

Pediatric allergic rhinitis and comorbid disorders

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Allergic rhinitis (AR) is rarely found in isolation and needs to be considered in the context of systemic allergic disease associated with numerous comorbid disorders, including asthma, chronic middle ear effusions, sinusitis, lymphoid hypertrophy with obstructive sleep apnea, disordered sleep, and consequent behavioral and educational effects. The coexistence of AR and asthma is complex. First, the diagnosis of asthma may be confounded by symptoms of cough caused by rhinitis and postnasal drip. This may lead to either inaccurate diagnosis of asthma or inappropriate assessment of asthma severity with over treatment of the patient. The term "cough variant rhinitis" is therefore proposed to describe rhinitis that manifests itself primarily as cough that results from postnasal drip. AR, however, also has a causal role in asthma; it appears both to be responsible for exacerbating asthma and to have a role in its pathogenesis. Postnasal drip with nasopharyngeal inflammation leads to a number of other conditions. Thus sinusitis is a frequent extension of rhinitis and is one of the most frequently missed diagnoses in children. Allergen exposure in the nasopharynx with release of histamine and other mediators can cause Eustachian tube obstruction possibly leading to middle ear effusions. Chronic allergic inflammation of the upper airway causes lymphoid hypertrophy with prominence of adenoidal and tonsillar tissue. This may be associated with poor appetite, poor growth, and obstructive sleep apnea. AR is therefore part of a spectrum of allergic disorders that can profoundly affect the well being and quality of life of a child. Prospective cohort studies are required to assess the disease burden caused by AR in childhood and to further assess the potential educational impairment that may result. Because AR is part of a systemic disease process, its management requires a coordinated approach rather than a fragmented, organ-based approach. (*J Allergy Clin Immunol* 2001;108:S9-15.)

Key words: Allergic rhinitis, asthma, cough variant rhinitis, postnasal drip, sinusitis

Allergic rhinitis (AR) is relatively easy to recognize in adults; however, it has a multiplicity of symptoms in the child (Table I). The clinical presentation varies, depending on the duration of allergy on exposure (perennial versus seasonal and episodic exposure), age of the child, and extent of comorbid disease.

Abbreviations used

AR: Allergic rhinitis
ETO: Eustachian tube obstruction
ICAM-1: Intracellular adhesion molecule
MEE: Middle ear effusion
OSA: Obstructive sleep apnea

The symptoms most easily recognized in adults include nasal pruritus, rhinorrhea, and sneezing. These early-phase symptoms, largely induced by histamine, may be less obvious in the case of children who are chronically exposed to allergen when chronic symptoms lead to a variety of clinical presentations. Unlike adults, young children rarely complain of nasal congestion. However, one common presentation of AR in childhood is recurrent sore throats and upper respiratory tract infections. Although allowances are made for frequent infections in young children, there are a significant proportion of children who appear to have recurrent upper respiratory infections. As soon as one episode subsides, it is followed by another. The diagnosis of AR is often missed in these children, who are thus treated inappropriately with multiple doses of antibiotics. Sometimes they are even referred for an immunologic evaluation to rule out immunodeficiency.

Children with chronic AR typically have hypernasal speech, fatigue, decreased appetite, and poor growth. Indeed, failure to thrive (or inadequate weight gain in children) has long been known to result from chronic infections and inflammatory conditions such as sinusitis, which frequently coexist with AR. Data document impaired growth in children with AR and tonsillar hypertrophy, in the absence of paranasal sinus disease.¹

One of the most important symptoms of AR in children is chronic cough, but there is little recognition of this in clinical practice. Cough in AR and sinusitis results from postnasal drip and irritation of the larynx. Although the importance of postnasal drip has been recognized for more than half a century by otolaryngologists, the recognition of postnasal drip as a cause of chronic cough has all but disappeared from modern pediatric practice.

AR is an organ-specific manifestation of allergic disease. As such, it coexists with other organ-specific disorders that have a common allergic basis. It is therefore rarely found in isolation but frequently has associated comorbid disorders. Thus, of 69 children with seasonal AR caused by grass pollen seen last summer in our allergy clinic, 80% had pharyngitis, 70% had conjunctivitis, 40% had seasonal asthma, and 37% had seasonal eczema.

