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Otolaryngologic surgeries are frequent in children with eosinophilic esophagitis

Elizabeth A. Kelly, M.D.¹, David Linn, M.D.¹, Robert H. Chun, M.D.¹, Kristina L. Keppel, DNP, CPNP¹, and Richard J. Noel, M.D., PhD²

¹Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin. 9000 West Wisconsin Ave, Milwaukee, Wisconsin

²Department of Pediatrics, Medical College of Wisconsin. 9000 West Wisconsin Ave, Milwaukee, Wisconsin

Abstract

Objective—To study the prevalence of otolaryngologic surgeries in pediatric patients with eosinophilic esophagitis (EoE).

Methods—Retrospective cohort study at a tertiary care center. The type of otolaryngologic surgeries performed in patients with diagnosis of EoE was recorded during a 5-year period.

Results—75% of patients were male, with average age of EoE diagnosis at 7.5 years with an 83% incidence of atopy. Cohort analysis revealed 33% (119/362) had a total of 275 otolaryngologic surgeries. Surgeries performed on 119 patients are as follows: 20% bilateral myringotomy with tubes, 14% tonsillectomy, 18.5% adenoidectomy, 1.4% sinus irrigation, 3.3% bronchoscopy, and 1.4% laryngotracheoplasty (LTP). 63% of patients underwent multiple procedures. 30% of patients undergoing BMT needed additional tubes. 4 of 5 LTP patients had successful operations. 12% of patients had EoE diagnosis prior to an otolaryngologic surgery.

Conclusions—33% of children with EoE required otolaryngologic surgical intervention and nearly one-third who underwent BMT required additional ear tubes. A large fraction of children with EoE will undergo an otolaryngologic surgery, only a minority with a preoperative EoE diagnosis. Until the nature of this relationship is clarified, the high coincidence with otolaryngologic surgeries dictates that otolaryngologists should be familiar with diagnosis of EoE in patients.

Keywords

Eosinophilic esophagitis; prevalence; pediatrics; otolaryngology; otorhinolaryngological surgical procedures

Corresponding author: Robert Chun, M.D., Division of Pediatric Otolaryngology, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, 9000 West Wisconsin Ave, Milwaukee, WI 53226, rchun@mcw.edu, Phone: 414 266 8383, Facsimile: 414 266 2693.

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Introduction

Eosinophilic esophagitis (EoE) is an inflammatory disease of the aerodigestive tract manifesting in the pediatric population with symptoms that include failure to gain weight, feeding disorder, vomiting often in younger patients and abdominal pain, dysphagia, and food impaction in older patients.^{1,2,3} EoE is a clinicopathologic diagnosis dependent upon clinical symptomatology, histologic criteria, and exclusion of other conditions that can produce esophageal eosinophilia, especially gastroesophageal reflux disease.^{4,5} While the contribution of detection bias cannot be excluded, the calculated incidence of EoE of 1 case per 10,000 pediatric population per year appears to be increasing.^{3,6} EoE is also strongly associated with atopic disease, with an estimated coincidence of 50–80%, leading some to consider EoE a manifestation of allergic response.^{2,7,8}

Despite mucosal inflammation that is limited to the esophagus, EoE should be viewed as an immune-mediated aerodigestive tract disorder that also can be associated with otolaryngologic symptoms. A prior study indicated 10–15% of pediatric patients presented to an otolaryngologist prior to a referral to a gastroenterologist.⁹ Additionally, EoE may produce sequelae in other regions of the aerodigestive tract, as has been seen with gastroesophageal reflux (GER).^{5,10–13} The chronic inflammatory response and eosinophilic infiltration in EoE has findings comparable with that seen in the airway mucosa in chronic rhinosinusitis and asthma.¹⁰ Given that EoE does not typically result in pharyngeal mucosal eosinophilia,¹⁴ how esophageal inflammation and airway symptoms are associated remains unclear, but may require cytokines and other inflammatory messenger molecules.

