ORIGINAL ARTICLE

Eustachian Tube Function in Patients With Eosinophilic Otitis Media Associated With Bronchial Asthma Evaluated by Sonotubometry

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Objective: To determine eustachian tube function in patients with asthma and with or without eosinophilic otitis media (EOM), a new middle ear disease entity with a highly viscous middle ear effusion containing many eosinophils and usually associated with bronchial asthma. One of the most important causes of otitis media (OM) is eustachian tube dysfunction.

Design: Retrospective case review.

Setting: A referral center.

Patients: Twenty patients with EOM and patients with asthma but without OM.

Main Outcome Measures: We studied eustachian tube function using sonotubometry and a questionnaire. Sonotubometry was also performed on 13 control patients with chronic otitis media (COM) and 7 normal controls.

Results: The tubal opening duration was significantly longer in patients with EOM than in patients with asthma but without OM, controls with COM, and normal controls, indicating the presence of patulous eustachian tubes in patients with EOM. Responses to the questionnaire also supported the presence of patulous eustachian tubes in the patients with EOM.

Conclusions: The presence of a patulous eustachian tube may be a major cause of EOM in patients with bronchial asthma. In patients with asthma who have a helper T-cell 2–dominant predisposition, a patulous eustachian tube easily allows the entry of antigenic materials into the middle ear, causing eosinophil-dominant inflammation.

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RECENTLY, THERE HAVE BEEN some reports of adult patients with intractable otitis media (OM) with effusion (OME) or chronic OM (COM) associated with bronchial asthma. These patients exhibit clinical characteristics markedly different from those of patients with common OM. The middle ear effusion (MEE) is yellow and highly viscous, and the middle ear symptoms are extremely resistant to conventional treatments for the common type of OM, such as eustachian tube inflation, myringotomy or the insertion of a tympanostomy tube for OME, and the administration of antibiotics or ear surgery for COM. In 1997, Tomioka et al[1] named this condition *eosinophilic otitis media* (EOM) because MEE contains numerous eosinophils regardless of the presence of type I allergy. In 2001, we reported 7 cases of EOM and proposed the following diagnostic criteria for the disease: (1) the presence of yellow and extremely viscous MEE predominantly containing eosinophils and (2) the precedence and association with adult bronchial asthma.[2] These patients experience hearing loss for a prolonged period of time and sometimes become deaf gradually or suddenly.[1-4] Most of the patients also exhibited nasal polyposis or chronic rhinosinusitis, and some of them underwent nasal surgical procedures.[2-4]

In patients with bronchial asthma, a high prevalence of nasal polyposis is well documented.[5] However, the incidence of EOM is lower than that of nasal polyposis in patients with asthma. The question is why some patients with asthma have EOM but others do not. The cause of OM is multifactorial, and one of the most important causes is eustachian tube dysfunction. In the present study, we evaluated the eustachian tube function of patients with asthma and with or without EOM and found that most of the patients with EOM had a patulous eustachian tube.

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METHODS

PATIENTS

Our study included 20 patients who were diagnosed as having EOM on the basis of the diagnostic criteria described in the previous paragraphs (hereafter, EOM group). The group

Table 1. Baseline Characteristics of the 4 Groups*

Characteristic	EOM Group	Asthmatic Control Group	Normal Control Group	COM Control Group
Patients, No.	20	17	7	13
M/F, No.	6/14	5/12	3/4	5/8
Age at first visit, y	52.0 (10.9), 30-74	54.5 (16.2), 24-86	35.9 (9.9), 25-54	49.9 (17.8), 22-72
Age at onset of asthma, y	39.3 (14.4), 19-73	45.2 (19.2), 3-80		
Other conditions, No.				
Asthma (atopic: nonatopic)	8:12	9:8		
Aspirin intolerance	7	6	0	0
Nose and paranasal diseases	18	13	0	0
Nasal polyposis	16	9	0	0
History of sinus operation	9	7	0	0
Eosinophils in PB, %	12.8 (12.0), 2-54	8.4 (4.8), 3-19		
BMI	21.6 (3.6), 16.0-29.1	22.0 (2.8), 18.6-26.6	21.2 (2.4), 18.5-24.7	24.1 (4.1), 19.5-32.5

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COM, chronic otitis media; EOM, eosinophilic otitis media; PB, peripheral blood.

