



Extranasal Manifestations of Allergy in the Head and Neck

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Abstract

Purpose of Review Allergic rhinitis and allergic asthma are well-described disease entities with broad exposure in clinical and research allergy forums. Associations between allergic inflammation and upper airway diseases of chronic laryngitis, otitis media, obstructive sleep apnea, and oral allergy syndrome are less well understood and described in the literature.

Recent Findings This review discusses the relationship between atopy and diseases of the upper airway, oral cavity, larynx, and ear. The similar respiratory mucosal lining the upper aerodigestive tract, with sensitized mast cells and inflammatory mediators in the submucosa, results in a variety of extranasal manifestations of allergic diseases in the head and neck which are less well characterized.

Summary Associations between allergic inflammation and upper airway diseases of chronic laryngitis, otitis media, obstructive sleep apnea, and oral allergy syndrome are less well understood and described in the literature. This review will summarize the relevant pathophysiology and symptomology, association with allergic sensitization, and clinical considerations of these disorders.

Keywords Atopy · Allergy · Oral allergy · Laryngitis · Otitis media · Eustachian tube

Introduction

Allergic rhinitis and allergic asthma are well-described and common chronic airway disorders caused by inhalation of allergens reacting with sensitized mast cells on the mucosal surfaces in the nose and lungs. Within the head and neck, there are other less-studied mucosalized surfaces which are also affected by mast cell sensitization to airborne allergens. The mucociliary blanket of respiratory epithelium extends beyond the nasal cavity and lungs to include the paranasal sinuses, eustachian tube and middle ear space, larynx, and some parts of the oral cavity and pharynx. Sensitized mast cells within these extranasal sites in the head and neck result in allergic manifestations that cause specific symptoms in the organ of disease (Table 1). Extranasal manifestations of allergic

sensitization in the head and neck affect the larynx, the middle ear, the oral cavity, and the pharynx. This review summarizes recent literature regarding current knowledge of the extranasal manifestations of allergy in the head and neck.

Laryngeal Manifestations

The laryngeal manifestations of allergy and the significance of allergy in causing acute and chronic laryngitis are controversial in the literature. There exist numerous reports of inflammatory changes in the larynx, without a definitive causal agent. The majority of chronic laryngitis is attributed to laryngopharyngeal reflux (LPR) as the primary culprit. However, given the lack of diagnostic criteria, consistent physical exam findings, or diagnostic tests, the large number of patients diagnosed and treated for this disorder raises the question of whether LPR has been over diagnosed or misdiagnosed [1•]. Alternative explanations for chronic laryngitis, including allergic laryngitis, have been studied.

Allergic inflammation can affect the larynx through both direct inhalant activation of type 2 inflammation in the laryngeal mucosa or through increased mucus production and trafficking of mucus through the laryngeal inlet from other

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Table 1 This table briefly presents several sites and systems of the head and neck that are affected by allergy, alongside typical presenting symptoms, exam findings, and important notes regarding the pathology

Affected site/system	Common symptoms	Physical exam/findings	Additional notes
Larynx	Dysphonia, throat clearing, throat itching, cough, and globus sensation	Sticky/stranding mucus within the endolarynx, laryngeal erythema/hyperemia, vocal cord edema	Laryngeal allergy can be difficult to differentiate from laryngopharyngeal reflux. Allergy testing and history are useful in differentiating one entity from another
External and middle ear	Hearing loss, inner ear itching, ear fullness	Middle ear effusion, occasional allergic rhinitis	The relationship between allergic rhinitis and otitic allergy is controversial. Although some data suggests that medical management of allergic rhinitis may improve middle ear effusions, this relationship has not clearly been established
Sleep disorder breathing	Seasonally worsened quality of sleep, more frequent apneic events and night-time awakenings	Seasonally worsened apnea-hypopnea index, edematous nasal, and oropharyngeal mucosa	Two theories exist for the observed relationship between sleep disorder breathing and allergic rhinitis: (1) increased airway inflammation results in more obstruction and higher frequency/quality of apneic events; (2) inflammatory dysregulation may result from circulating inflammatory mediators that disrupt sleep on a central level
Oral cavity and pharynx	Lip itching, oropharyngeal itching, paraesthesias. Less commonly stomach irritation, diarrhea, vomiting	Angioedema of upper aerodigestive track	Immunoelectrophoresis technique has demonstrated the existence of antigenic correlation between pollen and various foods. For instance, those allergic to birch pollen also cross-react with a myriad of foods such as apple, kiwi, beans, potato, hazelnut, and basil