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TABLE I. Pediatric rhinitis: Range of symptoms

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- Cough
 - Sneezing
 - Nasal pruritus
 - Nasal congestion
 - Sore throats – recurrent infections
 - Halitosis
 - Respiratory distress – infant
 - Hypernasality
 - Behavioral problems
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TABLE II. Pediatric AR and its comorbid disorders

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- Conjunctivitis
 - Pharyngitis
 - Sinusitis
 - Asthma
 - Eczema
 - Otitis media
 - Lymphoid hypertrophy/obstructive sleep apnea
 - Speech impairment
 - Failure to thrive
 - Reduced quality of life
-

Recent recognition of these associated comorbid disorders has prompted a debate as to whether early recognition and treatment of AR could diminish and prevent associated comorbid disorders. In this article, we discuss specifically the link between AR and asthma, chronic middle ear effusion with hearing loss, sinusitis, lymphoid hypertrophy and obstructive sleep apnea, sleep disorders, and consequent behavioral and educational effects (Table II). We conclude that AR is a systemic disease that significantly affects quality of life in children and whose treatment requires a systemic approach.

COMORBID DISORDERS

Asthma

Several possible relations exist between AR and asthma: (1) AR may confound the diagnosis of asthma; (2) AR may be statistically associated with asthma; (3) AR may exacerbate coexisting asthma; and (4) AR may have a causal role in the pathogenesis of asthma.

Confounding role of AR in asthma. The relation between AR and asthma is complicated by the fact that they share common symptomatology. AR and sinusitis have long been known to cause postnasal drip with resultant cough, particularly at night. In the past 2 decades there has been increasing awareness of the importance of nocturnal cough in poorly controlled asthma. Hannaway and Hopper² described 32 children with cough-variant asthma. These children had chronic cough, had never been heard to wheeze, and improved after bronchodilator treatment.

Recognition of the importance of cough in pediatric asthma and the emergence of cough-variant asthma as a separate entity has enhanced our clinical ability to recognize asthma. However, it has reduced our ability to detect rhinosinusitis.

More recently, in a community-based study, Faniran et al³ identified children with persistent cough but concluded that these children were different from asthmatic children and failed to identify cough-variant asthma. They concluded that "...cough variant asthma is probably a misnomer for most children in the community who have persistent cough." Importantly, a significant proportion of these children had been diagnosed as suffering from hay fever in the past 12 months, but the authors do not suggest that AR and postnasal drip could account for the chronic cough.

The diagnosis of AR in children with chronic cough is critical because incorrect diagnosis of cough-variant asthma leads to escalating treatment with inhaled steroids, β -agonists, and eventually oral steroids, with poor response to treatment. Identification of AR as the cause of cough allows the appropriate treatment for nasal inflammation: (1) allergen avoidance; (2) a course of non-sedating, long-acting antihistamine medication; and/or (3) intranasal steroids.

Furthermore, because AR and asthma often coexist, the asthma may appear to be worse than it really is because a significant proportion of the cough caused by postnasal drip is misattributed to asthma. Asthma may therefore be overtreated with high doses of inhaled steroids. Identification and treatment of AR in the setting of asthma therefore has a "steroid-sparing" effect because it allows a reduction in the total dose of inhaled steroids. This effect has important implications for clinical research. Studies that demonstrate that treatment of AR results in asthma improvement must not only show a decrease in cough but must document reductions in other parameters as well (ie, wheeze, medication usage, and improvement in objective measurements of lung function). A reduction in cough as the result of treatment of AR could incorrectly be interpreted as an improvement in asthma.

Thus failure to diagnose AR may result in inappropriate assessment of asthma severity, inappropriate treatment of patients, and increased steroid usage. The term "cough-variant rhinitis" is proposed for children in whom cough is the principal presenting symptom of AR (Fig 1).

