

Allergy: early, accurate diagnosis as a basis for effective treatment

Allergy is now recognised as a growing public health problem worldwide and is associated with decreased school and work productivity. While early accurate diagnosis using objective tests is now widely acknowledged as the standard of care, facilitating better patient outcomes, many patients suspected of allergy are still diagnosed without objective testing.

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What is allergy?

The term allergy is generally used to describe an immunoglobulin E (IgE) mediated immune response to substances that are not generally harmful to the body. Natural allergen sources, such as pollens, dust mites, dog dander, moulds, insect venoms and foods are identified by the immune system, and it is the reaction of the immune system to the allergen that produces the signs and symptoms associated with the disease. IgE is produced by B cells on first exposure to the allergen, and these IgE molecules then bind to mast cells and basophils. The individual is now sensitised, and when subsequent allergen exposures occur, the cell-bound IgE binds the allergen triggering the release of histamine and other mediators that produce the signs and symptoms. Diagnostic tests play a key role in the management of allergy, but a thorough medical history must be taken, as well as a physical exam carried out when tests are ordered, so that test results can be interpreted and accuracy maximised. Multiple different manifestations of allergic disease, such as eczema and food allergy or allergic rhinitis and asthma, are commonly found in a single patient, and frequently the patient experiences them in a defined sequential pattern known as the allergy march.

The allergy march

The allergy march is a series of allergic diseases that follow a fairly defined path as the allergic patient ages [Figure 1]. Typically, eczema occurs between birth and three months of age; gastrointestinal symptoms related to food allergens are most prevalent during the second year; allergic rhinitis and other upper respiratory conditions due to inhalant allergens, as well as recurrent otitis media, generally manifest between the ages of three and seven; and asthma is usually diagnosed between the ages of seven and fifteen. In the young child, elevated food-specific IgE antibody levels are associated with the significantly elevated risk of developing inhalant allergen sensitivities later in childhood [1]. Early diagnosis and appropriate treatment of allergies is vital in order to interrupt the disease progression and thus derail the allergy march.

The allergens most often associated with eczema include cow's milk, egg, wheat, soy and peanut: 30 percent of all skin disorders in toddlers are due to eczema [2-4]. Failure to treat eczema is associated with the development of the gastrointestinal symptoms that are frequently related to allergy [5-7], and evidence suggests that food allergy may

be the root cause of symptoms in 10 to 15 percent of colicky infants. In infants diagnosed with gastroesophageal reflux, 16 to 42 percent are found to be allergic to cow's milk, while among infants already diagnosed with allergy, 50 to 60 percent have gastrointestinal related symptoms [3,4,8,9]. Left undiagnosed, allergy-related gastrointestinal symptoms may result in growth retardation. In addition, it has been demonstrated that children with early and long-lasting food allergies are three times more likely to develop allergic rhinitis, and five times more likely to develop asthma [8-10].

Otitis media is yet another step in the allergy march and ten million children with otitis media are treated in the US every year for an approximate cost of five billion dollars per year. The prevalence of recurrent otitis media has increased steadily over the years, especially among infants: evidence suggests that this is linked to allergic disease, particularly allergic rhinitis. Allergic rhinitis can produce Eustachian tube inflammation and dysfunction thus providing an ideal environment for infection.

Overall, allergic rhinitis is estimated to affect 20 to 40 million Americans and is very common among children. It is also generally accepted as the step prior to asthma in the allergy march. In rhinitis, patients' medical history and physical exam alone only produce a correct diagnosis of allergic disease 50 percent of the time, so objective evidence is required. In children, allergic rhinitis often signifies the emergence of respiratory illness, and completion of the shift from food to inhalant allergen sensitivities.

Figure 1. The allergy march is a series of allergy related conditions that appear successively and culminate in asthma. As many as 40% of infants with atopic dermatitis (eczema) may become asthmatic by age 4 and it is estimated that 79% of children with otitis media have been diagnosed with allergic rhinitis.



More than 20 million people have asthma and for some it is the final step in the allergy march; among asthmatics 60 percent have allergic asthma. In children with asthma 90 percent also have established allergies. Approximately 40 percent of infants who have atopic dermatitis (eczema) may develop asthma by the age of three to 4 years [3]. The Canadian Childhood Asthma Primary Prevention Study demonstrated a 56 percent reduction of asthma frequency by the age of seven in high-risk children through an intervention programme, for the first year of life, that included avoidance of allergen exposure through avoidance of pets, secondhand smoke and dust mites [11]. This study clearly demonstrates that early intervention and appropriate treatment can prevent disease.

The importance of early diagnosis

The importance of early allergen identification is shown by evidence from several long-term multicentre prospective studies. In the study on the prevention of allergy in children in Europe (SPACE), a four percent reduction in sensitisation to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (house dust mites), egg and milk was observed at one year of age, when dust mite-impermeable mattress casings were used for newborns at high risk of atopy (a genetic predisposition to allergy, in this study evidenced by having at least one parent with a diagnosis of inhalant allergies confirmed by diagnostic tests) [12]. A similar reduction in sensitisation was observed in this study's cohort of young school-aged children (five to seven years) [5].