proximal and distal sites in the airway. Krouse et al. discussed the common presentations of patients with allergic manifestations of the larynx [1•]. These patients will typically present with dysphonia, throat clearing, throat itching, cough, and globus sensation in addition to sticky, stranding mucus within the endolarynx. While many of these symptoms are non-specific and often attributable to LPR, the symptom of throat itchiness may be more sensitive for atopic disease as it is a symptom more characteristic of the histamine response.

The pathophysiology of allergic laryngitis is not completely clear. In their study, Belafsky and colleagues utilized 24 guinea pigs to evaluate triggers for laryngeal inflammation [2]. The authors sensitized the animal model to dust mite antigen. They then exposed their guinea pigs to the antigen and to iron soot. The exposure to these substances was done either alone or in combination. They then examined the laryngeal and tracheal submucosa for eosinophilic inflammation. They were able to demonstrate that the combination of iron soot and dust mite antigen resulted in significant eosinophilic infiltration, but that the two substances on their own did not cause significant inflammation. Their data seems to suggest that environmental pollution and allergy work synergistically to cause laryngeal inflammation.

The symptoms of allergic laryngitis often overlap with those of LPR; hence, a thorough history and physical exam in addition to work-up are crucial in differentiating one from the other. The endoscopic diagnosis of allergic laryngitis can be difficult to differentiate from that of allergic laryngitis. In one study, Eren et al. examined endoscopic laryngeal findings and whether LPR can be diagnosed without knowledge of the patient's allergy status [3]. This study reviewed 108 patients referred for allergy testing. The patients underwent skin prick test in addition to endoscopic evaluation of the larynx. The exams were reviewed by three separate physicians, in a blinded study. The group demonstrated that the examiners were reliable in identifying laryngeal erythema/hyperemia, vocal fold edema, and thick endolaryngeal mucus. They noted that there was no significant difference in laryngeal appearance between allergy-positive and LPR-positive individuals. The authors did note that thick endolaryngeal mucus was a significant predictor of allergy, concluding that the presence of such mucus should alert the physician to the possibility of allergic laryngitis. This study seems to indicate that inflammatory findings in the larynx are therefore generally non-specific.

Brook et al. sought out to determine whether findings on fiberoptic nasolaryngoscopy could aid in diagnosing atopy [4]. They performed a case control analysis of patients undergoing fiberoptic nasolaryngoscopy and allergy testing at a single academic institution. Three board-certified otolaryngologists were blinded to the atopic status and symptoms of 88 patient nasolaryngoscopies. The specialists were asked to fill out an 8-item endoscopic rating questionnaire for each video

specific to subsites within the nasopharynx, oropharynx, and larynx. The only abnormalities noted to predict atopic disease were abnormalities of the torus tubarius and increased nasopharyngeal secretions. All other endoscopic measures did not reach significance. The team concluded that findings within the nasopharynx rather than the larynx are more predictive of atopic laryngeal disease.

Koç et al. compared acoustic and stroboscopic findings and scores on the voice handicap index [5]. They reviewed 30 patients with allergic rhinitis alongside 30 participants without allergy symptoms. They describe the s/z ratio and note this as an index of laryngeal disorder. The s/z ratio was calculated by measuring the maximum phonation time of single consonants /s/ and /z/ in two separate breaths. The best /s/ and /z/ effort of at least three attempts at each was used to obtain the ratio. The authors noted that voice handicap index and their s/z ratio were significantly elevated in the allergic rhinitis patients as compared with the control group, demonstrating a lesser result in the allergic rhinitis patients. The team concluded that there exists a relationship between dysphonia and allergy. Additionally, allergy should be considered a potential cause of dysphonia in the diagnostic process.

In addition, Lauriello et al. examined 76 patients who presented with vocal complaints and underwent endoscopic laryngeal evaluation [6]. In this study, the authors noted that there was a strong relationship between allergy and dysphonia, primarily noted in women. They concluded that an allergy evaluation is important in assessing patients who present with dysphonia.