*See the "Methods" section for group definitions. Unless otherwise noted, data are given as mean (SD), range.

comprised 15 women and 5 men (age range, 30-74 years) at their first visit to our hospital. As controls, 17 patients treated for bronchial asthma without OM (hereafter, asthmatic control group), 13 patients with COM without the association of bronchial asthma or allergic diseases (hereafter, COM control group), and 7 healthy adults (hereafter, normal control group) were also studied. In the EOM group, eosinophils were histologically or cytologically identified in the otorrhea or MEE unilaterally or bilaterally in all 20 patients. At the time of testing with sonotubometry the 40 ears of the 20 patients, 1 ear had been operated on, 30 ears had small to large perforations with or without otorrhea, and the remaining 9 ears had intact eardrums with or without MEE. The bilateral ears of all members of the asthmatic control and the normal control groups showed a type A tympanogram and had no otomicroscopic findings of disease at the time of the study. In the COM control group, 12 patients had unilateral eardrum perforation and 1 patient had bilateral eardrum perforation. At the time of testing, none of the ears showed otorrhea, and then they underwent tympanoplasty for COM to confirm histologically that there was no eosinophilic inflammation in the middle ear mucosa. The baseline characteristics of the 4 groups are shown in **Table 1**. There were no statistically significant differences between the EOM group and the asthmatic control group in clinical characteristics, namely, sex; age; types of asthma; presence of aspirin intolerance, rhinosinusitis, and nasal polyposis; percentage of eosinophils in peripheral blood; and body mass index (calculated as weight in kilograms divided by height in meters squared).

MEASUREMENT OF EOSINOPHILIC CATIONIC PROTEIN AND INTERLEUKIN-5 IN MEE

To determine the presence of eosinophilic inflammation in the middle ear, MEE samples were collected from a persistent perforation of the eardrum or by myringotomy in patients in the EOM group for the measurement of the concentrations of eosinophil cationic protein (ECP) and interleukin (IL)-5. At the same time, peripheral blood samples were obtained from these patients to analyze ECP and IL-5 concentrations in serum. The MEE samples were collected using a middle ear fluid aspirator/collector (Jun-Tym-Tap; Medtronic Xomed, Jacksonville, Fla). Fifty to 100 mg of each effusion sample was suspended in 1 mL of isotonic sodium chloride solution, and the fluid was homogenized by vigorously pipetting and vortexing at room temperature. The fluid samples were allowed to stand for 60 to 120 minutes and then centrifuged at 1000*g* to 1350*g* for 10 minutes. The resultant supernatants were collected and stored at –80°C until measurement. The concentrations of ECP and IL-5 in the samples were measured using a radioimmunoassay kit (Pharmacia-Upjohn, Uppsala, Sweden) and an enzyme-linked immunosorbent assay IL-5 kit (Immunotech [MBL], Tokyo, Japan), respectively, according to the manufacturers' instructions. The detection limits of the assays were higher than 2 µg/L for ECP and 5 pg/mL for IL-5. Bacterial and fungal cultivations of MEE or otorrhea were also performed at the same time.

SONOTUBOMETRY

To determine the eustachian tube function, sonotubometry (model JK-04; RION Co Ltd, Tokyo, Japan) was performed on all the patients and normal controls according to the manufacturer's instructions. In the EOM group, sonotubometry was performed after MEE or otorrhea in the mesotympanum was removed by suctioning or by myringotomy, if needed, followed by suctioning as much as possible. In the COM group, all the ears were dry at the time of testing. Two parameters were determined: the eustachian tubal opening duration and the opening area formed by a sound pressure level (SPL) change of more than 43 dB SPL produced by voluntary dry swallowing when 60 dB SPL of a 7-kHz bandpass sound was introduced through a nasal olive tip into one of the nostrils. The subjects were instructed to swallow twice in 10 seconds. The 2 parameters were measured using downloadable National Institutes of Health image software (http://rsb.info.nih.gov/nih-image/) as shown in **Figure 1**. In the measurement of the opening area, 1.0 second was considered equivalent to 1 cm. The data were expressed as the mean of the values obtained by 2 dry swallows for each subject.

QUESTIONNAIRE AND STATISTICAL ANALYSIS

We distributed a questionnaire consisting of 10 questions regarding the symptoms associated with a patulous eustachian tube as proposed by Yamaguchi[6] to all of the patients with asthma. Informed consent was obtained from all the patients and healthy volunteers prior to the examination.

Statistical analysis was carried out using the unpaired *t* test or χ^2 test. Two-tailed *P* values of less than .05 were considered significant.

