Allergic Diseases in Children: An Otolaryngologist's Perspective

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Introduction

Atopy, a term often used interchangeably with allergies, refers to the genetic predisposition to the development of allergic disease and is typically associated with heightened immune responses to common inhaled and food allergens. The phenotype associated with atopy appears to have a complicated and variable genetic origin, with significant genetic-environment interactions[1]. Risk factors for inhalant allergies in children include having a first-degree relative with allergies, food allergy in infancy, and atopic dermatitis.

When describing allergic disease in children, the allergic march hypothesis is often used to explain the progression of allergic findings. This starts with atopic dermatitis in the young child followed by a typical sequence of food allergy, rhinitis and asthma[2-5]. The temporal pattern described in the allergic march may not be a simple progression, and is strongly influenced by both genetic and environmental factors. Keeping this evolution in mind, children with chronic or recurrent upper respiratory inflammatory disease should be evaluated for inhalant allergies.

Allergic rhinitis

Allergic rhinitis (AR) is the most common chronic disease in children in the United States[6], with an incidence ranging from 20-40%[7,8.] In 2009, otolaryngologists surveyed by telephone as part of the Pediatric Allergies in America Survey, estimated that out of children 4 to 17 years old, 41% had allergic rhinitis7.

Allergic rhinitis, as defined by the Allergic Rhinitis and its Impact on Asthma guidelines (ARIA), is a chronic disorder of the upper airway, induced by IgE-mediated inflammation after exposure in sensitized patients to a specific allergen[9]. The symptoms include nasal congestion, rhinorrhea, sneezing, nasal itching and postnasal drainage. Depending on the duration of symptoms, allergic rhinitis is classified as intermittent (symptoms for <4 days per week or for a duration of <4 weeks per year) or persistent (symptoms that occur >4 days per week and are present for >4 weeks per year). The effect on quality of life is subdivided into either "mild disease" (no impairment of daily activities, no sleep interruption, and no troublesome symptoms) or "moderate to severe disease" (one or more of the previously mentioned symptoms). Other guidelines (and the Food and Drug Administration [FDA]) divide AR into seasonal and perennial[10].

Diagnosis

Allergic rhinitis has a varied clinical presentation in children, which depends on age, the duration of allergy on exposure, and extent of comorbid disease. In addition, its symptoms can be similar to those of recurrent upper respiratory infections, a common occurrence in childhood, leading to under diagnosis and treat-

ment of the allergic disease process in these children. Although allergic rhinitis is not life threatening, it can have a significant impact on the child's quality of life[11], affecting school performance, sleep, as well as physical and emotional health8.

The diagnosis of allergic rhinitis is based on a clinical evaluation and allergy testing.

A history of eczema or food allergy in infancy is a frequent manifestation of allergic disease and both are risk factors for the later development of inhalant allergy[12]. It has been shown that infants with atopic dermatitis have a 30% risk of developing asthma and a 35% risk of developing allergic rhinitis[13,14].

Typical history and symptoms associated with inhalant allergies include chronic nasal congestion with intermittent clear drainage, intermittent snoring, itchy watery eyes, sneezing, mouth breathing, pruritus of the nose or eyes, recurrent sinus infections, and chronic middle effusions. The symptoms are worse at certain times of the year, exacerbated by weather changes or with certain allergen exposures. There is often a positive family history of similar symptoms.

On physical exam, findings suggestive of allergic disease include a horizontal line across the bridge of the nose, often referred as an "allergic salute" which results from the constant rubbing of the nose in an upward fashion. Other findings include allergic shiners or dark circles under the eyes, congested nasal mucosa, turbinate hypertrophy, thin, watery nasal secretions, post-nasal drainage and pharyngeal banding among others. Further examination may reveal eczema or wheezing, that is often seen in allergic patients.

