

Review article

Allergic rhinitis and its impact on otorhinolaryngology

Allergic rhinitis (AR) is a disease with growing impact on everyday medical practice, as its prevalence has steadily increased during the last decades. Immunoglobulin-E (IgE)-mediated airway inflammation may manifest itself as AR, asthma or both. Allergic inflammation in upper and lower airways is now considered as one airway disease, with manifestation of symptoms in upper, lower or global airway. This insight into allergic inflammation of the whole respiratory tract has consequences for the diagnostic and therapeutic approach of affected patients, as highlighted in the ARIA document. In contrast to asthma, the link between AR and associated conditions in the upper airways like rhinosinusitis, nasal polyps, recurrent viral infections, adenoid hypertrophy, tubal dysfunction, otitis media with effusion and laryngitis remains less explored. It is however of utmost importance to consider the aetiological role of IgE-mediated inflammation of the nasal mucosa in several diseases of the upper respiratory tract, as they represent a large body of patient population seen by the general practitioner as well as the paediatrician, allergologist and otorhinolaryngologist. We here aim at reviewing the current literature on the relationship between AR and conditions in upper airways frequently encountered in everyday clinical practice, and highlight the need for further studies exploring the role of allergic inflammation in the development of these diseases.

P. W. Hellings^{1,2}, W. J. Fokkens³

¹Laboratory of Experimental Immunology and
²Department of Otorhinolaryngology, Head and Neck
Surgery, University Hospitals Leuven, Leuven,
Belgium; ³Department of Otorhinolaryngology,
Academic Medical Center, AMC, Amsterdam, the
Netherlands

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Peter Hellings
Department of Otorhinolaryngology, Head and Neck
Surgery
University Hospitals Leuven
Kapucijnenvoer 33
3000 Leuven
Belgium

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During the last decade, the link between allergic rhinitis (AR) and allergic asthma (AA) has been explored by a number of epidemiological (1) and experimental studies (2, 3). Both diseases share increasing prevalence, similar immunological mechanisms and respond, in part, to the same therapy. Besides induction of allergic inflammation in the nose and bronchi after allergen inhalation, a systemic allergic reaction takes place with involvement of bone marrow cell biology, mobilization of granulocytes in the blood and increase in allergen-specific IgE titres (4, 5). Hence, AR and AA can be considered as part of the global airway allergy syndrome (6). Novel insights into the link between AR and AA have resulted in the ARIA document (7), providing an extensive overview of the current knowledge on allergic airway disease and illustrating the concept of global airway allergy with both diagnostic and therapeutic consequences (Fig. 1). It is now being recommended that AR patients should be asked for bronchial symptoms and referred to the pneumologist in case of clinical suspicion of asthma. Alternatively, nasal symptoms should not be neglected in AA patients (8) and treated according to evidence-based guidelines of the

ARIA document (9). These guidelines aim at optimizing the treatment of patients with airway allergy (10, 11). Recent studies have demonstrated that the recognition and treatment of AR in AA patients results in reduced hospital admissions and emergency room visits for asthma (12). Novel therapeutic strategies such as anti-IgE, aiming at treating both AR and AA, have proved to be successful in improving the quality of life of patients with AR and AA (13). However, many clues to understanding the pathophysiological link between AR and AA are still missing. It remains unknown why bronchial allergic inflammation leads to asthmatic symptoms in some patients with AR and not in others, why bronchial inflammation is much more severe than nasal inflammation in asthmatic patients, what is the role of the systemic vs local allergic immune response in the induction of nasal and bronchial inflammation, and via which mechanisms treatment of the upper airways may be beneficial in asthma patients. In addition, the role of neural reflex mechanisms by which AR may aggravate allergen-driven lower airway inflammation is still largely unexplored. Moreover, the link between AR and the development of other upper airway diseases frequently encountered in everyday clinical practice such as sinus disease, nasal polyps (NP), recurrent viral infections, adenoid hypertrophy, tubal dysfunction,

Abbreviations: AR, allergic rhinitis; AA, allergic asthma; URTI, upper respiratory tract infection.

