AR) is a major health problem with a high and ever-increasing prevalence. At least one in five adults in Western Europe is estimated to have AR. It is well-known that AR has a substantial negative impact on daily activities and sleep, similar to that caused by asthma.

Costs

Despite the effects of AR on the quality of life it remains a condition where patients often do not seek appropriate treatment, are undertreated or do not adhere to treatment.

Bousquet at al. reported a total cost of about €350 per month, mainly due to reduced productivity, for each AR patient who had not received appropriate long-term therapy for their condition.

For these reasons, there is a need to radically improve the diagnosis, treatment and management of AR.

Allergic march

Because allergic rhinitis is the result of genetic predisposition and environmental exposure, there is a growing body of evidence to support the allergic or atopic “march.” The term “allergic or atopic march” refers to the natural history of atopic manifestations, which is characterized by a typical sequence of immunoglobulin E (IgE) antibody responses and clinical symptoms that appear early in life, persist over years or decades, and often remit spontaneously with age.

Eczema is a chronic relapsing inflammatory skin condition, characterized by dry skin lesions with lichenification, pruritic excoriations and a predilection for the skin flexures. It is the most common inflammatory skin disease in childhood, with most cases manifesting within the first year of life. However, there are 2 variants of eczema, an atopic form and a non-atopic form. The form of
eczema with sensitization to allergens is a high factor of risk for the development of allergic rhinitis, and/or asthma\textsuperscript{20}. The proportion of subjects with eczema who later develop asthma varies greatly ranging from 25\% to 80\%\textsuperscript{21}. Because the atopic march is described as a progression, this temporal association between eczema and childhood asthma could indicate that eczema may influence or act as a risk marker for asthma in childhood, although this does not appear to be the case in adult-onset asthma\textsuperscript{22}. Allergic rhinitis, however, is a stronger predictor of adult-onset asthma\textsuperscript{23}. The strong link between allergic rhinitis and asthma in children is also highlighted in the ARIA document, which recommends empiric evaluation for asthma in patients with allergic rhinitis, particularly in those with severe and/or persistent forms of allergic rhinitis\textsuperscript{11}.

Allergen immunotherapy has been well established as an effective treatment for allergic rhinitis,\textsuperscript{24-26} and data indicate that this treatment can actually decrease the risk of developing asthma\textsuperscript{27,28}. The possibility of decreasing the risk of developing asthma (the final step of the atopic march) by treating an earlier disease further supports both the conceptual validity and usefulness of the atopic march, as well as its sequential nature.

**Hygiene hypothesis**

A final important epidemiologic concept in atopic allergic diseases is the “hygiene hypothesis”\textsuperscript{3,20}.

The hygiene hypothesis was first proposed in 1989 by David Strachan’s epidemiological analysis on hay fever and household size. An inverse relationship was found between the number of older siblings and the prevalence of allergic diseases (hay fever and eczema), and Strachan inferred that childhood with infective diseases contracted from siblings, in particular older siblings, might offer protection later in life against allergy\textsuperscript{30}. Subsequently, the hygiene hypothesis was extended to include other allergic illnesses and autoimmune diseases\textsuperscript{31}. Many infection diseases childhood that were once common have been gradually reduced or even eliminated. Simultaneously, there has been a rise in the incidence of various immunological disorders in the developed nations and among the urban populations in the developing nations. An increased prevalence of asthma, for example, has been observed in many western countries in the past three decades\textsuperscript{32} and more recently in developing Asian countries\textsuperscript{33}. Unlike asthma, the high prevalence of allergic rhinoconjunctivitis and eczema appears not to be restricted to the developed countries\textsuperscript{34}, although there are large studies that both support and refute this theory\textsuperscript{31,34}.