Notwithstanding the high prevalence of EoE in otolaryngology patients, there is a paucity of literature on the subject. While data on frequency and type of otolaryngology diagnoses in EoE patients have been reported,⁹ the frequency of otolaryngologic surgeries (OS) in children with EoE has not been analyzed. The present study aims to describe the frequency and types of OS in a pediatric population with EoE. This information may provide an opportunity to increase awareness of an EoE and potential practice changes if a significant association is made between OS and EoE.

Methods

A retrospective chart review was performed for all pediatric patients with an International Classification of Diseases (ICD)-9 diagnosis of EoE seen at Children's Hospital of Wisconsin (CHW), a tertiary care academic facility, from January 2007 to January 2012. Institutional review board approval was obtained for this five-year period. Preliminary computer-based ICD-9 search reported 435 patients over this period. Individual review of these charts revealed a true diagnosis of EoE in 378 patients, with 57 of the original patients found to have a diagnosis of eosinophilic gastroenteritis, a diagnosis of EoE based on clinical symptomatology which was eventually ruled out upon biopsy, or in a few cases, a probable coding error. Final diagnosis of EoE was made based on clinical suspicion and confirmed with esophageal biopsy. Five of the 378 patients with a diagnosis of EoE had insufficient information in the medical chart, excluding them from further analysis. Additionally, patients were excluded from this analysis if they had other disease processes

that may contribute to the need for otolaryngologic surgeries. Eleven patients were identified with a documented history of cleft lip/cleft palate, Pierre Robin sequence, trisomy 21, or other chromosomal abnormalities that may cause otolaryngologic disease, or chromosomal abnormalities that are not well defined. These patients were then excluded. The remaining 362 patients' charts were reviewed for the date of EoE diagnosis based on the date of endoscopic esophageal mucosal biopsy, history of having an OS, personal and family history of atopic disease, household exposure to tobacco, and family history of EoE. With respect to the OS, charts were reviewed for surgical history in physician notes, patient intake forms, and anesthesia records where available to ensure that all procedures were accounted for, including those done by providers outside of the CHW system. Procedures, such as reductions of nasal fractures or those repairing other traumatic facial injuries, were not included in our analysis.

Results

Of the 362 patients analyzed, 119 patients (32.9%) had an OS performed, with 75 patients (20.7%) requiring multiple surgeries resulting in 275 total surgeries being performed on the study population. The majority of the surgeries were performed by providers at a facility outside of CHW. The average age at the time of first OS was 3.2 ± 2.7 years, and the average age of EoE diagnosis was 7.4 ± 4.9 years (mean $\pm$ standard deviation). The population was characteristically male (74.9%) and had a high frequency of personal (82.6%) and family (63.9%) history of atopic disease (Table 1). Four (1%) patients in this cohort of patients that had an OS performed reported household tobacco exposure and nine (2%) had a family history of EoE.

With respect to surgeries in the study population, the most frequently performed surgery was bilateral myringotomy with tube placement (BMT) (20%), followed by adenoidectomy (18.5%) and tonsillectomy (14.1%). Airway evaluations via rigid bronchoscopy accounted for 4.1% of cases. Minimally represented were maxillary tap irrigation or antrostomy (1.4%) and laryngotracheoplasty (LTP)/anterior cricoid split (1.4%) (Table 2).

A majority of patients (75.6%) were diagnosed with EoE after their initial OS. On average EoE was diagnosed approximately 3.8 years after the initial OS. An additional 12.6% of patients received an EoE diagnosis from biopsies performed at the time of their initial OS. A minority of patients (11.7%) had an EoE diagnosis prior to having any procedure.

Five patients required anterior cricoid split or LTP; of these, two patients had an EoE diagnosis prior to surgery, with the other three being diagnosed between eight months and three years following airway reconstruction. Four of the patients had successful operative outcomes; two required excision of subglottic granulation tissue in the postoperative period and the other two patients did not require any further surgical intervention. One patient failed airway reconstruction.

