ORIGINAL ARTICLE

Risk Factors for Eosinophilic Otitis Media in Patients with Eosinophilic Chronic Rhinosinusitis

Hiromi Kanazawa, Naohiro Yoshida, Mariko Hara, Masayo Hasegawa, Shingo Matsuzawa, Kozue Kodama, Akihiro Shinnabe, Yukiko Iino

Department of Otolaryngology, Jichi Medical University Saitama Medical Center, Saitama, Japan

Objective: This study aimed to determine risk factor(s) for developing eosinophilic otitis media (EOM) in patients with eosinophilic chronic rhinosinusitis (ECRS) associated with bronchial asthma.

Materials and Methods: A total of 47 patients with ECRS and bronchial asthma were divided into two groups: 31 patients with EOM (EOM(+) group) and 16 patients without EOM (EOM(-)group). We investigated the clinical characteristics, including eustachian tube (ET) function, based on results of sonotubometry and responses to a questionnaire in both groups. Sonotubometry was also performed in 12 healthy controls.

Results: There were no significant differences between the two groups regarding clinical characteristics, except for age at onset of the diseases. The average ages at onset of bronchial asthma and rhinosinusitis in the EOM(+) group were almost 10 years earlier than those in the EOM(-) group. The opening duration of the ET measured by sonotubometry in the EOM(+) group and EOM(-) group was significantly longer than that in the control group (p=0.009 and p=0.035, respectively). In addition, the incidence of symptoms suggesting insufficiency of tubal closing (Habitual sniffing*, Autophony*, Echo to an ambient sound**, Feeling of ear stuffiness**) was significantly more frequent in the EOM(+) group than in the EOM(-) group (*p<0.05, ** p<0.01).

Conclusion: Patients with ECRS associated with bronchial asthma are at risk of developing EOM with insufficient closing of the ET. Repeated actions inducing positive pressure on the nasopharyngeal ostium of the ET, such as blowing the nose and nasal irrigation, might lead to the development of EOM.

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Introduction

There are some reports of patients with intractable otitis media with effusion or chronic otitis media associated with bronchial asthma[1-7]. These patients exhibit clinical characteristics that are markedly different from those of patients with common otitis media. In 1997, intractable otitis media associated with bronchial asthma was named "eosinophilic otitis media" (EOM) because middle ear effusion contains numerous eosinophils, regardless of the presence of type I allergy [1]. Diagnostic criteria of EOM were established in 2011 and are shown in Table 1 [3]. Minor criteria include an association with bronchial asthma and nasal polyposis because there is a significantly higher prevalence of these diseases in EOM patients than in common otitis media patients. Chronic rhinosinusitis with nasal polyps is frequently observed in patients with bronchial asthma, with an incidence of greater than 50% [8]. In particular, most patients with aspirin-intolerant asthma show multiple nasal

Corresponding address:
Hiromi Kanazawa
Department of Otolaryngology, Jichi Medical University Saitama Medical Center
Saitama / JAPAN
Tel: +81 48 647 2111, Fax: +81 48 648 5188
E-mail: hkanazawa@jichi.ac.jp

polyposis. These conditions are called eosinophilic chronic rhinosinusitis (ERCS) because massive accumulation of eosinophils occurs in the polyps and sinus mucosa [9]. However, the cause of EOM in these patients has not yet been clarified. Some patients with ECRS develop EOM and others do not. Iino et al. [4] suggested that one possible factor for developing EOM was the presence of a patulous eustachian tube (ET). The presence of ECRS may alter ET function.

In the present study, we evaluated clinical characteristics, including ET function, in patients with ECRS with bronchial asthma with and without EOM, and identified the predominant factors leading to the development of EOM.