**Diagnosis of allergic rhinitis**

**History**

A patient’s symptom history is the most important element in determining an IgE-mediated hypersensitivity/atopic disease such as allergic rhinitis. Unfortunately, many of the symptoms of this kind of disease are also present in non-allergic diseases, therefore it is essential to confirm confirmatory allergy using a skin prick test and/or serum specific IgE assay. However, for primary-care physicians, who are usually the first to encounter patients with nasal symptoms, a good question might be: on the basis of what symptoms must the patient be referred to an allergist for diagnosis? The primary symptoms of allergic rhinitis are sneezing and nasal itching (which may be more specific signs\textsuperscript{35}), rhinorrhea and nasal obstruction\textsuperscript{1,35}. We reported that the age of onset of the nasal symptoms is below the fifth decade of life\textsuperscript{36}. A comparative study between allergic non-allergic rhinitis found that the percentage of women was significantly higher in the group of non-allergic rhinitis\textsuperscript{35}. It has been shown that allergic rhinitis is related to environmental exposure\textsuperscript{37}, yet few studies have investigated the relevance of triggers for diagnosing specific subtypes of rhinitis, indicating that this approach may be too simplistic and not reliable\textsuperscript{38,39}. Finally, most patients with allergic rhinitis are polysensitized, which complicates attempts to pair their history with patterns of exposure\textsuperscript{40}. A family history of allergies may also be useful, but allergic rhinitis, does not follow simple Mendelian inheritance laws\textsuperscript{40}.

**Clinical presentation**

Classically, allergic rhinitis is divided into seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR). However, the ARIA guidelines recommend the terms intermittent allergic rhinitis (IAR) and persistent allergic rhinitis, as they conclude that there are too many exceptions to the seasonal model, especially in the case of dust mites and molds\textsuperscript{1,36}. PAR is defined as more than 4 consecutive days per week or for more than 4 consecutive weeks per year\textsuperscript{40}. PAR tends to have nasal obstruction as its characteristic symptom, whereas...
IAR’s hallmarks are sneezing, itching, and rhinorhea. (1). The ARIA guidelines classify allergic rhinitis as mild when the following criteria are absent: impairment of daily activities (work, or school) or sleep disturbance; and as moderate/severe if one of the previous criteria is present and the nasal symptoms are troublesome\(^{(1)}\). Therefore, the severity of symptoms is subjective\(^{(39)}\). The presence of symptoms of wheezing or conjunctival irritation can help to differentiate between allergic and non-allergic rhinitis, as well as to decide on the assessments to be carried out and treatment to be performed.

**Physical examination**

Few studies have evaluated the importance of physical examination for allergic rhinitis\(^{(39-42)}\). The physical examination of patients with suspected allergic rhinitis should include an assessment of outward signs, in the nose, ears, sinuses, posterior oropharyngeal wall (area of the throat at the back of the mouth), chest and skin. Possible suggestive signs include: persistent mouth breathing, rubbing at the nose or an obvious transverse nasal crease, frequent sniffing or throat clearing and allergic shiners (dark circles under the eyes due to nasal congestion). Examination of the nose typically reveals swelling of the nasal mucosa and pale, thin secretions. An internal endoscopic examination of the nose should also be considered to assess for structural abnormalities and nasal polyps\(^{(39,41,42)}\). The ears generally appear normal, however, assessment for Eustachian tube dysfunction using a pneumatic otoscope should be considered. Valsalva’s maneuver (increasing the pressure in the nasal cavity by attempting to blow out of the nose while holding it shut) can also be used to assess for fluid behind the ear drum\(^{(42)}\).

Sinus examination should include palpation of the sinuses for evidence of tenderness, or tapping of the maxillary teeth with a tongue depressor for evidence of sensitivity. The posterior oropharyngeal wall should also be examined for signs of post-nasal drip (mucous accumulation in the back of the nose and throat) and the chest and skin should be examined carefully for signs of concurrent asthma (e.g. wheezing) or dermatitis\(^{(1,42)}\).

**Diagnostic tests**

Allergic and non-allergic rhinitis symptoms overlap substantially\(^{(41)}\). The diagnosis of allergy is primarily clinical, as positive allergy tests are frequently seen in individuals without clinical symptoms of allergy\(^{(44)}\). In subjects with clinical symptoms and correlating positive allergy tests, however, improvement has been demonstrated with allergy medication, environmental control and allergen-specific immunotherapy\(^{(1)}\). Allergy testing is imperfect, but useful in determining what patients might be allergic to. There are different methods of allergy testing, which are divided into in vivo and in vitro tests\(^{(45)}\).