The landmark Preventative Allergy Treatment (PAT) study results showed that progression of allergy to asthma could be prevented in grass and/or birch pollen-allergic children suffering from seasonal rhinoconjunctivitis (hay fever) by treatment with subcutaneous specific immunotherapy (SIT) [13]. This study enrolled children between the ages of six and fifteen years and followed their progress for over ten years. The prophylactic benefit of SIT persisted long after completion of therapy, resulting in approximately 50 percent reduction in the development of asthma for up to seven years after completion of therapy. These studies and others support the strategy of early accurate diagnosis using diagnostic tests in conjunction with other clinical information to facilitate early effective treatment.

The role of sensitive and specific tests in early diagnosis

According to the guidelines of both the American Academy of Allergy Asthma and Immunology (AAAAI) and the European Academy of Asthma, Allergy and Clinical Immunology (EAACI), therapy should not be initiated without specific identification of the allergen, which can be determined by either *in vivo* or *in vitro* (IgE) tests that are sensitive and specific [14]. Accumulating

evidence suggests that even levels below the traditionally accepted 0.35 kU/L cutoff are also indicative of allergic disease. (This cut-off was imposed by the technical limitations of early automated equipment.) Other studies have shown that low levels of IgE in umbilical cord blood in conjunction with hereditary factors may be the best predictors of inhalant allergen sensitisation later in childhood [15].

Allergy diagnosis: in vivo methods

In vivo allergy test is an umbrella term that encompasses several different procedures [Table 1], all of which entail directly exposing the patient to the suspected allergen. The test is positive if the patient has an objective response. These tests can be divided into skin based tests and food challenges. In the skin based tests (skin prick test, intradermal test, scratch test and skin patch test) the allergen is placed on or in the skin along with positive and negative controls for comparison. A positive response is characterised by redness and swelling generally termed the wheal and flare. Typically, the diameter of the wheal is used to determine the amount of reactivity to the allergen; larger wheals represent a greater level of reactivity.

Table 1. In vivo allergy tests

- Skin Prick Test
- Intradermal Test
- Scratch Test
- Skin Patch Test
- Food Challenge Test

Table 1. *In vivo* allergy tests.

In a food challenge the patient ingests the suspected allergen, and signs and symptoms are documented; this test must be performed in a facility that is equipped to handle potentially life-threatening reactions [2]. Ideally, the food challenge test is performed in a double-blind, placebo-controlled manner. With this method, neither the allergist nor the patient knows which sample contains the suspected allergen and which the placebo. This type of test is often performed as a last resort and open challenges (where the physician and the patient are aware of the allergen) are typically carried out instead. Food challenges are not performed in patients with a history of a severe allergic response as they have a very high risk for anaphylaxis and death.

Allergy testing: in vitro methods

Unlike *in vivo* tests, which rely on the release of histamine and other mediators for a positive result, *in vitro* tests measure the concentration of IgE in the circulation that is specific for a particu-

Table 2. Advantages of in vitro tests

- Antihistamines, antidepressants and other interfering drugs do NOT need to be discontinued
- Fully quantitative results
- One blood draw for multiple determinations

Table 2. Advantages of *in vitro* tests

lar allergen and thus have certain advantages over *in vivo* tests [Table 2]. A distinct advantage of *in vitro* testing is that it can be used effectively by physicians of all specialties to diagnose a specific allergy and does not require the extensive training that is needed for *in vivo* testing. *In vitro* testing also allows labs to be closely involved in the diagnosis of allergic disease by providing objective testing that is sensitive and specific. Moreover, since the patient is not exposed to the allergen, the risk of precipitating an allergic response that is life threatening is extremely low.

Despite the wide-spread use of *in vivo* allergy tests among allergists, there are certain situations where *in vitro* tests may be indicated over skin testing [Table 3].

In vitro IgE testing is a valuable diagnostic tool for allergists and primary care physicians because it is comparable to *in vivo* testing, and facilitates accurate diagnosis and appropriate therapeutic intervention. The use of 3gAllergy kit (Siemens Healthcare Diagnostics Inc.) and similar *in vitro*

Table 3. Situations in which in vitro tests may be preferred over skin tests

- Negative skin test despite high clinical suspicion of allergy
- Skin conditions such as eczema that preclude skin testing
- Patients taking long-acting antihistamines, tricyclic antidepressants and other drugs that limit response to allergens in skin tests
- Useful in very young or elderly patients because they generally have reduced histamine reactivity in skin tests.
- Patients with a clinical history that indicates an increased risk of anaphylaxis
- Pregnant patients (to avoid any possibility of a systemic reaction)

Table 3. Situations in which *in vitro* tests may be preferred over skin tests.

assays can foster a more effective collaboration among clinical laboratories, allergists and primary care physicians in the diagnosis and management of allergy.

Conclusions

In vitro tests are playing an increasingly important role in diagnosis and are well established tools that are endorsed by European and American professional allergy organisations. Current evidence supports the utility of diagnostic tests (*in vivo* and *in vitro*) to facilitate early diagnosis and thus prompt and effective treatment. It is not acceptable to treat presumptively without allergen identification. Early treatment has been shown to improve quality of life and prevent progression of the allergy march to asthma (a disease that is associated with significant morbidity and mortality) and thus it facilitates better patient outcomes.

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