Brook et al. once again sought out the utility of allergy evaluation in patients with chronic, refractory laryngeal symptoms [7]. In their study, a total of 998 patients who underwent in vitro allergy testing were reviewed. Their charts were reviewed for the primary indication for allergy testing which included rhinitis complaints, chronic sinusitis, otitis media, and refractory laryngeal symptoms. The positive yield of allergy testing in patients with primary laryngeal indications was 51.8%. The team concluded that allergy testing in patients with chronic laryngeal symptoms yields positive results in equivalent proportion to patients with other common presenting symptoms. In addition, dust mite sensitization was the most common sensitization in patients with allergic laryngitis.

Otologic Manifestations

Both clinical and basic science reports have examined the hypothesis that chronic otitis media with effusion (OME) is an allergy-mediated disorder. Similar to the larynx, allergy can affect the middle ear either through direct mucosal inflammation or through downstream obstruction of the eustachian tube in the nasopharynx. Numerous reports

indicated that middle ear mucosa, which evolves from the same ectoderm as the rest of the upper respiratory tract epithelium, has been found in animal studies to have the same immunologic responsiveness to antigens as the nasal tract, sinuses, and bronchi [8]. Smirnova et al. discussed immunoregulatory and allergy-associated cytokines including IL 4, IL 5 as crucial molecular regulators, responsible for chronic inflammation in the middle ear and the chronic condition of OME [9].

Nasal allergy has been proposed as a cause of chronic secretory otitis media (CSOM). This disorder is related to the disturbed function of the eustachian tube. Allergic edema in the nasal mucosa leads to release of various mediators and obstruction of the eustachian tube. These mediators affect the eustachian tube directly by causing swelling and edema within the tube or at the opening torus tubarius. This in turn causes obstruction of the nasopharyngeal portion of the eustachian tube, causing retention of fluid within the middle ear [10].

Zhang et al. performed a meta-analysis of 24 studies evaluating the risk factors for chronic otitis media (COM) and recurrent otitis media (ROM) [11•]. Among the numerous risk factors noted, allergy or atopy increased the risk of COM and ROM. The authors noted that these patients had an odds ratio of 1.36 in developing COM/ROM (95% confidence interval; $P=0.001$). They concluded that their meta-analysis provided reliable evidence that allergy and atopy are important risk factors for COM and ROM.

Recent epidemiological studies have reported the link between otitis media with effusion and allergic rhinitis. Kreiner-Møller et al. analyzed data obtained from 291 children in the 6th year of life from the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) [12]. They reported that OME was diagnosed in 39% of the cohort and was significantly associated with allergic rhinitis. Roditi et al. used data of 1,491,045,375 pediatric visits from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, between 2005 and 2010 [13]. They found that the age was an effect modifier of the association between allergic rhinitis and OME, and that a significant relationship was observed in children 6 years of age and older, whereas there was no significant association in younger children. These results are further corroborated by Midgley et al. that report that there is a decreased prevalence of OME with increasing age and a marked seasonal effect on the frequency of OME [14]. A link between allergic rhinitis and OME exists, but age effect is not yet clear. Inhalant sensitizations generally occur in childhood and it would be expected that the middle ear dysfunction seen in younger children is due to anatomic factors relating to the eustachian tube whereas older children may have an allergic inflammation causing dysfunction.

Sleep

Sleep disturbance is a common complaint in patients with allergic rhinitis—more than in the general population. Lin et al. performed a systematic review of 25 years of literature to determine the association between allergic rhinitis and sleep disorder breathing in children [15]. They reviewed 18 articles with 27,015 patients. Two thirds of the publications demonstrated statistical association between allergic rhinitis and sleep disorder breathing.

There are two theories for the observed relationship between sleep disorder breathing and allergic rhinitis. The obstructive model describes the nasal obstruction contribution to overall airway obstruction seen sleep apnea with arousals and awakenings secondary to obstruction. There also exists the inflammatory dysregulation model which supports the idea that circulating inflammatory mediators disrupt sleep on a central level.

The obstructive model purports that allergy results in nasal mucosal edema. The edema decreases the net radius of the nasal airway resulting in increased resistance and disrupted breathing. The disrupted breathing causes the night-time arousals. Stuck et al. reviewed this theory by recruiting 25 patients with seasonal allergic rhinitis into a prospective, controlled clinical trial [16]. Daytime sleepiness and quality of life were assessed using questionnaires, including the Epworth Sleepiness Scale. Additionally, 2 consecutive nights of fully attended polysomnography were performed before and during the pollen season. The study noted that daytime sleepiness, snoring, and apnea-hypopnea index (AHI) increase were related to seasonal allergies.