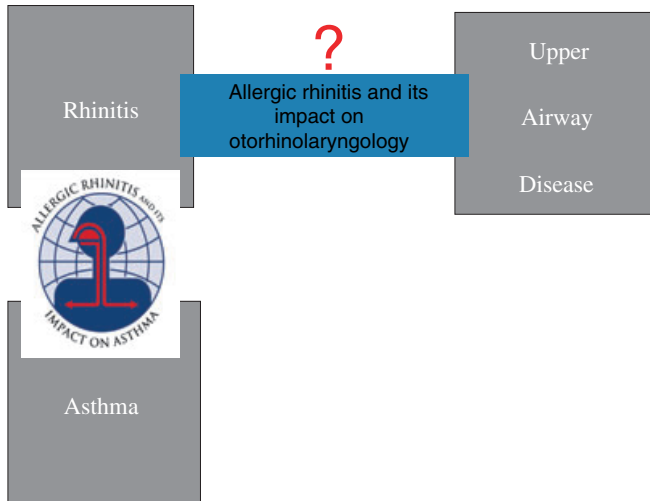


Figure 1. In contrast to the extensively studied link between allergic rhinitis and asthma, there have been limited studies exploring the aetiological role of allergic rhinitis in upper airway diseases.

otitis media with effusion and laryngitis remains far from completely understood (Fig. 2). The latter diseases constitute a major proportion of patients seen by general practitioners, paediatricians, allergologists and otorhinolaryngologists. We here aim at giving an overview of the current knowledge on the pathophysiological link between AR and other diseases of the upper respiratory tract.

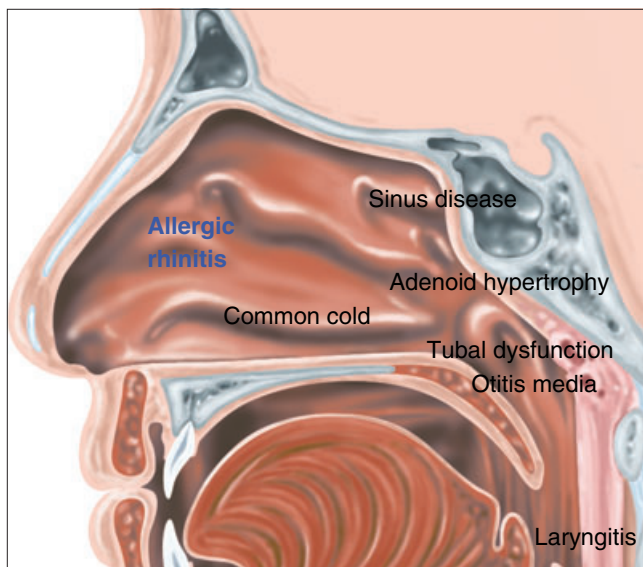


Figure 2. Allergic rhinitis and common cold manifest themselves in the same organ, and may aggravate each other's symptoms. Due to its close relationship to the sinus cavities, middle ear and pharynx, allergic rhinitis has been linked to the aetiology of sinus disease, adenoid hypertrophy, tubal dysfunction and otitis media with effusion, and laryngitis.

Allergic rhinitis and upper respiratory tract infections

Considering the correlation between AR and viral upper respiratory tract infections (URTI) (14), it may seem plausible that the presence of an inflammatory disorder of the upper airways such as allergy predisposes the patient to develop more frequent and/or more severe URTI. Indeed, allergic inflammation is known to induce the expression of adhesion molecules like intercellular adhesion molecule-1 (ICAM-1) on epithelial cells (15). Upregulation of the expression of ICAM-1, the principal receptor for rhinovirus, might increase tissue susceptibility to infection with rhinovirus. In addition, epithelial cells from asthmatic patients show a deficient innate immune system, hence favouring viral replication and invasion (16). Whether the latter observation also applies to epithelial cells from AR is unknown. From a clinical point of view, atopic children with asthma experienced more common colds than non-atopic asthmatic children, without difference in severity or duration of the common colds (17). Similar studies have not been performed in AR patients without AA. Computerized tomography (CT) studies reveal that patients with AR have more severe paranasal sinus changes during viral colds than nonallergic individuals (18, 19), concomitant with a reduced mucociliary clearance time. In the light of this observation, IL-13, which is a key cytokine in allergic airway inflammation, reduces ciliary beat frequency (20) by slowing down mucociliary clearance, thereby favouring viral invasion of the mucosa.