**In vivo testing**

- **Skin testing**

Reliable skin testing and the proper documentation of test results are essential in allergy practice. A recent survey including all physician members and fellows of the American College of Allergy, Asthma and Immunology practicing in the United States detected a significant degree of variability regarding skin test devices, extract concentrations, the interpretation and documentation of results and quality assurance procedures\(^{(46)}\). Skin testing is the most widely-used way of testing for allergies in the world. The extract of an inhaled allergen is placed beneath the skin’s surface via a scratch, prick, or intradermal injection. If mast cells in the skin degranulate after allergen exposure, histamine and other mediators produce a wheal (local edema) and flare (erythema). The skin reaction is compared with positive (histamine) and negative (diluent) controls and graded (or read) by the tester. Skin-testing results may vary according to technique, area of the body, test interpreter, medications and allergen extract, but they serve as a useful and effective tool for assessing the risk of allergy. A small risk of triggering a systemic allergic reaction is entailed with all types of skin testing\(^{(47)}\).

Scratch testing is not currently recommended, as reproducible results are difficult to obtain. Skin prick tests (SPT) can be reproduced with practice and are favored for their safety, cost, and reasonable correlation to clinical disease. Intradermal tests use a needle to raise a small wheal, which is observed for growth and erythema\(^{(48)}\). Single intradermal tests use more extract than prick tests alone and may generate a response when the SPT is negative, although studies have questioned if intradermal tests add any clinical value in this case\(^{(49)}\).

Intradermal testing is used for venom allergy testing. As there is no agreed gold standard for inhalant allergy testing, there is controversy about the best way to test for allergy, especially in...
patients reactive to only high amounts of allergen extract administered intradermally\(^{(50)}\).

- **Challenge testing**

  Challenge testing is used as the “gold standard” in food allergy but there are fewer consensuses for its use in inhalant allergy testing\(^{(51)}\). While it might seem logical that challenge testing would also be the gold standard for allergic rhinitis, testing for inhalant allergens tends to exceed amounts encountered in natural exposure. Additionally, it is difficult to standardize and can be biased by subjective responses\(^{(52)}\). Perhaps for these reasons, challenge testing has not correlated optimally with clinical symptoms\(^{(43)}\). Some authors indicate the conjunctival challenge as an additional diagnostic tool to define sensitization\(^{(53)}\).

**In vitro testing**

- **Serum total IgE**

  It is logical that allergic individuals should have high levels of total IgE. However, total IgE has not been found to be as helpful in distinguishing between who is allergic and who is not, since many patients with allergic rhinitis defined by positive tests and history have total IgE in the normal range\(^{(54)}\).

- **Serum specific IgE**

  Specific IgE (sIgE) antibodies are bound on cells that express IgE receptor or circulate freely in the bloodstream. Free sIgE can be sampled in the plasma or serum and is measured by allowing it to bind to an allergen attached to a matrix. Newer commercial versions of the in vitro test use a hydrophilic cellulose polymer. The patient’s bound IgE is tagged with a labeled anti-human IgE, which is then measured. Enzyme-based (fluorescent or colorimetric) and chemiluminescent detection systems are in common use\(^{(55)}\). This technique also allows the amount of sIgE to be indirectly quantified. In theory, any subject with an IgE-mediated allergy would necessarily produce sIgE to that allergen\(^{(56)}\). The advantages of sIgE are that results are not suppressed with antihistamine use and interpretation is not subjective\(^{(49)}\). sIgE correlate with the results of SPT. However, some evidence suggests that the higher the sIgE level, the more likely it is that (the) allergy is clinically present\(^{(44)}\). Conversely, the degree of skin reactivity and level of sIgE have not correlated well with the severity of clinical symptoms\(^{(57)}\).

- **Eosinophil count in nasal fluid**

  Eosinophil count in nasal fluid (ECNF) is easy to perform and provides relevant information about the predominant cellular infiltration. In addition, the type of inflammation can provide suggestions about the mechanism(s) involved. On this basis, several forms of rhinitis can be identified, including non-allergic rhinitis with eosinophilia (NARES)\(^{(58)}\). The results of our study demonstrated that ECNF performance was moderately accurate in distinguishing between patients with AR and NAR. However, ECNF showed high accuracy in distinguishing patients with mild rhinitis from those with severe rhinitis, both in patients with AR and those with NAR.

