

Allergy, immunology, and otitis media

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Investigations in the field of otolaryngic allergy and otitis media with effusion (OME) continue to focus on the mechanisms linking the two disorders. Allergic disease, with its disruption of nasopharyngeal function and the microorganismal environment, appears to predispose to OME, especially in the young and in immunocompromised patients. In the middle ear, there is a mucosal immune response as well as a humoral immune response that is produced by cells recruited from the systemic circulation. In younger children, the immaturity of the immune response appears to increase the severity and duration of OME when compared with OME in adults. Preliminary investigations of passive immunoprophylaxis and allergic immunotherapy for OME are encouraging.

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As the field of otolaryngic allergy expands, so does an appreciation of the contributions of allergic disease to common otolaryngic problems. Some subsets of otitis media with effusion (OME) appear to be a sequela of allergic disease. We review the current issues in allergy and OME and also the intimate relationship of the nasopharynx and eustachian tube to the middle ear. The immune response in these regions contributes heavily to the progression of OME, and therefore, it must also be discussed. An excellent review by Fadal [1•] of IgE-mediated hypersensitivity reactions is available in the recent otolaryngic literature; the reader is referred to this for basic explanations of the allergic response. In presenting this review, we hope to impress on our colleagues that OME is not caused simply by isolated bacterial infection but instead is a result of a multifactorial disruption of nasal, nasopharyngeal, eustachian tube, and microorganismal homeostasis.

Coincidence of otitis media with allergic disease

Otitis media with effusion appears to be associated with allergic disease. Two recent reviews by Bernstein and Doyle [2•] and Bernstein [3•] recapitulate their extensive experience with patients. In these series, 23% of children with OME showed evidence of coincident allergic disease, whereas 35% to 40% of children requiring insertions of ventilation tubes were allergic. A paper by Corey *et al.* [4•] compared 89 children with OME with 59 control subjects who were being evalu-

ated for problems not related to allergic disease. Serum specific IgE was found by radioallergosorbent testing in 61% of the OME patients versus 41% of the control subjects.

Several studies have addressed the levels of IgE in middle ear effusions versus the serum levels [5–8]. Some studies have found higher levels of IgE in the effusion [5,6], whereas others have not [7,8]. Bernstein and Doyle [2•] and Bernstein [3•] found that approximately 10% of children with OME have higher IgE levels in the effusion than in the serum.

Allergic disease appears to contribute to the development of otitis media through indirect and perhaps also direct effects, but the pathophysiology is not known. The changes seen in the nose and nasopharynx in response to the introduction of known allergens may include eustachian tube dysfunction, subsequent negative middle ear pressure, and often middle ear effusion [9,10]. The eustachian tube dysfunction is not a direct effect of nasal obstruction [3•], but appears to be an effect of IgE binding of allergen in the eustachian tube region and subsequent inflammatory swelling of the eustachian tube mucosa [2•].

Evidence for a direct effect of the allergic reaction on the middle ear is sparse. Previous investigators of sensitized animals that received direct inoculation of allergen into the middle ear cleft found no effusions despite the recovery of allergen from the middle ear [11]. However, in a recent study, Hurst and Venge [12•] found eosinophilic cationic protein (ECP) in middle ear effusions. ECP is a granule protein produced during allergic

Abbreviations

ECP—eosinophilic cationic protein; NTHi—nontypable *Haemophilus influenzae*; OME—otitis media with effusion; RSV—respiratory syncytial virus.

reactions; its high isoelectric point increases its adherence to biologic structures. This protein is thought to be a regulator of mast-cell activity during allergic inflammation. The levels of ECP in the middle ear effusions correlated with the presence of allergy in the patient, as confirmed by radioallergosorbent testing or skin testing, and did not correlate with serum levels of the same protein or of serum IgE. This finding suggests a localized inflammatory reaction rather than a systemic effect.

The contribution of food allergy to OME remains unclear [2•,3•]. Corey *et al.* [4•] demonstrated that children with OME had a higher incidence of allergy to various foods than did a control group. Some of these food allergy differences were statistically significant (soy and egg white) and others were not (cow's milk, cod, wheat, corn, and baker's yeast). Hurst and Venge [12•] also cite cases of OME that cleared with food elimination.