Materials and Methods

Patients

Forty-seven patients with ECRS associated with bronchial asthma were included in this study. They were diagnosed as having ECRS because, histologically, they all showed nasal polyposis with eosinophilic-dominant infiltration in the nasal polyps. We divided them into two groups: patients with EOM and those without EOM. The diagnosis of EOM in each patient was made on the basis of the criteria proposed by Iino et al. [3] as shown in Table 1. Patients with Churg-Strauss syndrome were excluded from the study. A total of 31 patients (62 ears) with EOM (EOM(+) group) and 16 patients (32 ears) without EOM (EOM(-) group) were evaluated on the basis of the following parameters: sex, age, computed tomography (CT) findings, peripheral blood eosinophil count (%), and total serum IgE level. ET function was evaluated by sonotubometry. A questionnaire was distributed to all of the patients. The questionnaire consisted of questions regarding ear and nasal symptoms that are associated with a patulous ET[10], age at onset of bronchial asthma, rhinosinusitis, and otitis media, a history of sinus operation, and use of nasal irrigation. All of the patients were treated with inhaled corticosteroids with or without systemic administration of corticosteroids for bronchial asthma, nasal corticosteroids for ECRS, and antileukotriene agents. Twelve healthy patients (24 ears) were also studied as controls for sonotubometry. None of the patients had medical histories involving significant body weight loss, pregnancy, or other conditions that affect the loss of fluid or adipose tissue around the peritubal lesion. Written informed consent was obtained from all of the patients prior to the study. The research and ethics committee of Jichi Medical University Saitama Medical Center approved this study.

Table 1. Diagnostic criteria of eosinophilic otitis media [3]

Major: Otitis media with effusion or chronic otitis media with eosinophil dominant effusion
Minor: 1. Highly viscous middle ear effusion
2. Resistance to conventional treatment for otitis media
3. Association with bronchial asthma
4. Association with nasal polyposis
Definitive case: Positive for major + two or more minor criteria
Exclusion criteria: Churg-Strauss syndrome, hypereosinophilic syndrome

CT image scoring

The extent of sinus disease identified by CT was evaluated using the Lund-Mackay scoring system [11]. To evaluate the sinus content, the five major right and left sinuses (frontal, maxillary, anterior and posterior ethmoids, and sphenoid) and the ostiomeatal complex were scored on a two-point scale as follows: 0, clear; 1, partial opacification; and 2, total opacification.

Sonotubometry

To evaluate ET function, sonotubometry (JK-05; RION Co, Ltd., Tokyo, Japan) was performed in all patients. In the EOM (+) group, we confirmed a lack of middle ear effusion and otorrhea in the mesotympanum by myringotomy and suctioning. After removal of rhinorrhea by suctioning, we measured the duration of eustachian tubal opening [4] induced by a sound pressure level change of >43 dB produced by voluntary dry swallowing when 60 dB of a 7-kHz bandpass sound was introduced through a nasal olive tip into one of the nostrils.

Statistical analyses

Statistical analyses were performed using the unpaired *t*-test or chi-square test. *p* values of less than 0.05 were considered statistically significant.

Results

Clinical characteristics

Clinical features of the patients in the three groups are shown in Table 2. There were no significant differences in sex and age among the three groups. Other parameters, such as CT score, peripheral eosinophil percentage, and serum IgE level showed no significant differences between the EOM(+)and the EOM(-) groups.

Responses to the questionnaire

The average ages at onset of bronchial asthma, rhinosinusitis, and otitis media in the EOM (+) group are shown in Table 3. The average ages at onset of bronchial asthma and rhinosinusitis in the EOM(+) group were almost 10 years earlier than those in the EOM(-) group. Most of the patients were affected by rhinosinusitis or bronchial asthma first, and otitis media developed more than 10 years later.

The incidence of symptoms suggesting the presence of a patulous ET (Habitual sniffing*, Autophony*, Echo to an ambient sound**, Feeling of ear stuffiness**) was significantly more frequent in the EOM(+) group than in the EOM(-) group (*p<0.05, ** p<0.01) (Table 4). In addition, most of the patients had undergone nasal irrigation, but 10 patients out of 13 in the EOM(+) group stopped nasal irrigation because of deterioration of their EOM after irrigation. In contrast, all 13 patients in the EOM(-) group, except for one, continued nasal irrigation.