Association of AR and asthma. The established association between asthma and rhinitis has long been recognized. Mullarkey et al⁴ evaluated 142 patients with rhinitis and found that 58% of patients with seasonal AR had asthma. Sibbald and Rink⁵ in a general practice-based survey found that wheezing was more common in patients with AR as opposed to nonallergic rhinitis (negative skin tests). A pediatric community-based study of 747 healthy children in the United States found asthma in 32% of those with AR and positive skin tests as compared with 8.4% of children with nonallergic rhinitis.⁶

A study by Setticone et al⁷ identified AR in college students in 1963. Follow-up evaluation 23 years later demonstrated that subjects who had AR in 1963 had a 3-

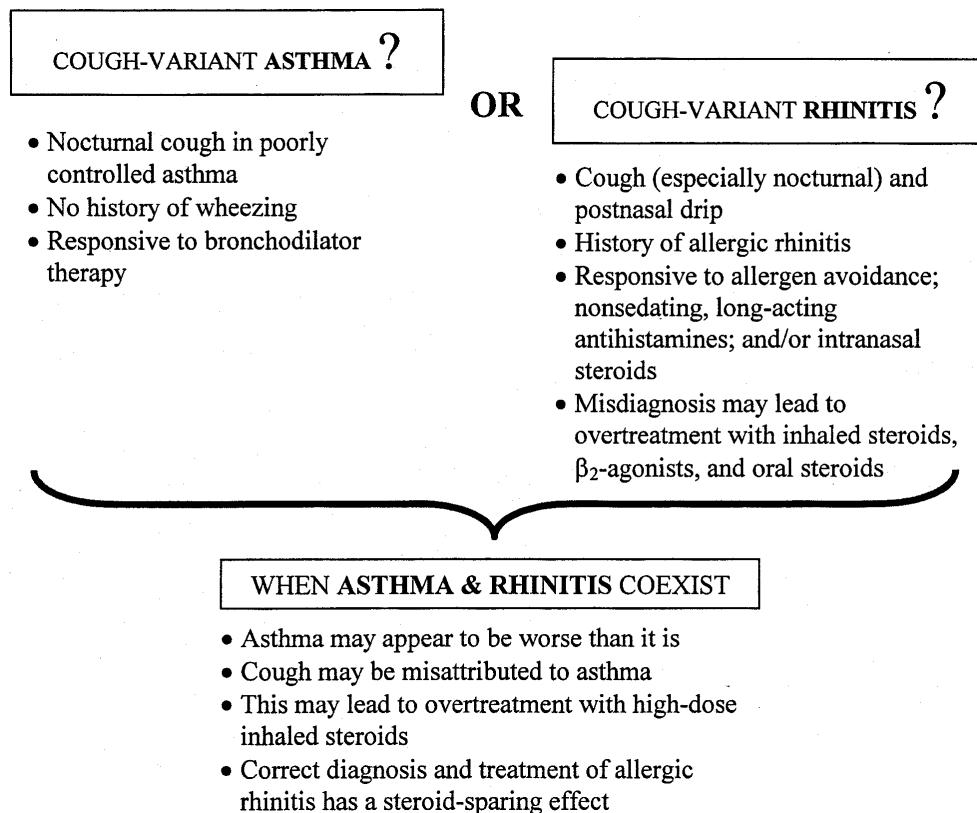


FIG 1. Clinical differentiation and treatment of pediatric AR and asthma.

fold greater risk of developing de novo asthma as compared with subjects without AR.

Causal relation between AR and asthma. Studies demonstrating a statistical association between AR and asthma do not allow us to conclude that AR causes asthma, even though it usually precedes the development of asthma. One possible explanation is that both AR and asthma have the same underlying cause, namely exposure to allergens with allergic sensitization. Indeed, studies show that exposure to allergens and sensitization are important risk factors for childhood asthma. Clinical experience tells us that not all children with asthma have AR, although such observations do not exclude the possibility of subclinical inflammation in the nasal mucosa.