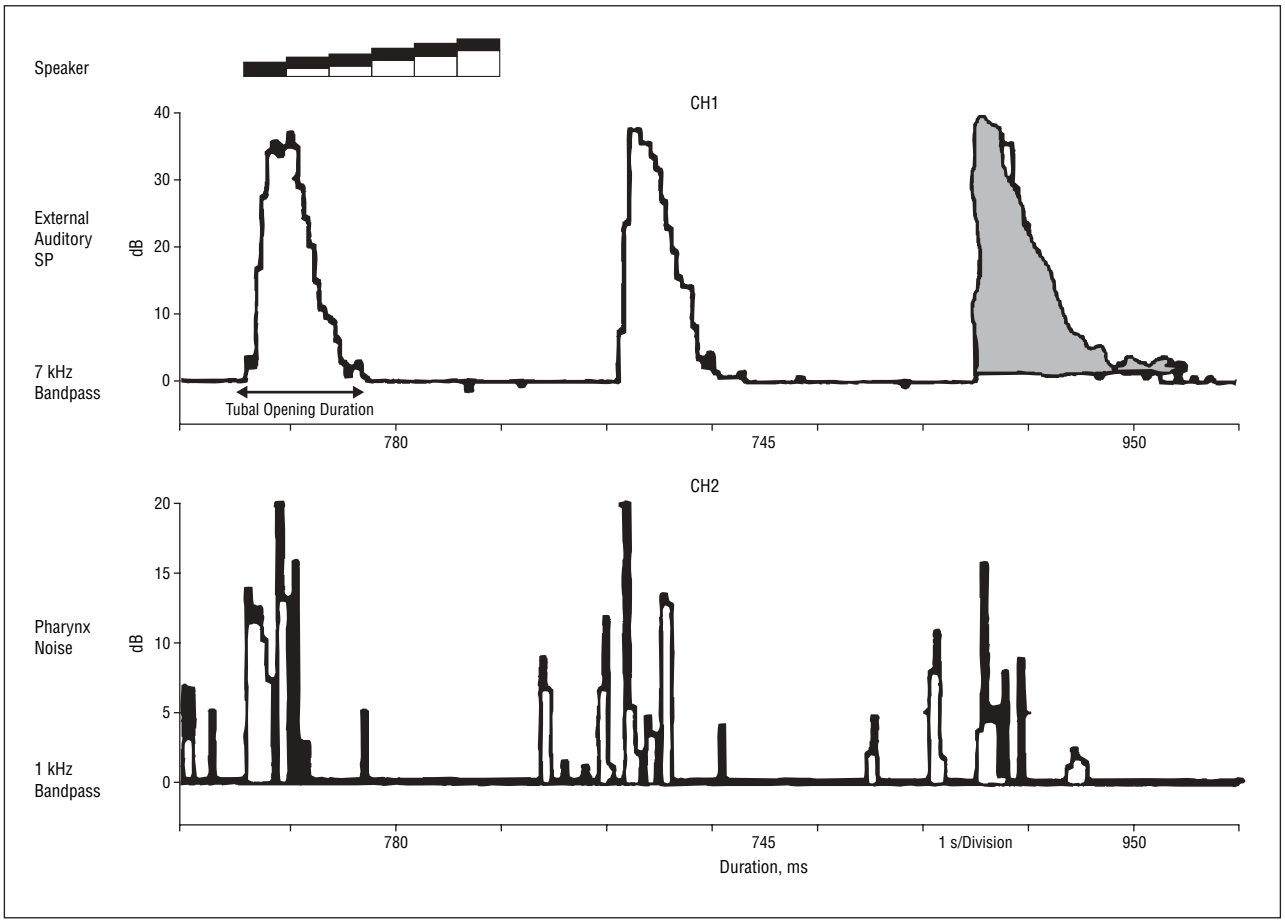

Figure 1. Method of measurement of opening duration (↔) and tubal opening area (shaded area) on sonotubogram. CH1 indicates channel 1; CH2, channel 2; and SP, sound pressure.

RESULTS

CONCENTRATIONS OF ECP AND IL-5 IN MEE AND SERUM

All of the patients in the EOM group had a more than 100-fold higher concentration of ECP in MEE than in serum, and the difference was statistically significant. An IL-5 concentration of less than 5 pg/mL (the detection limit) was noted in none of the MEE samples but was noted in 10 serum samples from the patients in the EOM group, and the IL-5 concentration in the MEE samples was significantly higher than that in the serum samples of the patients in the EOM group (**Table 2**).