On the other hand, allergic inflammation may be protective against viral URTI as well. In experimental rhinovirus 16 infection, previous nasal contact with the relevant allergen reduces the common cold symptom scores and duration of the cold (21). Mediators released by activated eosinophils, such as eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin, have antiviral properties (22). Besides the so-called Th2 cytokines, interferon- γ is produced by Th cells after allergen encounter (23), which also has antiviral activity. Furthermore, allergic inflammation is associated with increased nasal nitric oxide production, which is capable of reducing the virally induced IL-6 and IL-8 production (24). Taking together the immunological considerations, allergic inflammation has both protective as well as stimulatory potential for viral URTI. This may explain why some studies show that AR does not alter symptoms and/or inflammation related to URTI. Neither nasal symptoms nor the amount of nasal secretions differed between AR and non-AR subjects after inoculation with RV serotype 19 (25). During naturally acquired common colds, patients with AR presented with more eosinophils in the subepithelial layers than nonallergic individuals but without differences in clinical characteristics or symptom scores between patients with and without AR (26). Fraenkel et al. (27) reported no significant differences in inflammatory cell counts in nasal biopsies between allergen and nonallergic subjects after inoculation with

rhinovirus serotype 16. Factors such as the virulence of the strain, the innate immune system and environmental factors will determine the outcome of inflammation after viral contact.

Alternatively, viral infections of the upper respiratory tract may as well contribute to the initiation and/or manifestation of AR. In patients with AR, mast cells accumulate in the nasal mucosa during a natural cold (26), which may eventually lead to aggravation of a concomitant allergic condition. In asthma, current evidence strongly supports the concept that rhinovirus infections are the major cause of acute asthma exacerbations (28). The mechanisms by which rhinoviruses exacerbate underlying bronchial inflammation are incompletely understood. Activation of bronchial epithelial cells, the principal target for RV infection and replication, is believed to induce aggravation of asthma via the virally induced secretion of pro-inflammatory mediators (29). In addition to activation, viruses may cause epithelial damage leading to increased permeability of the mucosa and hence increased allergen contact with immune cells. In mice, Dahl et al. (30) reported that influenza virus infection favours the development of bronchial allergic inflammation, which in many respects models the clinical situation. Similarly, respiratory syncytial virus (RSV) infection in the murine lung has recently been shown to increase the mRNA expression of RSV-specific IgE, IL-4 and IL-13 (31), the typical landmarks of the allergic response.

Allergic rhinitis and rhinosinusitis

Allergic rhinitis and rhinosinusitis have overlapping symptomatology to a certain extent. Impairment of nasal breathing and nasal discharge are considered major symptoms of both AR and rhinosinusitis. In addition to the latter symptoms associated with both AR and sinusitis, sneezing, itchy nose and/or eyes are symptoms related to AR, whereas patients with sinus disease complain of headache, facial pressure, postnasal drip and/or smell disorder. In defining AR and sinusitis according to the recent European guidelines [ARIA (9) and EP³OS (European Position Paper on POLyps and Sinusitis (32))], nasal symptoms are a prerequisite for the diagnosis. When considering the role of allergy in sinus disease, one may speculate that nasal inflammation induced by IgE-mediated mechanisms favours the development of acute and/or chronic sinus disease. At present, whether and via which mechanisms the presence of allergic inflammation in the nose predisposes the individual to the development of sinus disease remains incompletely understood. So far, there are no published prospective reports on the incidence of infectious rhinosinusitis in populations with and without clearly defined allergy. Several epidemiological studies report a high prevalence of sensitization to inhalant allergens both in

acute (33) as well as in chronic rhinosinusitis (CRS) patients (34, 35), ranging up to 84% of patients undergoing revision sinus surgery (36). Compared with the general population where CRS is estimated to be found in up to 6% of subjects (37–40), patients sensitized to inhalant allergens seem to present more often with sinus complaints. On the basis of these epidemiological observations, one may however not conclude that AR predisposes to the development of CRS as these studies include a large referral bias. A predominance of allergy to perennial over seasonal allergens was found in chronic sinusitis patients at the time of indication for surgery (36). So far, epidemiological studies have failed to demonstrate a higher incidence of sinus disease during the pollen season in pollen-sensitized patients (34).