Chi-square analysis was performed to evaluate for a difference in surgery rates for EoE patients with or without history of atopic disease. The test did not indicate a significant difference, $\chi^2(1) = 0.16$. However, the study was initially designed to determine the

prevalence of OS in patients with EoE and not powered to investigate the differences in patients with and without atopic disease. For any surgery performed, 33.4% of patients with atopy had surgery and 31.7% of patients without atopy had surgery with $p=0.67$. For BMT, 21.7% of patients with atopy and 15% of patients without atopy had surgery with $p=0.32$ (Figure 1).

Discussion

Interest in the clinical manifestations and the underlying pathophysiology of EoE has grown among otolaryngologists, as patients occasionally present to otolaryngologists for initial evaluation of dysphagia or airway symptoms. Prior studies provided analysis regarding the otolaryngologic diagnoses in patients with EoE and demonstrated that eustachian tube dysfunction and adenotonsillar hypertrophy with sleep disordered breathing were among the most common coincident otolaryngologic diagnoses.⁹ We present the first study investigating the incidence of OS in the pediatric EoE population.

Overall, the demographics of our patient population were consistent with published studies on pediatric EoE.¹¹ There is a clear male predominance (75%), common atopic history (83%), and average age of diagnosis at 7.5 years.^{1-3,9,11} While we were unable to determine the average age of patients' initial symptoms from our retrospective review, prior studies quoted a median age of 4 years for symptom onset with a median age of diagnosis of 7 years.¹¹ Patients in our cohort, on average, presented to an otolaryngologist prior to a gastroenterologist with an average age of initial OS at 3.8 years old, four years less than the average age of EoE diagnosis. This temporal relationship between age of OS and EoE diagnosis is similar to the time frame between symptom onset and diagnosis seen in prior studies. Often patients present with nonspecific symptoms making diagnosis difficult initially and receive treatment for gastroesophageal reflux disease prior to considering diagnosis of EoE.¹¹ The data obtained from this study would suggest that there may be an association with an EoE diagnosis and need for OS, specifically tympanostomy tubes. The higher incidence of EoE in patients that have undergone OS, suggests that simple screening questions for EoE while taking a patient's history and increased awareness by the provider of the incidence of EoE may allow for an earlier diagnosis. A recently-published study describes average age of esophageal biopsy and EoE diagnosis to be 4.4 years, possibly due to increased awareness of this disease process.¹⁵

Though our study does not have a cohort of children without EoE for comparison, 32.8% of patients in our study population underwent an OS, which appears to be a relatively high percentage. More than half of these patients had more than one OS performed. A study from the Children's Hospital of Philadelphia calculated that 21.9% of children with EoE were evaluated by an otolaryngologist before or after EoE diagnosis,⁹ a number lower than our cohort's 32.8%. One probable explanation for the discrepancy could be the inclusion of OS performed by community physicians; of the 119 patients included in our study that underwent an OS, 35 of the patients had the surgery performed at a tertiary care center whereas the remaining 84 had them performed out in the community. We were unable to ascertain if patients had been to an outside otolaryngologist provider but not had surgery.

Therefore, unlike the Children's Hospital of Philadelphia study, we were unable to accurately present a breakdown of these patients' otolaryngologic diagnoses.

