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Review Article

A link between allergic rhinitis and otitis media with effusion

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Abstract

The role of allergy, particularly allergic rhinitis (AR), in otitis media with effusion (OME) is discussed. Because both OME and AR are common in young children, these disorders are occasionally seen in the same patient. Many clinical and experimental reports have discounted the allergies as a cause of middle ear effusion (MEE) because type I allergic reactions in the nose cause eustachian tube dysfunction but do not induce MEE, because the associated tubal dysfunction has a short duration. It has been shown that allergy-induced tubal dysfunction significantly disturbs the clearance of MEE. Since clinical and experimental studies have demonstrated the efficacy of allergy treatment in patients or animals having both diseases, combination treatment for allergy and OME in patients with both diseases should be initiated.

Key words: allergic rhinitis, nasal allergy, otitis media with effusion, pathogenesis, Type I allergy.

Introduction

The causes and pathogenesis of otitis media with effusion (OME) are considered to be multifactorial, involving infection of the tubotympanum, eustachian tube dysfunction, and allergy. Allergic rhinitis (AR) is a typical immunoglobulin E (IgE)-mediated allergic disorder. The role of allergy, particularly of IgE-mediated immune reactions, in OME has been debated. Although many recent laboratory and experimental studies have discounted an allergic reaction as a cause of OME, the continuity of the mucous membrane between the nose and tympanic cavity via the eustachian tube, suggests that the middle ear mucosa may respond functionally as a sensitized tissue in patients with respiratory allergy.

In this paper, we review the evidence of IgE-mediated allergic reactions in the etiopathogenesis of OME in order to examine the role of allergy in OME.

Incidence of allergy in otitis media with effusion

A number of studies have reported a high incidence of allergy in patients with OME. Jordan reported that allergy was associated with OME in 91 of 123 patients (74%).[1] Lecks tested 82 children with OME using skin scratch tests with common environmental, inhalant, pollen, and mold allergens and found a positive reaction in 72 (88%) patients.[2] Draper found OME in 270 of 520 (52%) children with allergic rhinitis.[3] Since the discovery of IgE in 1966,[4] more specific allergy tests have been developed. Bernstein and Reisman, using an objective definition of OME, examined 200 consecutive OME patients for evidence of allergy.[5] They reported that 46 of the patients (23%) were allergic. Hurst defined allergy using the radioallergosorbent test (RAST), serum IgE levels, and skin tests, and found that allergies were present in 97% of the patients with non-acute OME.[6] The results indicated that allergy and OME were correlated clinically in 89% of patients. Fig. 1 shows the incidence of OME in patients with AR from different age groups who were examined at our institution between 1982 and 1996. Diagnosis of allergic rhinitis was made based on the clinical symptoms, results of skin tests, eosinophils in nasal secretion, nasal provocation tests, RAST, and serum IgE levels. Otitis media with effusion was diagnosed by the presence of effusion in the tympanic cavity as determined by paracen-

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tesis. Because OME and AR are both common among children, we determined the ratios at which both occurred in three age-matched groups (mean age, 6 years; range 6–8). As shown in Fig. 2, the ratio of AR complications in 222 children with OME was 42%, whereas that of OME in 259 children with AR was 36%.[7] These ratios were significantly higher than those seen in the control group. Thus, findings of previous and recent studies indicate that the frequency of allergy in young patients with OME is high.

EOSINOPHILS AND IgE IN MIDDLE EAR EFFUSION AND MIDDLE EAR MUCOSA

Because eosinophil infiltration is a phenomenon characteristic of allergic reactions, many investigators have examined eosinophils in middle ear effusion (MEE) and in the middle ear mucosa. King studied 72 ears of 56 children and found that seven of 39 ears containing mucous secretion showed 5–10% eosinophils, while no child with serous effusion had eosinophil infiltration.[8] Ivstam reported smears from 33 case patients with secretory catarrh, and 13 of these had very small numbers of eosinophils.[9] Jordan reported 123 patients with MEE; 91 (74%) were diagnosed as allergic based on the presence of eosinophils in nasal smears, positive skin tests, and response to allergy therapy.[1] However, he also found that direct smears of the effusion only showed occasional eosinophils, scattered leukocytes, and no bacteria. Other studies also failed to find eosinophils in MEE.[10,11] Recent studies by Lim and Birck[12] Bernstein and Reisman,[5] and Spila and Karma[13] found no significant numbers of eosinophils in MEE or middle ear mucosa from patients with OME. Thus, a number of investigators have discounted MEE as an allergy-related fluid. More recently, however, Hurst[6] and Hurst and Venge[14] examined eosinophil cationic protein (ECP) in MEE and middle ear mucosa from 89 patients with OME and found elevated ECP in 87.5% of MEE samples. Hurst suggested that OME is a sign of allergic inflammation in the middle ear.[6]