  Nasal lavage is relatively noninvasive, easy and rapid to perform, well tolerated and repeatable over relatively short periods. Nasal brushing is easy to perform and is well tolerated in general, although some find that the procedure causes a transient unpleasant sensation and it is also difficult to standardize. However, nasal lavage offers the advantage of providing considerably greater information from the sample and its intra-assay variation was <8\%\(^{(59)}\).

**Allergy testing**

Allergy diagnosis is based on an accurate clinical history and the subsequent performance of in vivo SPT or on in vitro sIgE assay. In the last decade in vitro measurements have improved in terms of performance characteristics and response time thanks to the introduction of more reliable and completely-automated methods that provide results within a few hours\(^{(60)}\). A growing body of evidence demonstrates that the diagnostic sensitivity and specificity of in vitro measurements are similar, if not superior, to those of in vivo skin testing\(^{(61)}\). Agreement between in vitro and in vivo testing in the etiological diagnosis of allergic diseases is reported to be greater than 90\%\(^{(62)}\). However, SPT and sIgE measurement provide different information. One major difference is that SPT detects IgE attached to mast cells, while the in vitro test detects IgE in serum. Typically, the concentration of mast-cell-bound IgE is much higher than the concentration of serum IgE. This difference, however, does not imply that SPT is more sensitive than the in vitro test. Another difference is that while the in vitro test detects only the presence of specific IgE, SPT depends on another/other kinds of the physiological skin integrity. Although the pivotal event in IgE-mediated hypersensitivity is the association of specific IgE with an allergen, the pathophysiology of allergic diseases also depends on factors such as the
concentration of mast cells, tendency of mast cells to degranulate, sensitivity to histamine and vascular and neural responsiveness (63).

Treatment of allergic rhinitis

The treatment of allergic rhinitis is divided into 3 categories: environment control, pharmacotherapy and allergen-specific immunotherapy. The efficiency of the first and the third therapeutic approaches depends on a correct diagnosis.

Environment control

The first-line treatment of allergic diseases involves the patient avoiding the relevant allergens. While this is certainly effective for drug allergy, insect venom allergy and food allergy, in the case of respiratory allergic diseases environmental avoidance is indeed recommended in multiple position papers, but has poor support from controlled studies in consistently improving symptoms. We will examine the two strategies reported in clinical studies.

Patients physically removed from allergic source

Studies in patients with allergic asthma have shown that moving allergic patients to an allergen-free location, leads to an improvement in symptoms and in the markers of eosinophil inflammation (64-67). Although effective, however, this strategy is frequently impractical.

Environmental control

Many interventions have been proposed: dust-mite covers (68), acaricides (69), vacuum cleaning (70), use of high-efficiency particulate air (HEPA) (71), frequent washing of bed linen (72), removing carpets (73) and washing pets (74). Although these interventions do reduce the measured allergens, despite the reduction (of) in measured allergens their clinical implications of these interventions are less certain if evaluated using a systematic review with meta-analysis (75, 76).

Pharmacotherapy

The goal of pharmacotherapy in allergic diseases is to relieve symptoms. Pharmacotherapeutic options available to achieve this include: antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, systemic steroids, cromolyn nasal spray and decongestants.

Antihistamines

Antihistamines are divided into first and second generation drugs, with sedation being much lower in the second-generation medications (77). First-generation antihistamines, due to the sedation side-effect, do not have a rational role in the management of allergic rhinitis for most patients (1, 77). Antihistamines help with sneezing, itching and rhinorrhea, but are similar to placebo for nasal congestion (78). Antihistamines are used as a rescue medication.

Intranasal corticosteroids (INCS)

INCS represent the single most effective class of medical therapy for allergic rhinitis (79). There is little difference in clinical efficacy between the available INCS; however, differences in price, taste, and systemic effects exist (80). Local irritation, especially ulceration and bleeding from the nasal septum, is a common side effect with persistent use. (1).