Nasopharyngeal flora and immunology

Clearly, conditions in the nasopharynx affect eustachian tube function and middle ear pressure. However, the nasopharynx also influences the development of otitis media through bacterial colonization, infections, and the immunologic responses occurring in the nasopharynx. The ability of pathogens to adhere to the nasopharyngeal mucosa is well known; the nasopharynx of children is colonized by both viruses and bacteria. Common species known to colonize the nasopharynx include respiratory syncytial virus (RSV) [13•], *Streptococcus viridans* [14•], nontypable *Haemophilus influenzae* (NTHi) [15•,16], and *Streptococcus pneumoniae* [16].

The same bacteria or viruses that colonize the nasopharynx can become pathogens as their numbers increase [16], contributing to the development of acute otitis media. Harabuchi *et al.* [15•] showed that children with NTHi in the nasopharynx are more likely than those without to develop OME. Okamoto *et al.* [13•] reported that children with nasopharyngeal RSV are more likely to have RSV in their middle ear effusions. Indeed, the same strains of bacteria have been identified in the nasopharynx and in middle ear effusions [14•].

Nasopharyngeal immune responses influence the interplay between, as well as the colonization and pathogenicity of, viruses and bacteria. The nasopharynx appears to mount a local mucosal immune response that affects the type and number of resident bacteria. Bacterial colonization in the nasopharynx is thought to stimulate the production of secretory IgA by the ciliated epithelium, thereby reducing adherence of bacterial pathogens [14•]. Viral infection, however, appears to increase bacterial adherence [14•]. Yamanaka

and Faden [17•] have recently shown that nasopharyngeal secretions contain levels of IgA and secretory IgA against P6 (a highly conserved membrane protein of NTHi) that exceed serum levels. The authors demonstrated that higher IgA and secretory IgA levels against P6 correlate with reduced colonization by NTHi [17•]. Lindberg *et al.* [18•] found a similar inverse relationship between IgA activity against 6B (a capsular polysaccharide of *S. pneumoniae*) and *S. pneumoniae* colonization.

The child's nasopharynx appears to have two disadvantages when mounting a mucosal immune response. Lindberg *et al.* [18•] have shown that adults have higher levels of secretory IgA against 6B in the nasopharynx and less colonization by *S. pneumoniae* than do children. Indeed, as Bernstein *et al.* [19] demonstrated in 1994, the tonsils and adenoids of 3- to 16-year-olds showed defective interleukin-2 production in response to both mitogens and specific antigens, which reduced production of secretory IgA. This finding suggests that the pediatric nasopharyngeal mucosa has an inherent weakness of B- and T-cell maturation. Finally, in 1994, Harabuchi *et al.* [15•] noted an inverse relationship of bacterial colonization in infants to exogenous sources of secretory IgA: higher levels of secretory IgA in the human milk fed to breastfeeding infants correlated with reduced nasopharyngeal NTHi colonization.

Viral nasopharyngitis and otitis media

It has long been observed that the peak incidence of bacterial otitis media occurs during months in which the incidence of viral upper respiratory tract infections is high. The viruses most commonly associated with OME are adenovirus, RSV, influenza A, and influenza B [20•]. Each of these has been studied this year in both humans and animals. Bakaletz *et al.* [20•] found that inoculation with adenovirus both transnasally and via the bulla caused subsequent OME and often bacterial superinfection in chinchillas. When these animals underwent inoculation with both adenovirus and NTHi, the subsequent infection was worst when the viral inoculation was given several days in advance of the bacterial inoculation [21•]. Okamoto *et al.* [13•] found RSV messenger RNA in 53% of children with OME, whereas Park *et al.* [22•] found reduced eustachian tube ciliary function in animals after RSV infection. Doyle *et al.* [23•] challenged healthy adults with intranasal influenza A; the results were negative middle ear pressures and a 19% incidence of OME.