There are several possible causal mechanisms that have been postulated to explain a link between AR and asthma (Table III). The nasobronchial reflex is one such possible mechanism. Kaufman et al⁸ demonstrated in 1969 that silica particles in the nasopharynx of 10 male adult subjects caused an increase in airway resistance in all 10 subjects. Atropine ingestion prevented the increase in airway resistance, suggesting a neural pathway. Subsequently, it has been shown that application of a local cold stimulus to the nose produced bronchoconstriction.⁹

TABLE III. Possible causal mechanisms of an allergy-asthma link

• Nasobronchial reflex (nasal irritants, allergens, or cold stimuli)
• Rhinovirus adhesion theory (increased susceptibility to allergic inflammation and ICAM-1 expression)
• Postnasal drip (carriage of inflammatory cytokines/mediators from nasopharynx to lower airways)
• "Migration" of T-cell responses to other tissues after initial sensitization

Alternatively, it has been proposed that a blocked nose results in mouth breathing and increased exposure of the lower airways to dry or cold air and allergen.¹⁰ Although there are few data to support this mechanism, it may explain how an increased allergen load could reach the lower airways in asthmatic individuals who breathe through their mouths.

The rhinovirus adhesion theory suggests a possible link between allergic nasal inflammatory viral infections and asthma. Intracellular adhesion molecule (ICAM-1) expression in the nasal mucosa is increased following

allergen exposure¹¹⁻¹³ and is even expressed in asymptomatic patients with AR.^{14,15} Subjects with an increase in allergic inflammation and ICAM-1 expression are more susceptible to upper respiratory tract infections because ICAM-1 is the receptor for rhinoviruses.¹⁶ Rhinovirus infection is an important viral precipitant for asthma exacerbations. Thus allergic inflammation in the nose could facilitate rhinovirus infection in allergic individuals, with consequent asthma exacerbation.

Yet another postulated mechanism is that of postnasal drip allowing inflammatory cytokines and mediators from the nasopharynx to be inspired into the lower airways, causing inflammation and bronchoconstriction. Although there is no evidence to support this in human beings, there are animal studies demonstrating such a mechanism.¹⁷

Increased recognition of the role of lymphocytes, especially T cells, in the pathogenesis of allergic disease allows us to understand how sensitization to an allergen and subsequent local inflammation can lead to allergic inflammation in other tissues. The systemic production of allergen-specific IgE that follows local allergic sensitization, and the ability of T cells to migrate from regional lymph nodes and "home in" on other tissues, could explain how allergic inflammation in the upper airways may "spread" to the lower airways.

One approach to determining whether AR exacerbates asthma is to study the effects of treatment of AR on asthma symptoms in children with both diseases. A number of studies have addressed this question. Watson et al¹⁸ demonstrated in a double-blind, placebo-controlled, cross-over study that treating perennial rhinitis with intranasal steroids in children with coexistent asthma resulted in improvement in bronchial hyperresponsiveness and improved evening asthma symptom scores. Further confirmation of this effect is needed, not only in order to establish a causal link between AR and asthma, but to optimize treatment of asthma.

AR and sinusitis

Sinuses are not fully developed in young children, and the frontal sinuses may not develop completely before adolescence. In clinical practice, this fact has been overstated to create the misconception that young children do not have sinuses. Consequently, sinusitis is one of the most underreported diagnoses in young children. Furthermore, the clinical presentation of chronic sinusitis in children is more subtle; only rarely do children have acute signs of fever, headache, and purulent rhinorrhea. Usually children have chronic cough, recurrent upper respiratory tract infection, poor appetite, decreased weight gain, lethargy, halitosis, vomiting, and recurrent ear infections. Nasal symptoms are not always prominent. Consequently, the prevalence of sinusitis in children is not known. Numerous authors use the term "rhinosinusitis" rather than sinusitis, for several reasons: Normally, rhinitis precedes sinusitis; the absence of rhinitis is extremely rare in the presence of sinusitis; the nasal and sinus mucosa are contiguous; and the clinical

presentation of rhinitis and sinusitis may be very similar. Pediatric sinus disease is characterized histologically by marked tissue eosinophilia, with mast cells expressing the activation marker EG2.¹⁹ Although the association of allergy with sinusitis is not clearly established in adults, there is evidence of an association between AR and sinusitis in children.^{20,21} These studies document an increased association between AR, positive skin tests, and sinusitis, in the setting of pediatric allergy and otorhinolaryngology specialist clinics. There are, however, no studies that define sinusitis in a normal pediatric population, to determine the relative importance of allergy as a cause of sinusitis.