Microorganisms were isolated from unilateral or bilateral ears of 12 patients in the EOM group. The pathogen most frequently recovered from the ears was *Staphylococcus aureus*, and the next most frequently isolated pathogen was *Pseudomonas aeruginosa*. All ears infected by these pathogens had eardrum perforations with persistent otorrhea. The MEE or otorrhea culture samples of 8 patients were negative for bacteria. Fungi were isolated from the otorrhea of 3 patients, namely, *Candida albicans* and *Aspergillus niger*. The culture findings of the remaining 17 patients were negative for fungi.

Table 2. Concentrations of ECP and IL-5 in MEE and Serum Samples From 20 Patients With EOM*

Type of Concentration	MEE	Serum
ECP, µg/L	17 829 (21 691), 1760-82 280	28.1 (24), 6 to 92†
IL-5, pg/mL	2568 (2487), 156-9434	11.4 (12), <5 to 43‡

Abbreviations: ECP, eosinophil cationic protein; EOM, eosinophilic otitis media; IL-5, interleukin 5; MEE, middle ear effusion.
*Data are given as mean (SD), range.
†$P<.001$.
‡The data are presented as the mean (SD) of 9 serum samples because IL-5 concentrations of 11 serum samples were less than the detection level of 5 pg/mL. $P<.01$.

SONOTUBOMETRIC ANALYSIS

Five ears (13%) of the EOM group and 4 ears (12%) of the asthmatic control group could not be tested by sonotubometry because 60 dB of a 7-kHz bandpass sound was insufficient to record wave patterns from the external ear canal. Two ears (5%) of the EOM group showed no measurable peak on sonotubograms on swallowing. The tubal opening duration was significantly longer in the EOM group than in the asthmatic control, COM control, and

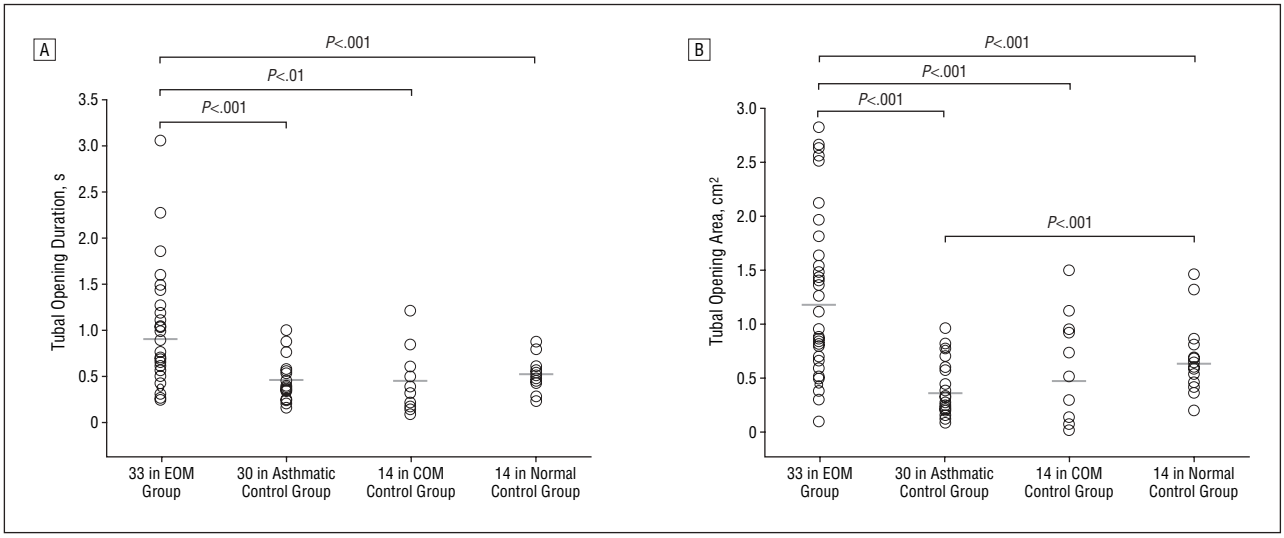

Figure 2. Eustachian tube function measured by sonotubometry in the eosinophilic otitis media (EOM) group and asthmatic control, chronic otitis media (COM) control, and normal control groups (see the "Methods" section for group definitions). A, Tubal opening duration of patients in the 4 groups; B, tubal opening area of patients in the 4 groups. A circle indicates the value of each patient, and a bar indicates an average value of each group.