Several pathophysiological mechanisms could explain an aetiological link between allergic inflammation and sinus disease. First, allergic inflammation of the nasal mucosa may give rise to mucosal congestion leading to impaired drainage of mucus at the ostiomeatal complex in predisposed patients. Otiomeatal pathology is considered to be essential for the retention of secretions within the sinus cavity, leading to the generation of sinus-related symptoms. So far, all studies conducted in chronic sinus disease patients failed to demonstrate more severe congestion in AR than in non-AR patients (34, 41), and showed that sinus abnormalities on CT scans contribute minimally to patient symptoms in pollen-sensitized AR patients (42). Emanuel et al. (36) reported relatively lower percentages of allergic patients in the group of patients with the most severe sinus disease on CT scans and Iwens et al. (41) found no correlation between the atopic state and the extent of sinus mucosa involvement on CT scans. The observation that allergy is not more frequently present in the most severe forms of sinus disease, reflects the fact that factors other than allergy are involved in the pathophysiology of severe sinus disease. Similar observations are made in asthma, where severe asthmatic patients are less likely to have an allergy than mild asthmatic patients.

Besides deposition of inhaled allergens onto the nasal mucosa, inhaled allergens may well reach the sinus mucosa and initiate an allergic reaction inside the sinus cavity, leading to congestion of the sinus mucosa with impaired evacuation of mucus. As a matter of fact, allergen provocation in AR patients induces opacification of the sinus cavity in half of the patients examined (43) and antral lavage fluids of CRS show contents that are similar to nasal lavage fluid of AR patients (44). However, inhalation of technetium-labelled ragweed by healthy individuals does not lead to detection of these particles onto the sinus mucosa (45). Whether this observation also reflects the situation in patients with sinus disease or after sinus surgery, where the basic nasal physiology and/or anatomy is altered, is unknown.

Local and systemic allergic inflammatory responses may explain an aetiological link between AR and CRS.

First, the cytokine milieu present in AR patients may facilitate bacterial infection. As mentioned above, IL-13 slows down ciliary beat frequency of airway epithelial cells *ex vivo* (20), contributing to a decreased mucociliary transport and favouring microbial adhesion and invasion of the mucosa. Blair et al. (46) illustrated in a mouse model that inflammation of the sinus mucosa induced by inoculation with *Streptococcus pneumoniae* and bacterial growth is more severe in the presence of the relevant allergen.

Other mechanisms by which allergen inhalation by sensitized patients may favour the induction of sinus disease is via the systemic route. Inhalation of allergens has been shown to induce a systemic release of IL-5 (47), concomitant with enhanced bone marrow eosinopoiesis and increase in peripheral blood eosinophilia (48). In line with the systemic allergic response after allergen inhalation, Piette et al. (49) reported the development of contralateral sinus mucosal thickening on CT scans after unilateral nasal provocation with cypress pollen in sensitized patients.

To date, only a limited number of studies have looked at the effect of anti-allergic therapy in atopic patients with sinus disease. Braun et al. (50) studied the effect of loratadine treatment as adjunctive therapy of atopic patients with acute sinusitis and reported improvement of sneezing and nasal obstruction by adding loratadine to the classic therapy. It is also noteworthy to mention here that half of the allergic patients with a history of sinus surgery and undergoing immunotherapy believed that surgery alone was not sufficient to completely resolve the recurrent episodes of infection related to their sinus disease (51). So far, well-conducted clinical trials showing beneficial effects of antihistamines in patients with sinus disease are missing.

Taken together, we do not fully understand the correlation between AR and the development of sinus disease. We should however realize that sinus disease has a multifactorial aetiology, in which not only allergic inflammation, but also anatomical, genetic, immunological, microbiological and environmental factors are involved. Notwithstanding the lack of precise insight into mechanisms, symptoms of IgE-mediated allergic inflammation should be asked for during history-taking in patients with CRS and skin prick tests or radioallergo-sorbent tests (RAST) performed in case of clinical suspicion. Despite limited evidence of effectiveness of anti-allergic therapy in patients with chronic sinus disease, it seems logical to add anti-allergic therapy to the treatment scheme of patients with chronic sinus disease and concomitant allergy.