Allergy skin testing can be performed in patients of any age[15], however, as previously mentioned, early sensitization to inhalant allergens in infancy occurs in-frequently[2] and there is rarely a need to test for them in children less than 4 years of age. Herr and colleagues[16] used a standardized questionnaire to evaluate 1850 infants at their 18-month check up, to identify children with allergic rhinitis-like symptoms defined as a runny nose, blocked nose and sneezing that was not from a cold. Both symptomatic and asymptomatic children were then allergy tested using a specific inhalant IgE screen. Testing failed to correctly identify those children with a history suggestive of allergic rhinitis. In addition, results of the testing revealed an elevated inhalant-specific IgE in patients without a history of allergic symptoms. This suggests that allergic rhinitis is rare at 18 months of age and that screening infants for elevated specific IgE lacks specificity in identifying infants with clinical symptoms. In older children, allergy testing should not be performed in the absence of clinically relevant symptoms as it yields unacceptable false-positive rates. This was demonstrated in the Third National Health and Nutrition Survey[17] where a positive skin prick test was obtained in 53.9% of 10,509 randomly sampled patients.

In children with a high degree of suspicion for inhalant allergies, testing for indoor allergens only, will identify the majority of sensitized children as demonstrated by Sahiner, *et al*[18]. In their study, 432 children, less than 2 years of age with asthma were tested with either a full panel of inhalant allergens, including indoor and outdoor allergens or indoor allergens alone. The rate of sensitization was equal between the two groups concluding that in the very young, testing for indoor al-

lergens alone, will identify the majority of affected children. It is also important to remember that negative allergy skin testing in early childhood does not exclude sensitization and allergic symptoms at a later age[19].

Treatment

Treatment of allergic rhinitis in children is similar to adults, and consists of avoidance, environmental controls, pharmacologic therapy, and specific allergen desensitization. For detailed information regarding treatment, I refer the reader to an excellent chapter "Update on the Treatment of Allergic Rhinitis" by Dr. F. Baroody and Dr.T Sih, which can be found in the XIV IAPO Manual of Pediatric Otorhinolaryngology. The key points to remember regarding each treatment modality are discussed below.

Avoidance and environmental controls

A labor intensive and expensive option is that of allergen avoidance and environmental controls. Unfortunately it has been demonstrated that despite successful avoidance measures, clinical efficacy in controlled studies is often disappointing[20-23]. The Clinical Practice Guideline on Allergic Rhinitis, considers allergen avoidance and environmental manipulation as an "option" for patients who have identified allergens that correlate with clinical symptoms[15].

Pharmacotherapy

Pharmacotherapy for allergic rhinitis is categorized as either targeted therapy (decongestants, antihistamines, leukotriene receptor antagonists, etc.) or immunomodulation (steroids, immunotherapy, monoclonal antibodies). The selection of a specific treatment option for a patient depends on multiple factors including the patient's age, symptom profile, medication cost, response to previous treatment, ease of administration, associated medical conditions and side effects..

The mainstay of treatment for allergic rhinitis is the use of intranasal steroids. They are strongly recommended for patients whose symptoms affect their quality of life[15]. Studies have shown their effectiveness in the reduction of nasal symptoms including congestion, sneezing, and rhinorrhea, as well as ocular symptoms, in both adults and children[24,25]. By reducing nasal symptoms, intranasal steroids significantly improved the quality of life[24] and sleep of patients with allergic rhinitis[26,27]. A concern regarding their use in children is the effect intranasal steroids may have on growth. This has been investigated in controlled studies and although the findings are mixed, they suggest that, of the intranasal steroid preparations studied in children, fluticasone propionate and mometasone furoate showed no effects on growth compared with placebo[28,29]. Therefore, in clinical practice, it seems prudent to use the intranasal steroid preparations shown to have no negative impact on growth in children.

Oral antihistamines have been shown to be beneficial in children with allergic rhinitis with complaints of sneezing and itching[31]. In almost all situations, less sedating, second generation antihistamines are preferred. Topical intranasal antihistamines have been shown equality or superiority over oral antihistamines for the treatment of nasal symptoms[15]. They have the advantage of direct delivery to the affected nasal tissues while limiting systemic effects[30], however in children they are limited to children 5 years or older.