Table 3. Questionnaire for Presence of Ear Symptoms

Symptom	No. (%) of Respondents		*P* Value for χ^2 Test
	20 in EOM Group*	17 in Asthma Control Group*	
Feeling of ear stuffiness	12 (60)	5 (29)	.06
Windy sound—like tinnitus	6 (30)	1 (6)	.06
Sound on swallowing	11 (55)	1 (6)	.001†
Autophony	9 (45)	3 (18)	.08
Hyperacusis	6 (30)	1 (6)	.06
Transmission of respiratory noise to the ear	6 (30)	1 (6)	.06
Fluttering eardrum on respiration and belching	8 (40)	0	.003†
Air passed in the ear on nose blowing	14 (70)	6 (35)	.04†
Improvement in above symptoms on lying or putting head down	2 (10)	1 (6)	.65
Unchanged or deterioration in above symptoms after catheter inflation	9 (45)	1 (6)	.008†
Total‡	**83/200** (42)	**20/170** (12)	<.001†

Abbreviation: EOM, eosinophilic otitis media.
*See the "Methods" section for group definitions.
†Statistically significant.
‡Number of total responders for 10 questions divided by the number of total questions for 20 patients of the EOM group or for 17 patients in the asthma control group.

normal control groups (**Figure 2**A). A tubal opening duration of more than 1.0 second was noted in 12 ears (30%) of the EOM group compared with 1 ear (3%) of the asthmatic control group and 1 ear (7%) of the COM control group. By contrast, a short and small peak pattern was noted in 3 ears (8%) of the EOM group, 5 ears (15%) of the asthmatic control group, and 6 ears (43%) of the COM control group. In addition, the opening area formed by an SPL change was significantly larger in the EOM group than in the asthmatic control, COM control, and normal control groups, and the opening area in the asthmatic control group was significantly smaller than that in the normal control group (Figure 2B).

RESPONSES TO QUESTIONNAIRE

The incidence of symptoms suggesting the presence of a patulous eustachian tube was significantly higher in the EOM group than in the asthmatic control group (**Table 3**). In particular, most of the patients in the EOM group complained of air passing into the ear during nose blowing. Catheter inflation therapy, which is a common and effective treatment for OME, did not improve the symptoms in most of the patients in the EOM group.

COMMENT

There are several diseases characterized by eosinophilic accumulation in the mucosa, such as bronchial asthma, eosinophilic pneumonia, and eosinophilic gastritis. In the upper respiratory tract, allergic rhinitis, allergic fungal sinusitis,[7] eosinophil dominant nasal polyposis,[8] and eosinophilic mucin rhinosinusitis[9] have recently been recognized as some of these conditions. Eosinophilic otitis

media is a new middle ear disease entity found in patients with asthma. The EOM group definitely had eosinophilic inflammation in the middle ear because high concentrations of ECP were detected in their MEE culture samples and many activated eosinophils were detected in their middle ear mucosa.[10] These patients have highly viscous MEEs containing numerous eosinophils. The middle ear symptoms are extremely resistant to conventional treatment for OME or COM, and the patients experience hearing loss for a prolonged period of time. Because the literature concerning EOM has been mostly reported from Japan, it might be thought that EOM occurs only in Japanese patients. However, Derlacki[11] reported a similar middle ear condition in 1952 that showed markedly different clinical characteristics compared with those of the common type of OME or COM, as follows: (1) a secretion having a remarkably viscous or gelatinous consistency with eosinophils, (2) a middle ear mucous membrane that is fairly thickened with numerous eosinophils, (3) a protracted time of healing, (4) occurrence in individuals of allergic disposition such as allergic rhinitis, and (5) a likely response to antiallergic treatment. He termed the middle ear condition *allergic otitis media*. Eosinophilic otitis media has not been widely recognized yet, but it is expected that a sizable population of asthmatic patients would be diagnosed as having this disease if it were properly recognized. Recently, the clinical surveillance of EOM has been performed in the otorhinolaryngology departments of major hospitals all over Japan, and 341 patients were diagnosed as having definite cases of EOM according to the criteria reported herein. Suzuki et al[4] summarized the clinical characteristics of all the patients and showed that the age at onset of EOM is generally approximately 50 years and the female-to-male ratio is about 2:1. Surprisingly, about 50% of the patients showed deterioration in the bone conduction hearing threshold, and among these, 6% became completely deaf. The cause of EOM is not fully understood, and the treatment of this disease remains a major problem.