Allergic rhinitis and nasal polyps

Nasal polyps (52) are considered a chronic inflammatory disease of the sinonasal mucosa, being part of the

spectrum of chronic sinus pathology (32). The role of allergy in the generation of NP is even more unclear than in CRS. Historically, NP were believed to develop as a result of an allergic reaction to an unknown stimulus, giving rise to mucosal swelling and protrusion of the sinonasal mucosa into the nasal cavity. Both AR and NP are characterized by an inflammatory response that shows many similarities (53), related to both the type of infiltrating cells, e.g. eosinophils, as well as to the mediators involved, e.g. IL-5 and leucotrienes. Some studies report a high prevalence of allergy in NP ranging up to 64% of NP patients (54), whereas others report a prevalence of allergy in NP which is similar between NP and non-NP patients (55, 56). Alternatively, 0.5–4.5% of AR patients have been found to have NP (55–57) which corresponds to the prevalence in nonatopic individuals (58). In aspirin-sensitive patients, higher percentages of NP are reported (55, 57), but these patients are usually not atopic. Of note, NP are found in 25–40% of children with cystic fibrosis, where genotype–phenotype correlations are reported for paranasal sinus disease (59).

Despite the lack of epidemiological evidence of allergy being a factor that aggravates NP-related symptoms, recent studies highlight the fact that a concomitant allergic reaction influences the inflammation of NP. Atopic patients with NP may present with higher tissue densities of the typical Th2 cytokines IL-4 and IL-5 on *in situ* hybridization than the nonatopic patients with NP (60). Recently, Bachert et al. (61) stated that local rather than systemic IgE production may be relevant in the pathophysiology of NP, which is unrelated to skin prick test results or RAST. One of the mechanisms involved in tissue IgE production in NP may be the presence of *Staphylococcus aureus* enterotoxins (62). By their super-antigenic activity, these enterotoxins may cause a polyclonal stimulation of B lymphocytes in NP tissue, ultimately leading to IgE production in NP tissue and perpetuation of inflammation. In addition to *S. aureus*, inhaled fungi have recently been suggested to contribute to the inflammatory spectrum seen in chronic sinus disease (63). *Alternaria* and *Penicillium* are capable of activating eosinophils *in vitro*, resulting in degranulation of eosinophils (64). Despite the ubiquitous nature of fungi, their role in chronic sinus disease seems limited. Six months of nasal antifungal therapy does not result in a significant reduction of nasal symptoms in patients with chronic sinus disease (65).

Besides inhalant allergens, positive intradermal tests to food allergens have been reported in 81% of NP patients compared with 11% of controls (66). Food and drug sensitivities are found in 31% of patients with NP (67). Apart from *in vitro* data on mizolastine-mediated reduction of release of leucotrienes, tumour necrosis factor alpha and granulocyte monocyte colony stimulating factor by dispersed NP cells (52), clinical studies on the effect of antihistamines on NP in atopic vs nonatopic patients with NP are lacking. Only one study by Haye

et al. (14) showed that oral cetirizine reduced nasal symptoms in the postoperative period after endoscopic sinus surgery for NP.

Taken together, the role of allergy in NP is far from clear. Further studies are needed to elucidate the relevance of local IgE production in NP and to explore the role of bacterial enterotoxins in local IgE production and perpetuation of the inflammatory cascade in NP.

Allergic rhinitis and adenoid hypertrophy

The adenoid is the peripheral lymphoid organ located in the nasopharynx that is part of the Waldeyer ring and contributes to the development of immunity against inhaled micro-organisms in early life (68). In all children, the volume of the adenoid increases with age with a maximal volume in the age group of 5–6 years, followed by a gradual decrease in volume by the age of 8–9 years. In a survey of asymptomatic school children (69), an enlarged adenoid was observed in one-third of 7-year-old children, in every fifth 10-year-old child and in every tenth 14-year-old child. Many triggers, among which are microbial stimuli such as moulds (70) or external irritants such as cigarette smoke (71), have been related to the enlargement of adenoid tissue and hence development of symptoms. Symptoms related to adenoid hypertrophy range from nasal obstruction, rhinolalia clausa, open mouth breathing and snoring, to the so-called ‘adenoid facies’. In children, both AR and adenoid hypertrophy may give rise to similar symptoms, and therefore AR and AHT need to be differentiated at the time of consultation.