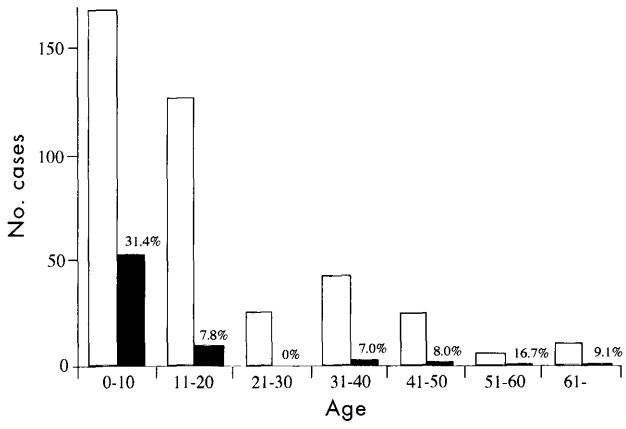


Fig. 1 Numbers of patients with otitis media with effusion (OME; ■) among patients with allergic rhinitis (□). Patients were managed in the Department of Otolaryngology, Oita Medical University between 1982 and 1996.

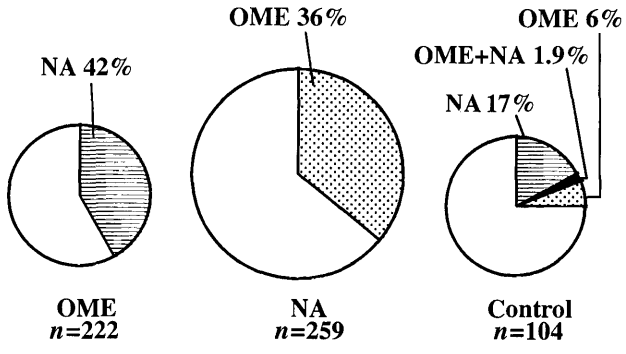


Fig. 2 Ratios of complications of nasal allergy (NA) in otitis media with effusion (OME) and of OME in NA.

Since the discovery of IgE,[4] many investigators have studied total IgE and specific IgE antibodies in MEE, comparing them with values in corresponding sera. Although Phillips *et al.* reported increased total IgE and IgE-bearing cells in all MEE samples ($n = 26$) collected from patients with OME,[15] suggesting that MEE is an allergy-related fluid, a majority of studies found that MEE did not contain total or antigen-specific IgE antibody concentrations exceeding those in matched serum samples, thus excluding MEE as a product of allergic reactions.[5,16–21]

There are few immunocompetent cells in the normal middle ear mucosa.[22] Mast cells are the exception. There are significant numbers of mast cells in the tympanic orifice of the eustachian tube and in other parts of the middle ear in rats and in adult, neonatal, and developing guinea pigs.[23,24] The evidence suggests that the middle ear acts as an allergic shock organ. Miglets induced OME in monkeys passively sensitized (with human anti-ragweed IgE antibodies) by daily delivery of ragweed pollen to the middle ear mucosa via an eustachian tube catheter.[25] Miglets found that the constituents of the provoked MEE were consistent with an allergic origin. However, a replicating study by Doyle *et al.* failed to discover any MEE, even though they confirmed that pollen was present in the middle ear mucosa.[26] Doyle *et al.*

reported that the histologic evidence of an allergic reaction was localized to the area of pollen–mucosal contact. Doyle *et al.* also suggested that using a catheter may injure the tubal lumen and cause tubal dysfunction and infection that could lead to middle ear inflammation and the production of effusion.[26] Because the eustachian tube is usually closed, only opening primarily during swallowing or yawning, and because it is the only potential pathway for antigen access to the middle ear, inhalant antigens do not enter the tympanic cavity easily.[26]

Tomonaga *et al.* developed an animal model of nasal allergy in guinea pigs by passive sensitization with serum from homologous animals containing an antigen-specific IgE antibody (dinitrophenilated [DNP]-ascaris).[27] They then injected antigen (DNP-ovalbumin) directly into the tympanic cavity of the passively sensitized guinea pigs. Although they found allergic changes in the mucosa lining the tympanic bulla, there was no macroscopic effusion. Results of their study agreed with those of Doyle *et al.*[26] Both authors discounted an allergic etiology of OME.