Differences among the type of OS performed in children with EoE can be compared to the published frequency of these surgeries in children without EoE. In a national study, 6.8% of children needed at least one set of tympanostomy tubes inserted during their first three years of life.¹⁶ Comparatively, 15% of our study population required tubes by the age of three years old. Of note, 30% of our patients who had tympanostomy tubes inserted required multiple sets of tubes. This is higher than previously cited rates for multiple sets of tubes of 17.6% to 20%.^{17,18} While this study was designed to primarily assess the incidence of OS, we can only hypothesize the reason for these differences in the rates of tympanostomy tube placement. Patients with EoE frequently have coincident atopic disease and have a strong development of eosinophilic inflammation from external allergic triggers and intrinsic Th₂ cytokines.¹ As mucosal eosinophilia is not directly extended proximally from the esophagus to the pharynx, airway inflammation could be mediated via cytokines and other inflammatory agents.¹⁴ The association of allergy and middle ear disease requiring tympanostomy tube placement has been controversial.^{19–21} While our study was not designed to settle this controversy, a chi-square analysis was performed to evaluate whether atopic disease is an independent reason for the increased number of OS in our EoE population. No significant differences were observed between the two groups. A limitation of this study is the inability to delineate the indication for tympanostomy tube replacement in our retrospective cohort.

Unlike high representation of BMT in our population, we were surprised to see only 1.4% of the population requiring sinus surgery, especially given the high association with atopy in patients with EoE. In our cohort, 18.5% of the patients underwent an adenoidectomy, but indications were not provided in all medical records. The adenoidectomy may have been performed for chronic rhinorrhea and sinusitis, but indications for a majority of our patients were unknown. The incidence of tonsillectomy in this study population also raises some points of interest, as the frequency of tonsillectomy performed in this population was observed to be 14%. While our EoE population cannot be generalized to the general pediatric population, just over 500,000 tonsillectomies are performed per year in an estimated population of children 0–18 years of age to be 73.9 million in 2011.^{22,23} There appears to be a greater incidence of tonsillectomies in that EoE population. However, our data on indications for performing the tonsillectomy are limited as many were performed by community physicians and up to 49% of patients did not have a specific reason stated in the medical record for further analysis. There has been some investigation of the inflammatory role in the development of adenotonsillar hypertrophy. (Peds Research ***) Release of inflammatory cytokines observed in patients with EoE could be hypothesized to contribute to adenotonsillar hypertrophy leading to symptomatic patients and need for tonsillectomy.

Published reports have also implicated EoE in the development of airway pathology.^{5,12,13} An increased failure rate after airway reconstructive surgery was previously observed in patients with EoE.^{15,24} Otteson et al. describes several patients that required tracheotomy after LTP in long-term follow-up of patients diagnosed with EoE in the interim.¹⁵ Our study had only five patients (< 2% of cohort) who underwent LTP or anterior cricoid split and four

had successful operative outcomes. Two of these patients underwent LTP after diagnosis of EoE and treatment with swallowed topical glucocorticoids. The other two patients were diagnosed eight months and three years after LTP and treated with swallowed topical glucocorticoids at that time without subsequent airway interventions needed. One patient with a complicated medical and neonatal history, had EoE diagnosed after having both an anterior cricoid split and an LTP and failed airway reconstruction. This patient was born prematurely at 24 weeks' gestation and developed subglottic stenosis secondary to prolonged intubation. An anterior cricoid split was performed at three months of age. He continued to have significant subglottic edema postoperatively and eventually required tracheostomy tube placement. He was never decannulated and subsequently required a LTP at two years of age. He continued to have difficulties with decannulation and was diagnosed with EoE at age three. He was started on swallowed topical glucocorticoids at that time with eventual control of inflammation. He is still tracheostomy tube dependent at five years of age and his airway outcome is pending. While his neonatal course was complicated by sepsis, prematurity, and tracheitis, EoE as the lone factor in failed airway reconstruction is unlikely. Though four out of five patients in our study had successful airway reconstructions, this subpopulation was not well represented in our cohort and we cannot draw broad conclusions beyond noting that EoE may be associated with failed airway reconstruction in some cases.

