

What Role Does Allergy Play in Chronic Ear Disease and Laryngitis?

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Abstract IgE-mediated allergy plays a well-established role in both nasal and pulmonary diseases due to the common epithelium and shared mediator responses of the upper and lower airways. This “unified airway” concept has also been described in other sites within the head and neck that contain similar respiratory mucosa: the middle ear and the larynx. This review will highlight the data suggesting a role for IgE-mediated allergic disease in chronic laryngopharyngeal and middle ear disease and the role for allergy testing to aid in diagnosis and treatment of these disorders.

Keywords Chronic ear disease · IgE-mediated allergy · Unified airway · Allergic rhinitis · Allergic laryngitis · Middle ear disease

Introduction

The concept of the unified airway has become increasingly accepted as more evidence comes to light showing a relationship between upper and lower respiratory diseases of allergic rhinitis and asthma. Conceptually, this model envisions the upper and lower airways as integrated units within one overall system [1], and the appreciation that an insult leading to a reaction in one

unit will trigger broader inflammation in both the upper and lower airways. In several studies, introduction of allergenic material into one area of the respiratory system has led to an inflammatory response in remote airway locations [2–5]. Epidemiologic evidence suggests a strong link between allergic rhinitis and the development of asthma [6, 7], and several studies have also demonstrated that treatment of allergic rhinitis can help control concomitant asthma [8, 9] or, in the case of immunotherapy, reduce the risk of developing asthma [10]. Given that the Eustachian tube, middle ear, and larynx are all portions of the upper respiratory tract, it stands to reason that allergic disease can cause inflammation in all of these regions and that treatment of allergic disease could play a role in Eustachian tube dysfunction, otitis media and chronic laryngitis.

Allergic Laryngitis

Clinical Presentation

Allergic laryngitis may present as either a vocal disorder or with laryngopharyngeal symptoms. Voice disorders include any detriment in function, performance, or sound quality of a patient’s voice [11]. Vocal disorders are a relatively common conditions in the USA and have a yearly prevalence of approximately 6–8 % [11, 12], with an overall lifetime risk of approximately 30 % [11]. In addition to vocal disorders, chronic laryngeal and pharyngeal irritation can lead to other non-specific laryngopharyngeal symptoms including cough, throat clearing, globus sensation, excessive mucous, sore throat, and post-nasal drip [13–15].

Evidence for Allergic Laryngitis

Although small, a growing body of literature has examined and put forth evidence of an association between allergic

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disease and chronic laryngopharyngitis or allergic laryngitis. Several authors have published studies showing a link between allergic disease and vocal symptoms. Simberg et al. examined a population of 49 students undergoing a 3-year immunotherapy course for allergic rhinitis symptoms, and 54 control patients with no known allergic disease. The authors found that allergic patients reported increased numbers of vocal complaints compared to non-allergic control patients, but that the number of vocal complaints decreased with the duration that patients had been undergoing immunotherapy [16•]. Millqvist and colleagues examined both allergic and non-allergic control patients in and out of birch allergy season, noting significantly higher Voice Handicap Index (VHI) scores for allergic patients when in birch season compared to out of season [17•]. Krouse et al. noted increased VHI scores in patients with positive dust mite allergen testing when compared to controls [18•], and similarly, Koç et al. found higher VHI scores and s/z ratios in allergic patients when comparing VHI, acoustic, and stroboscopic exams in patients with and without allergic rhinitis [19].