However, based on the results of investigations on ECP in MEE and eosinophils in the middle ear mucosa, Hurst[6] and Hurst and Venge[14] asserted that OME is a sign of allergic inflammation in the middle ear, and is associated with an increase in eosinophils and a concomitant release of ECP into the effusion in individuals with allergy. Hurst argued that suggestions that allergies cannot produce MEE, because of the gatekeeper function of the eustachian tube,[26] ignore the current understanding of immune-mediated disease as exemplified by asthma and atopy.[6]

Hurst cited Denburg[28] to explain why allergic inflammation occurs in the tympanic cavity of allergic subjects, even though allergens do not reach that region. In allergic persons, a dynamic state exists between the structural epithelial cells of the airway and the progenitors of basophils, eosinophils, and mast cells. These progenitors are primed by allergen challenge, circulate in increased numbers in the blood of patients with various forms of airway inflammation, and become programmed to react to exogenous stimuli.[28] Therefore, Hurst suggested that the allergic patient is more prone to develop OME after having developed acute otitis media.[6]

Interference of Eustachian Tube Function by Allergic Reactions in the Nasal Mucosa

The nasal mucosa communicates anatomically with the nasopharyngeal and tubal mucosae. Therefore, allergic inflammation of the nasal mucosa may cause edema and elevated secretion by the eustachian tube mucosa, resulting in tubal obstruction and dysfunction. Crifo *et al.* demonstrated that intranasal allergen challenge decreases tubal patency or causes complete tubal obstruction in patients with perennial AR.[29] Ackerman *et al.* observed eustachian tube obstruction after intranasal pollen insufflations with different doses in patients with AR to ragweed or timothy grass.[30] They compared the dose responses and duration of eustachian tube obstruction to the patients' levels of serum-IgE antibodies against the causative pollen and found that the induced tubal obstruction was dependent on and related to serum-IgE antibody activity. Skoner *et al.* conducted a similar study of patients with nasal allergies to house dust mites and obtained similar results.[31] Osur *et al.* used the nine-step pressure-swallowing test to evaluate eustachian tube obstruction in 15 children with ragweed hay fever prior to, during, and after seasonal exposure to ragweed pollen.[32] They reported that the development of eustachian tube obstruction correlated with ragweed skin test wheal size and daily patient symptom-medication scores during pollen exposure. They suggested that children with ragweed hay fever develop eustachian tube dysfunction during natural pollen exposure, but that eustachian tube obstruction increased by seasonal allergy is not, by itself, sufficient to produce MEE, since only one child in their study developed evidence of MEE. Taken together, these findings suggest that inflammation of the nasopharynx and tubal orifice is important in the development of eustachian tube dysfunction. Although persistent tubal obstruction induces MEE,[33] the tubal dysfunction caused by the allergic inflammatory process does not cause OME.

Tomonaga *et al.* studied the eustachian tube histologically and functionally in passively sensitized guinea pigs after nasal antigen provocation.[27] They found significant allergic reactions, such as marked eosinophil infiltration, mast cell infiltration, edema, and hypersecretion, in the mucosa of the nose, nasopharynx, and eustachian tube, even though the histologic changes were limited to the area near the pharyngeal orifice. These changes were noticeable within 1 h of the nasal antigen challenge. Tubal function was evaluated by inflation and deflation tests using tympanometry after the eardrum was perforated. Tomonaga *et al.* reported a significant increase in the opening pressure of the tube at 30 and 60 min after the antigen challenge, in comparison with values before the antigen challenge. The tubal mucociliary activity was also disturbed significantly upon nasal allergic attacks.[6] The results of their study indicate that the morphological

and functional dysfunctions of the tube evoked by nasal allergic reactions were transient, culminating in no MEE. These studies suggest that type I allergic reactions of the nose are not an etiologic factor for OME.

In order to investigate the influence of nasal allergic reactions on the clearance of MEE, Mogi *et al.* generated an animal model of simultaneous AR and OME in the guinea pigs by passive sensitization with IgE antibodies (for AR), and inoculation of immunocomplexes into the tympanic cavity (for OME).[34] After inoculation with the immunocomplexes, intranasal antigen challenges were performed. The disappearance of MEE appeared to be delayed in animals with induced nasal allergic reactions; however, MEE was not found in ears that had not been inoculated with the immunocomplexes. The results of this study indicate that IgE-mediated allergic reactions in the nose, nasopharynx, and eustachian tube are indicative of a chronic disease state and do not cause OME. This finding is consistent with the results of an epidemiological study by Pukander and Karma of 753 infants with acute otitis media.[35] They reported a significantly longer persistence of MEE in infants with a history of allergy compared with those in a nonallergic control group. Mogi *et al.* recommended that allergy treatment be combined with OME treatment in patients with both AR and OME.[34]

EFFECT OF ANTIALLERGIC DRUGS ON OTITIS MEDIA WITH EFFUSION IN ASSOCIATION WITH ALLERGIC RHINITIS

A total of 53 patients diagnosed with OME accompanied by perennial AR were enrolled in a clinical study conducted by Kawauchi *et al.*[36] The patients were randomly allocated into two groups: group A, consisting of 30 patients who received azelastine hydrochloride (AZ) and s-carboxymethyl cysteine (s-CMC), and group B, consisting of 23 patients who received s-CMC only. Azelastine hydrochloride, an anti-allergy medicine, was developed for the treatment of AR, asthma, and atopic dermatitis.[37] S-carboxymethyl cysteine has been shown to accelerate the clearance of MEE.[38] As shown in Fig. 3, global improvement ratings (GIR) between nasal and ear symptoms in group A were significantly correlated. However, the correlation was not significant in group B.