The retrospective study has limitations that should be taken into account. The data was obtained from a single tertiary care center and surrounding community and may only represent this geographical region. The retrospective nature of the study can lead to bias in data selection and inability to determine the impact of unidentified confounding variables. Therefore, only associations were able to be observed from this study. The data available to determine the indications for specific procedures that were more common in patients with EoE is limited and prevents the opportunity to provide further conclusions on these observed trends. Additionally, the limited access to community physician records precluded further data collection regarding indications for the surgeries performed and timeframe for initial EoE symptoms. Also an age-matched cohort with atopy or allergic disease was not included to provide direct comparison of incidence of these OS in patients without EoE. However, in comparison to historical incidence of the number of myringotomy with tubes in children (6.8%), our cohort did have a higher incidence to this average.

In our cohort 75.6% of our patients had a diagnosis of EoE following an OS. This finding is contrary to the study by Smith et al.,⁹ which had 54.9% of patients having a pre-existing diagnosis of EoE at the time of their otolaryngologic consultation. Furthermore, Otteson et al., diagnosed 92 children from 2429 patients undergoing esophageal biopsy from an pediatric otolaryngology practice.¹⁵ While these two studies indicate an awareness of EoE by otolaryngologists and large percentage of children presenting to otolaryngologist following EoE diagnosis, our cohort may suggest that awareness of EoE may still be insufficient. Including a brief inquiry of a young patient's feeding ability and any further gastrointestinal symptoms in the initial evaluation and having an elevated awareness of this disease process may improve the earlier recognition of EoE. As the association of otolaryngologic disease and EoE is being developed, further research may focus on the

etiology of this association and the potential need for different management of these otolaryngologic disease processes.

Conclusion

Nearly one third of children in our EoE cohort required an OS, often prior to diagnosis of EoE. The incidence of BMT and need for additional myringotomy and tube placement was higher than prior reports, suggesting an association between EoE and middle ear pathology. Furthermore, five patients in our cohort underwent airway reconstruction, with one continued tracheotomy decannulation failure that could be attributed to inflammation associated with EoE. Lastly, a suspicion for EoE should be considered especially when children with a history of feeding difficulty or other gastrointestinal symptoms may require general anesthesia for an otolaryngologic surgery. While the understanding of EoE and its' natural history continue to evolve, children with EoE may have overlapping presentation of otolaryngologic pathology and are better served by otolaryngologists who are aware of EoE and able to properly refer for treatment.

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Figure 1.
Influence of atopic disease on performed otolaryngologic surgeries in children with EoE.
Abbreviations: BMT, bilateral myringotomy with tube placement; ENT, ear, nose, and throat; EoE, eosinophilic esophagitis.

Table 1

Patient Demographics of Study Population.

Patient Characteristic	No. (%)
Age, mean, y	
At EoE diagnosis	7.4
At first ENT procedure	3.8
Sex	
Male	271 (74.9)
Female	91 (25.1)
Patients with ENT procedures	119 (32.9)
Patients with multiple ENT procedures	62 (16.6)
Personal history of atopic disease	299 (82.6)
Family history of atopic disease	220 (64.8)
Family history of EoE	26 (8.1)

Abbreviations: ENT, ear, nose, and throat; EoE, eosinophilic esophagitis.

Table 2

Otolaryngologic Surgeries Performed in Patients With Eosinophilic Esophagitis.

Procedure	Total No. of Patients (% of 362)	No. of Patients With Combined/Additional OS (% of Total)
BMT (total)	74 (20.4)	48 (64.8)
1 set of tubes	52 (14.4)	26 (50)
> 1 set of tubes	22 (6.1)	22 (100)
Adenoidectomy (total)	67 (18.5)	61 (91)
Revision adenoidectomy	1 (0.3)	1 (100)
Tonsillectomy	51 (14.1)	43 (84.3)
Rigid bronchoscopy	12 (3.3)	4 (33.3)
Maxillary tap irrigation or antrostomy	5 (1.4)	5 (100)
LTP/anterior cricoid split	5 (1.4)	5 (100)

Abbreviations: BMT, bilateral myringotomy with tube placement; LTP, laryngotracheal reconstruction; OS, otolaryngologic surgeries.