Some research has also explored a causal relationship between allergen introduction and laryngopharyngeal symptoms. Belafsky and colleagues used a guinea pig model to demonstrate that introduced dust mite allergen and iron soot could cause laryngeal eosinophilia when animals were exposed to both. This paper suggested a synergistic relationship between allergic sensitization and environmental exposure to allergen and toxins, as eosinophilia was higher in animals exposed to both [20]. In a series of two papers, Reidy et al. and Dworkin et al. introduced inhaled dust mite allergen into the larynx in patients with known *Dermatophagoides pteronyssinus* dust mite sensitivity [21•, 22••]. In the first of the two studies, the dust mite allergen was nebulized and inhaled orally at a concentration of 1:200 wt/vol. The authors did not find any significant differences between baseline and post-allergen inhalation VHI and stroboscopy, but did note that at baseline nearly all of the patients had an increase in endolaryngeal mucous from what the authors would have expected [21•]. In follow-up to this study, the same group conducted a second study with increased concentrations of dust mite antigen, 1:100 and 1:40 wt/vol, again in patients with a dust mite allergen sensitivity. This study was designed as a randomized controlled trial, but had to be aborted because two patients developed chest tightness, voice difficulties, and coughing after introduction of the highest concentration on antigen into the larynx. The authors also noted that both patients demonstrated vocal cord edema and viscous secretions within the larynx, and that there was no reaction in the single control patient or at lower antigen concentrations [22••]. Finally, Roth et al. performed a randomized controlled trial with oral inhalation of allergen in sensitized patients, and then measured the phonatory threshold pressure [23••]. On day 1, patients inhaled placebo, and on day 2, patients inhaled allergen extract. They

found a significant increase in phonatory threshold pressure after inhalation of allergen extract and concluded that laryngeal allergen inhalation does have a causal relationship with laryngeal inflammation in sensitized patients [23••].

In a recent paper, Krouse examined current research that has explored a potential link between allergic sensitization and laryngeal symptoms [24]. After reviewing a number of epidemiological and experimental studies, it appeared that an association between these two phenomena appeared to be likely. Krouse concluded that “allergy may be a valid trigger and causative mechanism in some individuals with laryngeal inflammation and symptomatology” (p. 221).

Diagnosis and Treatment of Allergic Laryngitis

Often diagnosing the underlying cause of vocal disorders and chronic laryngopharyngitis is difficult because exam findings are non-specific, and there is substantial overlap between different inflammatory conditions, leading authors to question whether patients are currently being overdiagnosed with laryngopharyngeal reflux (LPR) and underdiagnosed with allergic laryngitis [13, 15, 25, 26]. Brook et al. studied the prevalence of sensitization in patients undergoing in vitro allergy testing for different presenting complaints and found that patients with laryngopharyngeal symptoms had rates of sensitization that were the same as patients presenting with rhinitis and sinusitis, diseases more traditionally associated with allergen sensitization [15]. Randhawa and colleagues published a prospective observational study of 15 patients with a new diagnosis of a vocal disorder and performed standardized LPR screening and allergy testing. They found that the prevalence of allergen sensitization was much higher than reflux by questionnaire, and that in their cohort, all patients diagnosed with reflux also had positive allergy testing [25]. Garrett and Cohen published a review article on the topic, suggesting that the diagnosis of LPR is being made on a constellation of non-specific symptoms that may represent several underlying conditions including muscle tension dysphonia, LPR, environmental irritants, and allergic disease [25].

The treatment of allergic laryngitis has received even less attention in the literature. A case report of a singer suffering from asthma and allergic rhinitis noted objective improvement in her methacholine challenge test as well as subjective voice improvement after 23 months on allergen-specific immunotherapy [27]. As noted earlier, Simberg and colleagues determined that patients with allergic sensitization undergoing immunotherapy had a higher prevalence of vocal complaints when compared to a matched control group. In addition, they noted a decreasing number of vocal complaints based on the length of time that the sensitized group had been undergoing immunotherapy [16]. While suggestive, the study was not performed longitudinally and only captured a small number of patients at one discrete time interval, limiting its overall

applicability. Future study will need to determine improvement in vocal and throat complaints using validated patient-related outcome measures such as the VHI in conjunction with clearly defined allergy treatment.

Chronic Ear Disease

The Clinical Presentation

Otitis media (OM), inflammation of the middle ear, encompasses the spectrum of acute otitis media (AOM) to chronic otitis media with effusion (OME) and subsequent chronic ear disorders. AOM represents the accelerated onset of signs and symptoms of active inflammation including pain, irritability, and fever [28]. Exam findings can include an erythematous and bulging tympanic membrane and possible otorrhea [29]. Otitis media with effusion in contrast is the presence of middle ear fluid without evidence of acute infection [30]. Both AOM and OME can impact hearing, pressure equalization, and tympanic membrane retraction, leading to chronic ear disease and increased risk of cholesteatoma formation [30]. The impact of OME on the economy has been estimated to cost the USA \$4.0 billion annually [31]. In addition, the lifetime prevalence of OME was found to be 53–90 % of children [32–35]. As such, having a better understanding for the mechanisms of ear disease including allergic contributions is important.