Chronic middle ear effusions, hearing deficit, and speech impairment

There is a widespread belief among pediatricians and ENT surgeons that allergy plays an important role in otitis media. One hypothesis is that mediators and cytokines released by mucosal mast cells and other inflammatory cells of the nose and nasopharynx cause eustachian tube obstruction (ETO). Thus the eustachian tube is unable to ventilate the middle ear, leading to increased nitrogen absorption in the middle ear. The persistent negative pressure will, over time, lead to middle ear effusion (MEE).^{22,23}

There are currently experimental data, albeit in a small number of patients, to support the idea that histamine and allergen exposure play an important role in causing ETO. Thus in one study, 15 patients who received intranasal histamine had significant ETO.²⁴ Pretreatment with terfenadine reduced the frequency of ETO, but this effect was not significant. Similarly, instillation of other inflammatory mediators in the nose (bradykinins, methacholine, prostaglandin D₂, and PGF₂- α) also resulted in ETO.²⁵ Further studies suggest a hyperresponsiveness of the nasopharyngeal and/or tubal mucosa to histamine in subjects with AR.²⁶

Similarly, studies demonstrate ETO after intranasal challenge with house dust mite,²⁷ intranasal ragweed, and intranasal grass pollen²⁸ in allergic children. In vivo exposure to pollens has been shown to cause ETO and negative middle ear pressure. In one study of 198 adult subjects, 24% had evidence of ETO early in the grass-pollen season; 2 weeks further into the pollen season the prevalence of ETO had increased to 48%.²⁹

In a pediatric study of 15 children allergic to ragweed, seasonal pollen exposure was associated with an increase in ETO from 14.7% preseasonally to 33.3% during the ragweed season. Antihistamine medication did not prevent the development of ETO.³⁰

Data on the occurrence of MEE in children with allergies comes mainly from highly selected groups of children attending ENT or allergy clinics. Such uncontrolled studies report the prevalence of respiratory allergy in children with chronic MEE as ranging between 40% and more than 90%.^{31,32} Thus one study of 519 children with chronic MEE reported that 98% had associated nasal allergy, 34% had asthma, and 25% had eczema.³³ How-

ever, these children were seen in a pediatric allergy clinic and therefore reflect a strong selection bias.

There have been a number of controlled studies that have established an increased prevalence of allergy in children with chronic MEE. Corey et al³¹ reported positive radioallergosorbent (RAST) tests in 61% of patients with MEE as opposed to 41% in a control group. A study from Japan found a significantly increased prevalence of nasal allergy in children with secretory otitis media as compared with a control group of randomly selected children from a kindergarten.³⁴ Such studies, however, are difficult to control for age, sex, and other important factors, such as duration of breast feeding and exposure to cigarette smoke. These studies highlight the importance of conducting cohort studies in a normal population to establish the role of allergy in chronic MEE, allowing for confounding variables.

Given the difficulties in selecting appropriate control groups in cross-sectional studies, and in carrying out large prospective cohort studies, one approach is to evaluate children with seasonal AR for ETO and MEE during the pollen season and outside the pollen season. In this manner, subjects with AR can act as their own controls. A study of children with ragweed pollen allergy found an increase in the rate of ETO and clinically significant hearing loss compared with preseasonal assessment in the same group of children.³⁰

Children with AR, in addition to having MEE and hearing impairment, may have a characteristic hypernasal quality to their voice. Indeed, one study documents disorders in vocal quality and/or articulation in 50% of patients with AR, with 13% suffering from reduced auditory acuity.³⁵

Because MEE with hearing loss can cause delay in speech development during childhood, there is concern that AR with chronic MEE or other comorbid disease could significantly affect speech development in children. Regrettably, there are no data that compare speech development in this group of children with that of nonatopic children.

Obstructive apnea and sleep impairment

Children with AR usually have lymphoid hypertrophy of the upper airways. This is particularly evident in the cervical lymph node chain, and the adenoids.

One study from an otolaryngology department found an association between tonsillar hypertrophy and AR. Only 8% of children in 6th grade without tonsillar hypertrophy had AR, whereas AR was apparent in 29.7% of children with tonsillar hypertrophy.¹

Children with AR often become mouth-breathers and snore at night as a result of nasal obstruction and adenoidal hypertrophy. Indeed, patients with AR complain of difficulty falling asleep at night and of disrupted sleep during the night. To date there are no controlled polysomnography studies on quality of sleep in children with AR.