In regard to the inflammatory dysregulation model, several studies have shown that histamine affects the sleep wake cycle. Leukotriene D4 is associated with increased slow-wave sleep in animal studies and IL-1, IL-4, and IL-10 are associated with decreased latency to sleep onset and decreased total time in REM sleep. Ni et al. report that there also exist increased pro-inflammatory cells and decreased immune tolerance cells in children with obstructive sleep apnea and allergic rhinitis as compared with those with OSA only [17•].

Treatment of allergic symptoms and allergic rhinitis in children has been noted to improve mild childhood OSA. Chan et al. performed a double-blinded, placebo-controlled trial of intranasal mometasone furoate versus placebo in children aged 6 to 18 years with mild OSA [18]. The primary outcome was the change in AHI after 4 months of treatment. The authors concluded that treatment with intranasal mometasone furoate effectively reduces the severity of mild OSA in children. This conclusion was further corroborated by the work of Liu et al., who published a meta-analysis of randomized controlled trials to assess the efficacy of intranasal corticosteroid therapy in the treatment of obstructive sleep apnea [19]. Five randomized controlled trials were included, 3 pediatric and 2

adult. Inclusion criteria included patients with OSA; however, not all patients had a diagnosis of allergic rhinitis. The results indicated that intranasal corticosteroid therapy has a better effect in decreasing the AHI compared with those participants who received placebos. They concluded that patients who received intranasal steroid therapy had a significant improvement in OSA.

Although there exists a great deal of information in the literature regarding the relationship between obstructive sleep apnea and allergic rhinitis, no study has clearly established a causal relationship between both of these entities. However, appropriate treatment of allergic rhinitis has been shown to improve sleep quality and reduce daytime somnolence in both children and adults [18, 19]. In many cases, the AHI of these patients has been noted to decrease. This relationship has become significant enough that the allergic rhinitis clinical practice guideline recommends that clinicians should assess patients with a clinical diagnosis of allergic rhinitis for the presence of sleep disorder breathing.

Oral Allergy Syndrome

Oral allergy syndrome (OAS), also known as “pollen-food allergy syndrome,” is thought to be due to cross-reactivity to conserved epitopes found in both pollen and raw fruits, raw vegetables, spices, tree nuts, and many other foods. Patients will most often present with mouth and throat itching that will begin immediately when food is placed in the oral cavity. These symptoms tend to persist for several minutes after the food has been swallowed. OAS is most often found in individuals with a history of pollen allergies. In particular, patients with birch, grass, ragweed, and mugwort allergies may all have an association with pollen-food allergy syndrome resulting in responses to a number of foods.

Ma et al. estimates that the frequency of OAS in patients with pollen allergy was 5–8% [20]. In their study, 122 randomly selected US allergists were surveyed regarding their treatment methods of OAS. Fifty-three percent of allergists recommended complete avoidance of causal foods to all patients while 9% did not advocate any restrictions. Thirty percent never prescribed epinephrine for OAS, 3% always did, and the remainder did so on the basis of symptoms. They concluded that there is significant discrepancy in the diagnosis and treatment of OAS.

Patients with OAS who are exposed to oral allergens will often complain of lip and oropharyngeal itching and paraesthesias. Additionally, these individuals can also present with angioedema of the oral mucosa, tongue, palate, and oropharynx. Less commonly, these patients will complain of symptoms outside of the oral cavity such as itching, nausea or stomach irritation, vomiting, or diarrhea [20].

Andersen et al. used crossed-line immunoelectrophoresis technique to demonstrate the existence of an antigenic correlation between birch pollen and hazelnut [21]. In 1999, Kazemi-Shirazi et al. combined multiple food and pollen antigens in quantitative RAST and immunoblot inhibition assays [22]. They identified that food specific IgE epitopes in OAS patients resembled pollen allergens. This in turn prompted them to conclude that pollen allergens themselves may be responsible for the elicitation and maintenance of oral allergy symptoms, through cross-reactive allergens.