Evidence for Allergic Middle Ear Disease

Chronic ear disease and its potential association with allergic pathologies continue to be controversial. OM has traditionally been associated with infectious or functional anatomical issues such as Eustachian tube dysfunction, but there is growing evidence of an association between allergen induced inflammation and chronic ear disease [36–39]. In addition, Hurst et al., Nguyen et al., and Marple have published evidence that the middle ear can demonstrate similar inflammatory and allergic mechanisms when compared with the nasal cavity and upper aerodigestive tract, suggesting that middle ear disease may function as part of a unified airway process [40–42].

Several authors have demonstrated clinical relationships between allergic rhinitis, Eustachian tube dysfunction, and otitis media [36–39, 43, 44]. Lazosaenz et al. compared tympanometry results in 80 patients with allergic rhinitis to results in 50 control subjects. The authors found that adults and children with allergic rhinitis were more likely to have negative middle ear pressures compared to control subjects [37]. In addition, patients with asthma or other atopic conditions have shown higher rates of chronic ear disease [45–48]. Alles et al. studied 209 children with chronic otitis media with effusion and found that 89 % had allergic rhinitis, 36 % asthma, and 24 % eczema, and that 57 % were sensitized to an

inhalant aeroallergen [49]. Another study, however, demonstrated only a 24 % prevalence of allergic rhinitis in patients with OME [48]. Chantzi et al. went further and completed a multivariate analysis for independent risk factors in 56 patients with OME versus 52 controls. They found that family history of OM, wheezing, and IgE sensitization were the three most predictive variables increasing the relative risk of OM by 8.17, 4.39, and 2.52 times, respectively [50]. While clinical correlation is only associative, there is a growing foundation of basic science evidence demonstrating an allergic component to chronic ear disease.

To show a histopathological difference in atopic patients compared to controls, Iino et al. compared middle ear mucosa samples from patients with intractable otitis media. Eight of those patients were diagnosed with bronchial asthma compared with the 18 controls; all of whom still had intractable otitis media but without atopic secondary diagnoses. The results revealed that atopic patients had extensive eosinophilic submucosal infiltration, but more notably, IgE was found on both mast and plasma cells, and the concentration of eosinophilic-derived proteins in the middle ear was greater in the atopic group [51]. In addition, Nguyen et al. showed similar results from biopsies and samples of middle ear effusions, mucosa of the torus tubarius, and adenoidal tissue [40]. Wright et al. expanded on this work by demonstrating increased levels of CD-3, IL-5, and major basic protein (MBP) within the middle ear mucosa of atopic patients compared to controls [52]. Immunological analysis of middle ear effusions by Yellon et al. also showed additional evidence of elevated Th-2 related cytokines within the middle ear [53]. Finally, Kim et al. developed a murine allergic otitis media model in which the authors induced otitis media with an allergic middle ear response. They demonstrated that allergic mice had higher levels of Th-1 (IL-2 and IFN- γ) and Th-2 (IL-5 and IL-13) cytokines within the tympanic membrane and middle ear mucosa compared to controls [54]. Both clinical and basic science evidence demonstrate a relationship between allergy and otitis media although the pathophysiology remains poorly understood and further research is required.