In this study, we determined the eustachian tube function of patients with asthma and with or without EOM by using sonotubometry and a questionnaire and found that a patulous eustachian tube may predispose a patient to the disease. The MEE samples of the patients with EOM in this study exhibited higher concentrations of ECP and IL-5 than the serum samples, which indicated that eosinophilic inflammation was present in the middle ear, in agreement with previous reports.[10,12] It has been reported that in sonotubometry findings of healthy adults, 89.8% showed positive opening and closing patterns on voluntary swallowing and that the mean (SD) duration of tubal opening was 394.8 (286.4) milliseconds.[13] The normal and asthmatic control groups of the present study generally showed similar opening durations. In adult patients with OME, sonotubometry findings usually reveal a low or negative amplitude and a short tubal opening time on swallowing, which indicates tubal stenosis.[13] The asthmatic control group showed a significantly smaller area than the normal control group, which suggests that the eustachian tube functions of these patients were rather stenotic. This may be due to the high incidence of nasal polyposis and rhinosinusitis in the asthmatic control group. However, regardless of the high incidence of nasal polyposis and rhinosinusitis, the patients in the EOM group tended to have long tubal opening durations, and some of them showed a typical sonotubometric pattern of a patulous eustachian tube. It seems to be difficult for the subjects with patulous eustachian tubes to close the eustachian tube after voluntary dry swallowing, which results in a sawlike pattern on the declining line with a long tubal opening time on sonotubograms.[13-15]

Regarding the responses to the questionnaires, the most frequent episode was passing air into the ear when blowing the nose. Indeed, we frequently encountered patients with EOM who complained of hearing loss or aural fullness after nose blowing. In addition, we encountered several patients with EOM who had aural discharge whenever they blew their noses. Although catheter tubal inflation therapy seems to be one of the most effective treatments for OME and usually immediately improves the symptoms of hearing loss and aural fullness, most patients in this study did not detect an improvement in their symptom following this therapy. Findings from the present study support the presence of patulous eustachian tubes in patients with EOM. The cause of patulous eustachian tubes is generally the loss of fluid or adipose tissue in the peritubal region, secondary to body weight loss, use of contraceptive drugs, and pregnancy, among other causes.[16] However, the patients with EOM in this study rarely presented with any of these medical histories. Recently, Tsuji et al[17] reported that a history of OM is a causative factor for a patulous eustachian tube. They suggested the following hypothesis: after inflammation of the middle ear has ceased, fibrosis of the eustachian tube mucosa occurs, leading to a diseased, patulous eustachian tube. By contrast, Virtanen and Palva[18] reported that in 100 ears undergoing surgery for COM, about one third of the ears showed no tubal passage for sound during swallowing, 1% to 2% of the ears showed patulous patterns, and the remaining ears showed positive and normal patterns on findings from a sonotubogram. They concluded that patulous eustachian tube is a rare condition in patients with COM. We also studied the eustachian tube function of the patients in the COM control group who had no active inflammation and found that most of them showed normal or slightly stenotic sonotubometric patterns, consistent with the results of Virtanen and Palva.[18] In the present study, OM itself resulted in patulous eustachian tubes in the EOM group. Further studies should be performed to elucidate the cause of patulous eustachian tubes in patients with EOM.

To our knowledge, the mechanism underlying the infiltration of eosinophils in the middle ear, regardless of the presence of type I allergy, has yet to be determined. We have recently demonstrated that ECP, IL-5, and eotaxin concentrations in MEE were higher in patients with EOM than in controls with OME, and the concentration of ECP positively correlated with that of IL-5.[19] We also showed immunohistochemically that the numbers of cells positive for EG2 and ecalectin, an eosinophil chemoattractant, were significantly higher in the EOM group than in the control group. It is suggested that some antigenic materials can cause eosinophilic infiltration in the tis-

sue as a result of the proliferation and activation of helper T cells, followed by the secretion of eosinophil chemoattractants such as IL-5,[20] eotaxin, and ecalectin in helper T-cell 2–dominant predisposition. The bronchi, lungs, and nose are always exposed to the invasion of antigenic materials. However, the middle ear is usually protected from the invasion by the mechanical and immunological defense systems of the eustachian tube. The present results suggest that in helper T-cell 2–dominant predisposition, a patulous eustachian tube allows the entry of antigenic materials such as bacteria, viruses, and fungi into the middle ear, resulting in eosinophil-dominant inflammation. Once an eardrum perforation occurs, such antigenic materials easily invade the middle ear through the perforation and cause a more severe and intractable OM.

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