Little is known about the correlation between AR and AHT in children. The presence of sensitization to inhalant allergens has been reported to alter the immunology of adenoid tissue. Vinke et al. (72) found more CD1a⁺ Langerhans cells and eosinophils in the adenoids of allergic children, which was later confirmed by Nguyen et al. (73) who reported more eosinophils, IL-4 and IL-5 mRNA-positive cells in adenoids of atopic vs nonatopic patients. Furthermore, atopy is being associated with increased numbers of IgE-positive cells in adenoids irrespective of the presence of AHT (74). However, no correlation was observed between the atopic state and the degree of adenoid hypertrophy by Cassano et al. (75).

Despite the lack of knowledge on the exact aetiological role of allergy in AHT, allergy should be asked for in children with symptomatic AHT, and tested by skin prick tests or RASTs in case of positive history. In view of their different therapeutic approach, it is important to recognize the sensitization state in children prior to adenotomy in order to prevent dissatisfaction. However, properly conducted clinical trials on antihistamines in allergic children with AR and AHT are missing. In

contrast, nasal steroids are capable of reducing adenoid-related symptoms (76–78) without difference in responses between atopic and nonatopic children (76). In these studies, the effects of nasal steroids on symptoms of allergic inflammation in nose and adenoid cannot be dissociated from their anti-inflammatory effects on the adenoid itself. Recently, a short treatment with oral steroids, followed by prolonged oral antihistamine and nasal steroid spray therapy, reduced adenoid volume and associated symptoms (79).

Allergic rhinitis and tubal dysfunction

The Eustachian tube exerts a major function in middle ear homeostasis via its role in ventilation and protection of the middle ear and mucociliary clearance. In the light of the concept of global airway allergy, the Eustachian tube lined with respiratory epithelium may be involved in the allergic response after allergen inhalation. Nguyen et al. (73) reported that the mucosal lining at the tubarian tube, i.e. the nasopharyngeal orifice of the Eustachian tube, contains an allergic inflammatory infiltrate in AR patients. It is therefore not surprising that allergic inflammation with concomitant mucosal swelling may impair the function of the Eustachian tube. Nasal challenge with house dust mite induces nasal obstruction and tubal dysfunction in allergic individuals (80). Research in rodents shows that transtympanic challenge with the relevant allergen leads to tubal dysfunction and the development of otitis media with effusion (OME) (81, 82). At present it remains to be elucidated whether nasal allergen inhalation leads to deposition of allergens at the tubarian tube with induction of a local allergic response, or gives rise to a systemic immune response involving the airway mucosa at the site of the tubarian tube. Both mechanisms may be involved in the generation of allergic inflammation and swelling of the tubarian tube, ultimately leading to OME in predisposed patients.

Allergic rhinitis and otitis media with effusion

Otitis media with effusion remains a significant problem in children. It is estimated that more than 80% of all children have at least one episode of otitis media by the age of 3 and that 40% will have three or more episodes (83). There remain several controversies with regard to the pathogenesis of OME, among which is the relationship between allergy and OME. In view of the concept of global airway allergy, it can be expected that in the middle ear, an allergic inflammatory response can take place. Indeed, all cells and mediators that contribute to the allergic inflammation are present in the middle ear fluid of OME patients. Wright et al. (84) demonstrated increased expression of IL-5 and major basic protein in the middle ear mucosa of patients with OME. In the

supernatant of middle ear fluid of atopic patients, increased levels of ECP was reported by Hurst et al. (85). Recent data by Nguyen et al. (73) nicely illustrate that the middle ear fluid of atopic patients with OME contains more eosinophils and IL-4 and IL-5 mRNA-positive cells than in nonatopic patients with OME, suggestive of a role of allergic inflammation in OME. It remains difficult to interpret epidemiological data as we cannot estimate to what extent the enhanced prevalence of allergy in otitis media patients reported by some authors (86, 87) represents a true finding or rather reflects a referral bias.