Treatment

Several studies have examined the impact of allergic rhinitis treatment on chronic otitis media, including randomized trials for both systemic and topical medications. Simpson et al. completed a systematic Cochrane review for oral steroid, and topical steroid use that measured the outcomes of OME resolution and hearing loss improvement in children. The study included 945 participants and demonstrated increased resolution of OME in patients taking oral steroids or oral steroids and antibiotics within 1 month of treatment. The study however did not show any improvement in OME resolution for topical steroids nor did it show any improvement in long-term (>1 month) hearing results

[55•]. In contrast, Bhargava and Chakravarti published the results of a double-blinded randomized controlled trial of mometasone furoate intranasal steroid for children with OME and evidence of significant adenoid hypertrophy. The study randomized 62 patients and demonstrated a 93 % OME resolution rate in the treated group compared to 50 % in the control group after 24 weeks [56]. In adult OME, Finkelstein et al. prospectively analyzed 167 consecutive patients to determine a causative mechanism in adult OME. The authors found that 66 % of patients had paranasal sinus disease including acute or chronic sinusitis, 19 % with adenoidal or smoking-induced nasopharyngeal lymphoid hyperplasia, and 4.8 % secondary to head and neck tumors [57].

Antihistamine and decongestant use has also been extensively studied in the literature, with no evidence of benefit in a number of papers. Griffin and Flynn published a Cochrane review of antihistamine use in otitis media with effusion. In their review, 16 randomized controlled trials were included, with an aggregate sample of 1880 participants. This thorough review and meta-analysis did not show any benefit from antihistamine or decongestant use in resolving OME [58]. These results question the role of an allergic mechanism in many cases of OME.

Additionally, leukotriene antagonists have been trialed in order to understand their role in allergy-associated otitis media. Three randomized controlled trials report mixed benefit. Schoem et al. initiated a randomized control trial assessing the role of montelukast in resolving OME but discontinued the trial early given a trend toward no significant difference between treatment and placebo groups [59]. Ertugay et al. conducted a four-arm trial with a placebo group, antihistamine group, leukotriene antagonist group, and combination group treated with both antihistamine and leukotriene antagonist. The authors found a greater resolution in OME in the combination group after 1 month of treatment compared with the other three groups, but the study size was small with only 30 patients in each arm, and the combination of leukotriene antagonist with antihistamine confounds the interpretation of their results [60]. Coombs et al. found a small benefit compared to placebo but also included a course of antibiotics in the treatment arm, again confounding the effect of the leukotriene antagonist [61].

Immunotherapy for the treatment of otitis media with effusion has not been thoroughly investigated and few publications are available. Hurst published in 2011 a non-randomized prospective cohort study of 89 patients to investigate the efficacy of targeted subcutaneous immunotherapy for OME. Sixty-eight patients underwent immunotherapy and were followed for 2–8 years, and 21 patients elected not to have immunotherapy and were subsequently followed as controls. Hurst demonstrated 85 % resolution of OME affected ears in those who underwent immunotherapy compared to 0 % spontaneous resolution in the control cohort [62•]. Again, this trial was limited in its failure to assign subjects randomly to treatment groups. Randomized controlled trials are needed to

better understand the qualitative and quantitative role for immunotherapy treatment in patients with chronic ear disease.

Conclusion

The role of allergen sensitization in the pathogenesis of chronic laryngopharyngeal symptoms and chronic otitis media is still poorly defined. Despite evidence implicating allergic sensitization in the development of both diseases, the precise contribution is difficult to define and treat. In the larynx, direct challenge with antigen has demonstrated objective measurable changes in the phonatory threshold pressure and laryngeal appearance on examination, and allergic disease has been associated with measurable impairments in the VHI. Some observational work has demonstrated improvement in the VHI and laryngeal symptoms in patients receiving allergic treatment. Similarly, in the middle ear, allergic disease has been clinically associated with chronic otitis media, and basic science studies have demonstrated elevated inflammatory markers consistent with allergy in middle ear mucosa and effusions. Well-designed prospective interventional studies demonstrating improvement in middle ear status with treatment of allergy are lacking. Further research is needed to define the major allergen classes involved in laryngeal and otologic allergic disease, as well as to delineate the contribution of allergy in conjunction with other suspected causes of disease in these locations, such as chronic bacterial infection in the middle ear and laryngopharyngeal reflux disease in the larynx. Additionally, prospective randomized-controlled trials demonstrating the efficacy of allergy treatment and immunotherapy on chronic laryngitis and otitis media are needed.

Compliance with Ethical Standards

Conflict of Interest Drs. Platt, Brook, Kuperstock, and Krouse declare 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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