ET function evaluated by sonotubometry

The duration of ET opening measured by sonotubometry in the EOM(+) group, EOM(-) group, and control group are shown in Fig. 1. The tubal opening duration in patients with ECRS which was not significantly different between the EOM (+) and EOM (-) groups was significantly longer than that in the

Table 2. Clinical characteristics of the three groups

	ECRS with bronchial asthma		Normal control
	EOM(+)	EOM(-)	
No. of patients (ear)	31(62)	16(32)	12(24)
M/F, No.	10/21	7/9	5/7
Age a	53.0±11.0 (32-75)	58.0±12.0 (29-72)	44.5±17.7 (30-77)
AIA	7	3	
CT score a	18.1±4.0 (4-30)	14.0±6.0(1-24)	
Eosinophils in PB,% a	7.0±5.2 (0-15.4)	10.4±5.2 (5-17.5)	
Serum IgE a (20-921)	685.1±849.7 (13.6-4160)	367.9±268.5	
Past history of FESS	19 (61.3%)	14 (87.5%)	
History of nasal irrigation	13	13	

ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media;
PB, peripheral blood; AIA, aspirin intolerance asthma;
FESS, functional endoscopic sinus surgery
a Mean ± standard deviation (range)

Table 3. Ages at onset of the diseases in patients

	EOM(+)	EOM(-)	P value
Bronchial asthma	34.1±11.9	43.0±13.0	P< 0.05
Rhinosinusitis	35.3±12.9	44.6±12.0	P< 0.05
EOM	46.3±11.9	-	

Table 4. Responses to the questionnaire for ear and nasal symptoms

	No. (% of respondents)		
	ECRS with bronchial asthma		P value
Symptom	EOM(+)	EOM(-)	(χ2 test)
Rhinorrhea	27(87.1)	11(68.8)	0.13
Habitual sniffing	20(64.5)	4(25.0)	0.01*
Echo to an ambient sound	29(61.3)	2(12.5)	0.005**
Audition of loud breathing sounds	12(38.7)	2(12.5)	0.06
Autophony	17(54.8)	3(18.8)	0.02*
Feeling of ear stuffiness	23(74.2)	5(33.3)	0.003**

ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media

Statistically significant (*p<0.05, ** p<0.01)

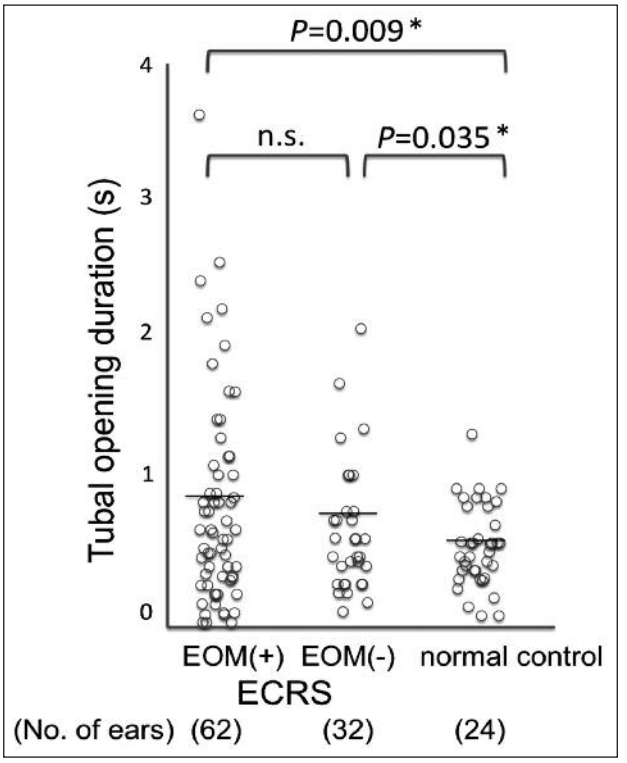

Figure 1. Tubal opening duration measured by sonotubometry in the three groups. ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media.

controls (p<0.05), suggesting that tubal closing may be insufficient in ECRS patients, regardless of the association with EOM. However, insufficiency of tubal closing appeared to be more severe in the EOM(+) group than in the EOM(-) group, as suggested by the smaller p value of the control group compared with the EOM(+) group than that of the control group compared with the EOM(-) group.