Leukotriene receptor antagonists (LTRAs)

LTRAs montelukast and zafirlukast are also effective in the treatment of allergic rhinitis. However, they do not appear to be as effective as intranasal corticosteroids (83). Longer-term studies have found intranasal corticosteroids to be more effective than the combination of LTRAs and antihistamines for reducing night-time and nasal symptoms (81).

Cromolyn

Cromolyn requires frequent application. Efficacy is mild, but safety is excellent (1).

Decongestants

Decongestants are effective against nasal congestion and rhinorrhea but can have significant side effects, including sleep disruption and hypertension (1).

Allergen Specific Immunotherapy (ASI)

The use of ASI for the treatment of allergic diseases was first reported in the Lancet in 1911 (82). The English physician Noon injected an aqueous extract of timothy grass pollen in incremental doses into hay fever patients and found that the dose of extract needed to elicit a conjunctival reaction was increased by 100-fold after treatment. Others soon confirmed his observations. It was not
until 1954 that the first randomized placebo-controlled study on immunotherapy was published. In 1986, the British Committee for the Safety of Medicines reported several deaths caused by subcutaneous immunotherapy (SCIT) and raised serious concerns about the safety and the risk-benefit ratio of specific immunotherapy (SIT). This benefit was also further questioned when cheaper and effective drugs (e.g., oral H1-antihistamines and topical corticosteroids) became available for the treatment of respiratory allergy. For this reason, the idea of administering the allergenic extracts via non-injection routes was (has been) evaluated. The first clinical attempts were made via the ‘oral’ route, but in several clinical trials performed during the 1980 the clinical results were inconsistent, and in some cases adverse gastrointestinal events were reported. Subsequently, other routes were proposed, such as local bronchial and local nasal administration. The oral route, after revision, has been substituted by the sublingual route.

Sublingual immunotherapy (SLIT) has been the subject of considerable skepticism over the past century, being commonly dismissed as the extreme of a spectrum of anecdotal treatments for allergy that belong more to the realm of homoeopathy than to evidence-based medicine. Today there is a significant body of literature documenting the efficacy and safety of SLIT in Europe. However, in the USA SLIT has not been approved by the FDA.

Specific immunotherapy products are sold as either unregistered, named patient preparations or nationally registered formulations. Recently, Graminaceae grass pollen extract SLIT tablets were registered in many European countries as pharmaceutical specialities. However, the randomized controlled trials (RCTs) performed for the registration of the grass-pollen pharmaceutical preparation showed conflicting results as to the degree of benefit of SLIT in AR. We performed a systematic review of double-blind, placebo-controlled randomized clinical trials of commercially-available grass pollen SIT modalities for the treatment of seasonal allergic rhinoconjunctivitis in adults and children. We showed that SLIT is an effective treatment, especially in adults, but its clinical benefit was modest. However, in Europe SLIT is prescribed nearly as frequently as SCIT, and, in particular, in southern Europe it is preferred to SCIT, accounting for about 80% of immunotherapies. SLIT has also been shown to be safe and well-tolerated. These advantages explain the increasing use of SLIT seen in Europe in recent years: it is safer and easier to administer compared to SCIT.

However, the relative efficacy of SCIT and SLIT has not yet been determined. The only published comparative studies, one performed with grass allergens and another with birch pollen, were far too small for a reliable conclusion. Therefore, to clarify this issue, we compared SCIT and SLIT by a meta-analysis of a fairly large number of double-blind, placebo-controlled trials on SCIT and SLIT (updating our previously published meta-analysis) in patients with seasonal allergic rhinitis to grass pollens. The results of our new meta-analysis provide indirect, but solid evidence, that SCIT is more effective than SLIT in controlling symptoms and reducing the use of anti-allergic medications in seasonal allergic rhinoconjunctivitis to grass pollen.

Conclusions

Technological advances have improved both the diagnostic possibilities and the therapeutic approach in many fields of Internal Medicine. This, however, has also led to an increase in the physician’s responsibility for the accuracy of diagnosis and therapy. As regards the allergic diseases misdiagnosis results in sanctions for the doctor only for drug allergy and in selected cases of food, while for other patients it is cause of a low quality of life. This last sentence explains why the allergy of a patient, interest only the patient who is, or his family.

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