Currently, Oral Leukotriene Receptor Antagonists (LTRAs) are not recommended as primary therapy for patients with allergic rhinitis[15]. However, there is conflicting evidence as to their efficacy when used in combination with an oral antihistamine. Some studies have shown better clinical response when used in combination than when either medication is used alone[32,33], while others showed no effect[34,35].

Immunotherapy

Immunotherapy should be considered for children with diminished quality of life, who fail to respond to pharmacotherapy, with or without environmental manipulation. Both subcutaneous and sublingual immunotherapy in children has been shown to be effective[36-38]. Allergen specific immunotherapy is the only proven treatment for allergic rhinitis that has the potential to change the natural history of the disease. It is unique in its beneficial effect on allergies after the treatment is discontinued, in reducing additional sensitizations, and in the reduction in development of allergic asthma in children[36]. Immunotherapy has also been shown to improve the control of comorbid conditions such as asthma, conjunctivitis, and improve disease specific quality of life[15]. Risk, time, and expense of immunotherapy needs to be carefully weighed against the severity and ability to control allergic disease.

Other considerations in the allergic patient

Allergic rhinitis is rarely found in isolation and needs to be considered in the context of systemic allergic disease, which can be associated with numerous comorbid disorders. The following are some of the more commonly seen disorders in children with allergic disease.

Allergic conjunctivitis

There is a large overlap between allergic rhinitis and allergic conjunctivitis and it is often considered one disease: rhinoconjunctivitis. Bielory[39] estimates that there is 80% overlap based on several epidemiologic studies with 10% having allergic rhinitis alone and 10% having allergic conjunctivitis alone. The large ISAAC studies looked at rhinoconjunctivitis as single diagnosis and reported symptoms in 8.5% of 6 to 7 year olds and 14.6% in 13 to 14 year olds. As such, children with allergic rhinitis should be assessed for allergic conjunctivitis and topical antihistamine considered[39-41].

Otitis media with effusion (OME)

The role of allergy in the pathogenesis of middle ear disease has been a matter of debate for many years. A true causative association between the two has not been well established, though a recent study looking at a large database of pediatric visits found that in children 6 years and older, the presence of allergic rhinitis significantly increased the likelihood of OME and Eustachian tube dysfunction[42]. Well-designed trials, with better-defined subpopulations are needed to further evaluate the possible causality between AR and OME in the older child. At this time the resulting literature, including the recent Clinical Practice Guidelines on Otitis Media with Effusion update[15], do not support the treatment of isolated OME with antihistamines, decongestants, oral or topical steroids in children[43-46].

Rhinosinusitis

The close anatomical proximity of the nose and paranasal sinuses as well as common inflammatory processes, has led to the concept of a unified airway[47]. There is a great deal of evidence that, especially in atopic individuals, rhinitis and rhinosinusitis are manifestations of a systemic response. Both are characterized by inflammation with overlapping symptoms such as impaired nasal breathing and rhinorrhea. The relationship between allergic rhinitis and rhinosinusitis has been investigated in both adults and children. For example, more than 80% of children with rhinosinusitis have a family history of allergy, as opposed to a general population allergy frequency of 15-20%[48].

Rhinosinusitis is commonly seen in patients with asthma and allergic rhinitis and is a significant trigger of asthma in children and adults[49]. Allergic rhinitis has also been linked to children with asthma and otitis media with effusion, with these patients exhibiting a higher incidence of rhinosinusitis[50]. From the standpoint of treatment outcomes, Ramadan and Hinerman[51] in a retrospective cohort study noted that immunotherapy before endoscopic sinus surgery in children with allergic rhinitis significantly improved the surgical success rate from 64 to 84%. However, there are also studies suggesting a lack of correlation between allergic disease and pediatric rhinosinusitis[52].