OAS has been a diagnostic challenge since its early reports, given that today's diagnostic testing continues to vary in sensitivity and specificity, as a result of OAS's multiple causative antigens and their potential lability. The double-blinded, placebo-controlled food challenge (DBPCFC) is primarily accepted as the standard for diagnosing food allergy. In one study, Rodriguez et al. demonstrated that 53 patients with a history of OAS to melon, only 25 had a positive open food challenge result, and of those, only 17 had positive DBPCFC results [23]. Given these results, many diagnostic tests have been compared with DBPCFC as the standard. However, other practitioners argue that a careful clinical history is sufficient to diagnose OAS and may better reflect true disease [24, 25]. Nonetheless, there still does not exist an agreed upon diagnostic criteria, and clinical impression based primarily on history is essential in diagnosis.

The treatment of food allergy is avoidance, education, and emergency management with injectable epinephrine for anaphylactic or obstructive symptoms. Although OAS is not a traditional food allergy, the same principals of treatment may apply since it is often impossible to differentiate whether the reaction will be self-limited or result in overt anaphylaxis. Because OAS is believed to be initiated by a primary aeroallergen sensitization, the role of immunotherapy has been reexamined as a potential therapy specific to OAS. Kelso et al. demonstrated a case report of fresh fruit tolerance after a year of pollen immunotherapy [26]. Since then, multiple studies have examined the role of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) on OAS [27, 28].

Asero et al. prospectively followed 49 birch-sensitive patients with OAS to apple after receiving 1 to 3 years of birch SCIT [29]. Forty-one of 49 patients reported subjective improvement in OAS symptoms. Additionally, the same author reported a case study of a single patient with OAS to fennel and cucumber in addition to laryngeal edema to melon [30]. This patient was initiated on SCIT to grass, mugwort, and ragweed pollen. At 36 months of immunotherapy, the patient tolerated an oral challenge to fennel and cucumber without experiencing any symptoms, and at 43 months of therapy, she underwent an oral challenge to melon, without developing edema.

Bucher et al. compared pretreatment and post-treatment open food challenge on patients with OAS to apple and hazelnut after a 12-month period of birth SCIT [31]. Thirteen of 15 patients could eat more apples or hazelnuts before provoking clinical symptoms. The patients tolerated the quantity of apple increasing from 12.6 to 32.6 g. While statistical significance was noted, the authors did note the limited clinical significance of these findings.

Although the above studies do demonstrate potential desensitization during active pollen immunotherapy, Asero et al. published a follow-up study suggesting questionable long-term benefit. Of their initial study, 27 of 30 patients remained tolerant to apple 6 months after completing SCIT [32]. However, this number diminished to only 11 of 30 remaining without symptoms after 30 months and progressively decreased. At the 42 month follow-up, only 3 patients were still followed up, and only 2 remained apple tolerant. The authors suggested that a higher antigen quantity may be required to induce an appreciable effect on OAS when compared with traditional pollen-related symptoms.

In addition to SCIT, some authors have reviewed the effect of pollen-specific SLIT in modifying OAS. Kinaciyan et al. evaluated 15 patients with apple OAS undergoing birch pollen SLIT [33]. They noted no significant change in OAS tolerance, despite subjective improvement in aeroallergen symptoms in 9 of 15 patients.

Overall, it remains unknown whether inhalant allergen desensitization improves symptoms of OAS as there are conflicting reports. The safest treatment for OAS remains avoidance of allergenic foods and preparedness in case of accidental ingestion or unexpected severe reaction.

Conclusion

The extranasal manifestation of allergic sensitization within the head and neck involves the larynx, oral cavity, middle ear, and pharynx. In addition, pathologies such as OSA have also been noted to be affected by allergic sensitization. While these disorders commonly present with allergic rhinitis and asthma, patients often do not relate their otologic, laryngeal, oral, or sleep problems to atopic disease. Additional treatment beyond blockade of the allergic cascade is often needed to improve symptoms related to otitis, laryngitis, and sleep apnea. Practitioners should have a complete understanding of the extranasal manifestations of allergic disease to improve care for patients who suffer from these extranasal manifestations of allergy within the head and neck.

Compliance with Ethical Standards

Conflict of Interest Dr. Platt and Dr. Brook are consultants for GI Reviewers, LLC, reading blinded studies for biologic therapies for nasal

polyps. Dr. Mur declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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