Discussion

EOM is recognized as an intractable otitis media and is characterized by the accumulation of eosinophils in middle ear effusion and middle ear mucosa. In 2011, diagnostic criteria were established[3], but the mechanism of accumulation of eosinophils in the middle ear has not been determined yet. A patulous ET detected by sonotubometry in patients with EOM was thought to be a possible factor for developing EOM because it might easily allow foreign materials to enter the middle ear and cause eosinophilic inflammation[4], but the cause of the patulous ET itself is unknown.

Sonotubometry is not routinely used to assess ET ventilatory function because its value for clinical practice and reproducibility has not been adequately demonstrated. However, the technique of sonotubometry has gradually improved and its results are currently at least as good as those of other function tests [12]. The occurrence of a false positive (no signal) in normal cases was considered as a problem, but this suggests that the ET does not necessarily open with each swallowing [13]. Electromyographic activity for paratubal muscles has been reported to be associated with peak ET opening evaluated by sonotubometry[14], and we believe that it is a simple and useful examination.

The sonotubometry of a patulous tube were classified into three types by Virtanen in 1978 [15]: type I, a

relatively sharp peak of increase (normal); type II, well opens on swallowing and for some time afterwards, and closes little by little; and type III, remains open for a long time or is continuously open, and is closed by bending the head forward, by lying down, and (or) sniffing. We used the tubal opening duration to detect insufficient closing, which was mostly observed for type II.

In this study, the tubal opening duration in patients with ECRS and bronchial asthma as evaluated by sonotubometry was significantly longer than that in the controls. This finding suggests that closing of the ET may be insufficient in these patients, regardless of the association with EOM. Although the tubal opening duration was not significantly different between the EOM(+) and EOM(-) groups, the insufficiency of tubal closing appeared to be more severe in the EOM(+) group than in the EOM(-) group. Additional factors leading to EOM should be considered in the future.

ECRS patients with asthma who undergo functional endoscopic sinus surgery (FESS) have a worse postoperative condition than do chronic rhinosinusitis patients without asthma [5][16] and require aggressive medical management to prevent polyp recurrence, even after FESS. The standard medical therapy for ECRS patients is oral or topical corticosteroids and antileukotrienes [5]. Most of the patients in the present study had already received such medications for long periods of time as a treatment for asthma or ECRS. Some drugs may alter ventilatory function of the ET. Application of histamine solution around the nasopharyngeal ostium of ET-induced mucosal swelling has been observed to deteriorate ET function as measured by sonotubometry [17]. In patients with EOM, medications, such as corticosteroids and antileukotrienes, may reduce mucosal swelling around the ET, causing insufficiency of tubal closing.

Repeated nose blowing triggers the occurrence of EOM in patients who undergo FESS [7]. The most frequent episode in patients with EOM is the passing of air into the ear when blowing the nose [4]. An increase in nasopharyngeal pressure by blowing the nose might be one of the causes leading to EOM, particularly in the post-FESS state without polyposis. Therefore, patients with ECRS associated with asthma might have a risk for the onset of EOM because their ET function is unstable.

The effect of nasal irrigation is another possible factor that leads to EOM. Our questionnaire revealed that some patients had episodes of a feeling of ear fullness after nasal irrigation, and therefore, stopped doing it. Saline nasal irrigation itself is considered to be a safe treatment and is recommended for ECRS [18]. There are many types of douches, and some of them have difficulty in controlling water pressure. High-pressure irrigation might be a risk factor for the onset of EOM in the presence of insufficient tubal closing. This insufficiency allows antigenic materials to enter through the ET to the middle ear, causing eosinophilic-dominant inflammation. We recommend using a low-pressure douche and stopping nasal irrigation when the patient complains of aural symptoms.

This study clearly showed that most patients were affected by rhinosinusitis or bronchial asthma first, and otitis media developed approximately 10 years later. EOM may be the endpoint of eosinophilic inflammation involving the upper and lower airway tracts. In addition, the average age at onset of bronchial asthma in the EOM(+) group was almost 10 years earlier than that in the EOM(-) group. The early onset of adult-type asthma is also a risk of developing EOM. Further study is necessary to elucidate the onset of EOM.

Conclusion

Patients with both ECRS and bronchial asthma are at high risk of developing EOM. These patients should be carefully monitored regarding their ear symptoms, particularly when undergoing FESS and using nasal irrigation.

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