Middle ear immune response

The middle ear mucosa has been thought to contain no immunocompetent cells [24•]. Instead, studies of OME by Kato *et al.* [24•] and Takahashi *et al.* [25] continue to demonstrate that macrophages, granulocytes,

and antigen-specific T and B cells are recruited to the middle ear mucosa from the systemic circulation. Takahashi *et al.* [25] also noted that suppressor T cells appear to be underrepresented in OME. IgA and IgG continue to be demonstrated in middle ear fluids in OME [17•,26,27]. These immunoglobulins are thought to represent the local immune response to infection and to reduce the intensity and duration of the infection. In Yamanaka and Faden's [17•] study of OME in children, those children with higher levels of IgG against P6 of NTHi had lower NTHi counts. Middle ear IgA and secretory IgA appear to be produced in the middle ear cleft, whereas IgG appears to come from the systemic circulation [17•].

Many inflammatory mediators have been identified in OME fluid. Mediators found in OME include interleukin-1 β , interleukin-6, tumor necrosis factor- α , interleukin-2, interferon gamma, collagenase, interleukin-8, and ECP [12•,13•,24•,28,29•]. Some of these factors have been identified in human patients with OME [12•,13•,28,30], and some in animals that had mechanical obstruction of the eustachian tube [25]. The presence of ECP is of particular interest because it suggests a larger role for eosinophils in OME than was previously suspected.

Therapy

Otitis media with effusion is often a disease of the immunoincompetent. OME is seen in younger children who are less able to mount an active immune response than their older counterparts. In addition, patients with immunodeficiencies (such as deficiencies of IgA and IgG3) have higher rates of OME [18•,31]. Clearly, the immune response weighs heavily in the balance between colonization and infection, and immunotherapy for OME has been explored [32]. Vaccination in animals appears to increase the IgA-mediated mucosal immunity against pneumococcal disease [32]. Vaccines against RSV, adenovirus, and influenza virus presumably should reduce the incidence and severity of the nasopharyngeal congestion and obstruction that appear to predispose to bacterial superinfection [27]. However, in children under 2 years of age, immunocompetence is low, and vaccination may not induce sufficient IgA-mediated activity to prevent infection. Therefore, immunoprophylaxis has been investigated as a means to "bridge this gap" [27] until the patient becomes more immunocompetent.

Several studies on the use of passive immunoprophylaxis in young or immunocompromised patients have been reported this year. Intravenous IgG against 14 *S. pneumoniae* serotypes appeared to reduce the incidence and severity of acute pneumococcal otitis media in two pediatric studies [33,34] and to reduce the incidence of otitis and sinusitis in another

study of immunodeficient patients [31]. The number of cases in these studies is low, and in some the variability in results is so broad that it is difficult to be confident about a clear benefit of intravenous immunoprophylaxis. Passive mucosal immunity of breastfeeding infants via maternal milk is again suggested in a study by Harabuchi *et al.* [15•]. Bernstein *et al.* [14•] suggest another line of defense by bolstering native defenses against OME through recolonization of the nasopharynx with *S. viridans*.

Hurst and Venge [12•] have reported on immunotherapy directed against the contribution of allergy to otitis media. Several allergic patients were reported to have cleared their persistent OME after beginning specific immunotherapy, and one is reported to have recovered after food elimination and immunotherapy. In an older study, McMahan *et al.* [35] reported a similar success with immunotherapy.

Conclusions

Allergic disease appears to contribute to the development of OME through the interruption of eustachian tube function and through the development of subsequent negative pressure in the middle ear. The congestion and increase in secretions associated with allergy are also very likely to contribute to bacterial superinfection, much as does viral infection. Lymphocytes and tissue immunocompetent cells are recruited to the middle ear cleft and mucosa both in infection and in OME secondary to eustachian tube dysfunction. The robustness of the immune response determines the severity and duration of bacterial superinfection, and therefore, OME is seen in young children whose immune response is weaker than the adult response.

It is very important in treating OME to recognize its multifactorial etiology. Often, antibiotics alone cannot alleviate the problem, and other underlying causes must be identified. In addition to the immature immune response seen in young children, viral infection, allergy, and imbalance of the normal nasopharyngeal flora all appear to contribute to the progression to OME. Also, treatment should ideally be tailored to these multiple factors.

References and recommended reading

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