Allergic rhinitis and laryngitis

Dry cough is often found in patients with AR. Recent studies suggest that neuro-chemical alterations in the allergic airway with release of substance P may be responsible for the induction of cough in AR patients (88). On the other hand, allergic mediators like histamine, PG-E2 and PG-F2 directly stimulate cough receptors in bronchi and may elicit a cough reflex. Whether cough in AR patients is induced by stimulation of receptors in the nasal mucosa or at a distance via the systemic release of the above-mentioned mediators, is difficult to discriminate. Whatsoever, nasal treatment for AR with a steroid spray (89) as well as oral antihistamines (90) have been reported to alleviate cough in AR patients.

In patients with dysphonia, the presence of inhalant allergy is considered to be a hidden, though common cause of vocal cord dysfunction (91). However, vocal cord oedema has not been demonstrated to be induced by allergic inflammation, nor is there any study showing deleterious effects of allergen provocation on voice quality in atopic patients or beneficial effects of anti-allergic therapy on laryngeal oedema or voice quality. It is noteworthy to mention here that allergic airway disease in professional voice users may have some therapeutic consequences. Oral antihistamines are known to cause some dryness of the laryngeal mucosa, and should therefore be started after explanation of advantages on nasal symptoms and potential side effects on the laryngeal mucosa. Inhaled steroids are often prescribed in patients with AA, and may cause a reversible vocal cord dysfunction (92). Oedema of the laryngeal mucosa, laryngeal erythema and candidiasis may all be found in a minority of patients treated with inhaled corticosteroids (93), but is not reported after prolonged use of nasal steroid spray.

Conclusion

As the prevalence of allergic diseases is increasing, it is of utmost importance to recognize the presence of

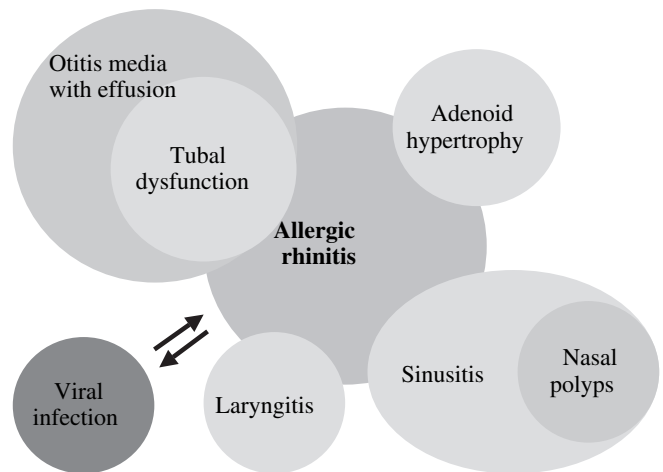


Figure 3. Schematic overview of the involvement of allergic rhinitis (AR) in different pathological conditions of the upper airway. Despite the lack of full understanding of the aetiological role of allergic inflammation in tubal dysfunction, sinusitis with and without nasal polyps, adenoid hypertrophy, and cough, AR can be considered as one aetiological factor in the manifestation of these diseases. The pathophysiological link between allergy and viral infections is multifactorial, with AR and viral infection having synergistic effects on the symptoms related to AR and common colds.

sensitization to inhalant allergens in patients presenting with sinusitis, NP, recurrent upper airway infections, tubal dysfunction, dysphonia and in children with otitis media with effusion and adenoid hypertrophy. In each of these conditions, allergic inflammation may contribute to the disease manifestation. A schematic overview of the involvement of allergy in these conditions is presented in Fig. 3. Notwithstanding the lack of insight into the exact pathophysiological mechanisms linking AR with these diseases, it should be clear that failure to address allergy as a contributing factor diminishes the probability of success of treatment, albeit medical or surgical. Therefore, nasal symptoms related to AR should be asked for during history-taking of patients presenting with chronic sinusitis with and without NP, recurrent viral infections, tubal dysfunction, otitis media with effusion, adenoid hypertrophy and dysphonia. In case of suspicion of inhalant allergy, skin prick tests or RASTs should be performed to confirm the presence of an underlying sensitization and the patients treated accordingly. In case of sensitization to inhaled allergens, therapy should be conducted following recently developed evidence-based guidelines for treatment (94).

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