Sleep disordered breathing (SDB)

Sleep disturbance has emerged as one of the major impacts of allergic rhinitis, and has been demonstrated to be more common in patients with allergic diseases than in the general population[53-55]. Nasal congestion is believed to be the most important mechanism behind poor sleep and daytime sleepiness,, and allergic rhinitis has been identified as a potential risk factor for sleep disordered breathing[56]. In a survey of patients with allergic rhinitis, 49% of children and 51% of adults reported waking up and 49% of children and 48% of adults difficulty falling asleep because of nasal congestion[57]. Epidemiological studies both support and refute the hypothesis that sleep disordered breathing and allergic rhinitis are interconnected in adults and children[58-62].

A qualitative systematic review of the last 25 years was published examining the evidence of the association between allergic rhinitis and SDB in children. The authors identified 18 articles with 27, 015 patients that met inclusion criteria[63].

Two-thirds of the articles demonstrated a statistically significant association between allergic rhinitis and SDB. It should be noted that the majority (61%) of the articles did not utilize formal polysomnography for the diagnosis of SDB and allergy testing was not frequently utilized (39%) to diagnose allergic rhinitis.

From the immunologic standpoint, Ni and colleagues[64] looked at the role of Th17/Treg ratio in children with SDB and its relationship with allergic rhinitis. Their study revealed that compared to the control group, children with SDB exhibited a significant increase in the number of peripheral Th17 cells (pro-inflammatory) and dramatic decreases in the number of T reg cells (involved in immune tolerance). In addition, the increase was significantly larger in children with SDB who also had allergic rhinitis compared to the SDB group without allergic rhinitis. They concluded that Th17/Treg imbalance may increase the risk of developing SDB, and that allergic rhinitis may promote the development of the disease.

In conclusion, it seems appropriate that preoperative evaluation and proper management of allergic rhinitis should be considered in children with SDB

Asthma

Because of the epidemiologic link between chronic upper and lower airway inflammation[65], awareness of asthma is important for the otolaryngologist.

In children considered at risk for asthma, asking specific question regarding sleep disturbance, breathing difficulty with sports, coughing at night, wheezing not associated with acute illness or after exposure to irritants or allergens, can help identify those children that warrant further evaluation and treatment.

Studies regarding therapeutic aspects of allergic rhinitis and asthma indicate that treatments targeting either of them may alleviate the coexisting condition[66,67]. There are strong indications from observational data that treating allergic rhinitis may result in better asthma outcomes in terms of symptoms, emergency department visits and hospitalizations, and lower overall costs68.

There is currently little proof that allergen avoidance or pharmacotherapy may be able to affect the long-term natural history of respiratory allergy, in particular the development of asthma[21,69,70]. Much more promising is the field of allergen specific immunotherapy. Allergen-specific immunotherapy is an important treatment modality that may alter the natural course of allergic disease, including interfering with the development of allergic asthma in some patients[71].

Asthma is under diagnosed, impairs quality of life, and even mild persistent asthma is potentially life threatening[72]. The ability to identify asthma, initiate treatment, and ensure appropriate continued care should be the goal of every specialist who cares for children that are known to be at increased risk of this common disease.

Conclusion

Because allergy is a common contributor of upper airway inflammation, allergic rhinitis can present with multiple other co-morbidities. Allergic rhinitis can impact performance at school and the quality of life of the child and family.

The treatment modalities of allergic rhinitis include avoidance and environmental controls, pharmacotherapy and immunotherapy. Though the majority of patients respond to pharmacotherapy, allergen specific immunotherapy offers the only treatment that results in long term control of symptoms, with disease modifying effects including the prevention of additional allergy sensitizations and avoidance of allergic asthma in some children.

A working knowledge of pediatric allergy is beneficial in the evaluation and treatment of children presenting to the otolaryngologist and offers an opportunity to substantially improve the quality of life in these children.

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