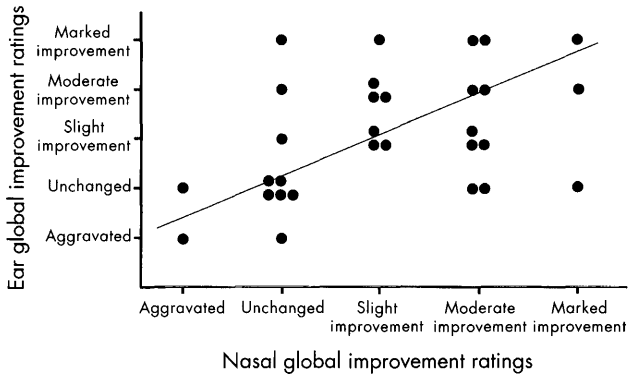


Fig. 3 Correlation of global improvement ratings (GIR) between nasal and ear symptoms in a patient group treated for both OME and AR. $r = 0.43$; $P < 0.05$.

In order to confirm the efficacy of AZ in OME associated with AR, we recently performed experiments in an animal model. Allergic rhinitis and OME were induced in the same guinea pigs simultaneously using the method reported previously.[34] A total of 51 guinea pigs passively sensitized with guinea pig IgE antibodies against DNP-ascaris, had immunocomplex injected into the tympanic cavity. Otitis media with effusion developed within a few days and subsided approximately 10 days after instillation of the immunocomplex. Thirteen animals received no treatment (group A), 13 were given 1 mg/kg of AZ (group B), and 13 were given 2 mg/kg of AZ (group C). Azelas-

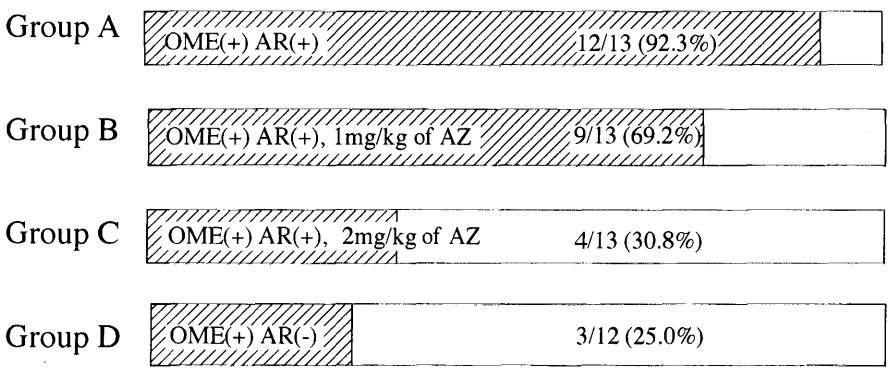


Fig. 4 The presence of middle ear effusion (MEE; ▨) on the eleventh day after immunocomplex instillation into the tympanic cavity of guinea pigs. OME, otitis media with effusion; AR, allergic rhinitis; AZ, azelastine hydrochloride.

tine hydrochloride was administered by gastric intubation from the 3rd to 10th day after immunocomplex injection. As a control, the 12 remaining guinea pigs were given saline drops nasally instead of DNP-ovalbumin and did not receive AZ (group D). All animals were killed on the 11th day after immunocomplex instillation into the tympanic cavity and the degree of MEE stagnation was determined. Fig. 4 shows the incidence of MEE in each group. In group A, 92.3% of guinea pigs had MEE, while the incidence of MEE was significantly lower (30.8%) in group C animals, compared with that of both group A and B animals (69.2%). These findings suggest that administration of AZ significantly accelerates the clearance of MEE.

In order to see whether AZ (2 mg/kg) inhibits MEE production, 14 non-sensitized, normal guinea pigs were randomly assigned to one of two groups (seven each, groups E and F). Group E animals received 2 mg/kg of AZ for 5 consecutive days before immunocomplex instillation into the tympanic cavity and for the 3rd day after instillation. Group F animals, in which OME was induced by immunocomplex instillation, served as non-treatment controls. Group E and F animals were killed on the 4th day after immunocomplex instillation because the MEE stagnation peaks on that day. All group E and F animals were found to have MEE, which suggests that AZ does not alleviate experimental OME.

Because allergy-induced tubal dysfunction disturbs the clearance of MEE and because the control of nasal allergic inflammation may improve the eustachian tube dysfunction induced by allergic reaction, combined treatment of allergy and OME in patients with both diseases should be indicated.

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