One study by McColley et al³⁶ assessed 39 children with habitual snoring (aged 1 to 7 years) by nocturnal polysomnography. Thirty-six percent of these patients

were sensitized to allergens, as determined by RAST, which is significantly higher than expected for the normal pediatric population. The frequency of obstructive sleep apnea (OSA) in subjects with positive RAST tests was about 50% greater than in the nonatopic group of children who snored. The authors suggest an association between snoring and allergy and report an increased frequency of obstructive sleep apnea in allergic children. OSA represents an important pathology in children that causes nocturnal hypoxia and can result in cor pulmonale. The pediatrician must consider this possibility in the assessment of children with AR who snore and have disturbed sleep.

Fatigue and learning impairment

Children with AR frequently complain of disordered sleep, daytime somnolence, and inability to concentrate. Recent studies document daytime somnolence in children with AR. Craig et al³⁷ reported an association between daytime somnolence and nasal congestion in a group of patients with AR. Treatment with nasal steroids caused a significant reduction in nasal stuffiness and sleep disturbance and a trend toward a reduction in daytime somnolence, which was not statistically significant. Baraniuk et al,³⁸ in a study of chronic fatigue syndrome, failed to document an increase in AR in these patients. They compared symptoms of fatigue among normal subjects and groups of patients with chronic fatigue syndrome, symptomatic AR, normal subjects, and patients with rheumatologic disease. Interestingly, patients with AR (unlike the group with rheumatologic disease) had significantly increased symptoms of fatigue intermediate between levels of fatigue seen in normal subjects and patients with chronic fatigue syndrome.

Although adolescents with AR are less likely to complain of insomnia than adults, they report having problems with concentration, particularly with schoolwork. Regrettably, there are no studies evaluating academic performance in patients with AR as compared with normal controls. One might expect that symptoms of rhinoconjunctivitis, accompanied by sinusitis, MEE with hearing impairment, asthma, impaired quality of sleep, daytime somnolence, and decreased concentration, would lead to impaired learning ability and a decline in academic performance. Indeed, Vuurman et al³⁹ reported that hay fever significantly impairs academic performance in children as measured by a battery of tests that assesses the ability to learn new tasks. They found that treatment of AR with short-acting, sedating antihistamine medication causes a further decline in learning ability. The decline in learning ability seen in children with AR was only partially relieved by the use of a nonsedating antihistamine.

SUMMARY

Pediatric AR and its associated disorders cause significant morbidity. This results in significantly impaired quality of life in both young children and adolescents.

Pediatric AR should be considered as part of a systemic disease process and should not be treated in isolation. AR must be treated as part of a systemic allergic inflammatory process, with attention paid to its comorbid disorders. This has important implications for the evaluation and treatment of patients with AR. A multidisciplinary approach involving pediatric allergists, otolaryngologists, respiratory pediatricians, dermatologists, and ophthalmologists is required to improve both patient care and quality of life. Conversely, fragmented, specialist-based care that is not coordinated can be detrimental to the patient. The child with AR, asthma, and eczema may receive treatment for many months with inhaled steroids, intranasal steroids, topical cutaneous steroids, and occasional courses of oral steroids. A coordinated approach is required to prevent such steroid loading and its potential side effects.

Identification and treatment of AR has important implications for the treatment and prevention of comorbid disorders and asthma in particular. First, AR must be carefully differentiated from asthma. As recognition and early treatment of AR could have important consequences in terms of reducing the prevalence and severity of asthma, there is a need to perform further clinical studies that address these issues.

Reliable data on the effects of AR on the development of MEE with hearing impairment, sinusitis, impaired sleep, and reduced academic performance in children need to be gathered in the community. Such information can only be derived in prospective cohort studies of normal children in which AR and its comorbid disorders are carefully defined and analyzed. It is imperative that this information be obtained so that we understand the full impact of AR on child health. This will lead to improvement in health care provisions for this increasingly prevalent pediatric disease.

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