Prevalence of Laryngeal Cleft in Pediatric Patients With Esophageal Atresia

Monica Londahl, MPH; Alexandria L. Irace, BA; Kosuke Kawai, ScD; Natasha D. Dombrowski, BA; Russell Jennings, MD; Reza Rahbar, DMD, MD

IMPORTANCE Esophageal atresia (EA), with or without tracheoesophageal fistula (TEF), and laryngeal cleft are rare congenital anomalies that often occur together. Previous reports have established a link between EA/TEF and laryngeal cleft, but there have been no large case series to further characterize this relationship.

OBJECTIVES To assess the prevalence of laryngeal cleft among patients with EA/TEF, identify associations between types of laryngeal cleft and EA/TEF, and identify factors associated with the timing of diagnosis for both conditions.

DESIGN, SETTING, AND PARTICIPANTS Retrospective analysis of 270 patients. The Esophageal Atresia database was used to identify patients seen at the Esophageal and Airway Treatment (EAT) Center at Boston Children's Hospital, Boston, Massachusetts, a tertiary referral hospital, from August 1, 2009, to August 1, 2016. Patients were included if they were younger than 18 years at the time they were diagnosed with EA, TEF, or both and had undergone a procedure or examination by a surgeon from the EAT Center. Patients with acquired airway or esophageal problems were excluded.

MAIN OUTCOMES AND MEASURES Data regarding patient demographics, primary diagnoses, dates of diagnosis, comorbidities, and airway/esophageal surgical interventions were collected and analyzed. Association between type of EA/TEF and laryngeal cleft type was evaluated. Secondary outcomes were age at diagnosis between patients who resided in Massachusetts and those who resided outside the state.

RESULTS Of 270 patients diagnosed with EA/TEF during the 7-year period, 138 (51.1%) were male, and the median age at diagnosis of EA/TEF was 1.0 years (IQR, 0.4-2.0) and at diagnosis of laryngeal cleft was 1.1 years (interquartile range [IQR], 0.6-2.8). Laryngeal cleft was diagnosed in 53 of the 270 patients (19.6%) (95% CI, 14.9%-24.4%). No apparent difference was found in the distribution of types of laryngeal cleft by type of EA/TEF. Among patients with EA/TEF type A or B, 9 patients (56%) had a type I cleft, 6 (38%) had a type II cleft, and 1 (6%) had a type III cleft. Among those with EA/TEF type C or D, 20 (57%) had a type I cleft, 11 (31%) had a type II cleft, and 3 (9%) had a type III cleft. Out-of-state patients were more likely to be diagnosed with EA/TEF at an older age than in-state patients (mean difference, 1.5 years; 95% CI, 0.2-2.9 years).

CONCLUSIONS AND RELEVANCE Pediatric patients with EA/TEF have a much greater prevalence of laryngeal cleft than the general population. Multidisciplinary esophageal and airway programs serve as an ideal clinical setting for management of EA/TEF.
Esophageal atresia (EA) is a congenital discontinuity of the esophagus that forms upper and lower blind esophageal pouches. Esophageal atresia is commonly associated with congenital tracheoesophageal fistula (TEF), an abnormal connection between the trachea and esophagus. The prevalence of EA, TEF, or both is approximately 1 in 3500 to 5000 live births. In more than 50% of cases, EA/TEF occurs with other anomalies, such as laryngeal cleft and tracheomalacia.

The Gross classification describes 5 types of EA/TEF. Type A manifests as EA without TEF, whereas types B, C, D, and H have variable fistula formation. Type B presents as EA with a proximal TEF and a blind distal pouch and accounts for approximately 5% of patients. Types A and B are considered “long gap” EA because there is no distal fistula to elongate the lower esophageal segment by attachment to the airway. Type C is characterized by a blind proximal esophageal pouch and distal TEF to the lower esophagus. This type is the most common, accounting for approximately 85% of EA anomalies. Type D presents with a fistula to the airway from the upper and lower esophageal pouches and occurs in approximately 4% of patients with EA/TEF. Types C and D are generally considered “short gap” because the lower esophagus is usually long enough to attach to the airway. The least common form of TEF is the H-type fistula, which connects the esophagus and trachea (creating the appearance of a capital H) but does not involve EA. An H-type fistula affects between 1% and 4% of patients with EA/TEF.

During embryonic development, the trachea and esophagus share a common lumen. Esophageal atresia and TEF result from failed development of the tracheoesophageal septum. Failed fusion and incomplete development of the tracheoesophageal septum may also lead to the formation of a laryngeal cleft. Laryngeal cleft is a rare congenital deficiency of the interarytenoid region of the larynx, tracheoesophageal wall, or both. It is associated with a spectrum of clinical symptoms, ranging from mild stridor to substantial aspiration and recurrent pneumonia. The prevalence of cleft is reported as 1 in 10,000 to 1 in 20,000 live births. Clefts are typically classified using the Benjamin-Inglis system, which designates 4 types. Type I is the least severe and extends to the vocal cords. Type II extends below the vocal cords but not through the cricoid cartilage. Type III extends through the cricoid into the posterior cervical tracheal membrane, and type IV, the most severe, extends into the thoracic trachea. Types III and IV are associated with severe tracheomalacia.

Previous reports in the literature have already established a link between EA/TEF and laryngeal cleft. The objectives of the present study were to assess the prevalence of laryngeal cleft among patients with EA/TEF and to identify whether any types of EA/TEF are linked to a specific type of laryngeal cleft. A secondary objective was to review the age at diagnosis for both conditions and identify factors associated with an early diagnosis.

**Methods**

The Esophageal Atresia database was used to identify patients who were seen at the Esophageal and Airway Treatment (EAT) Center, a multidisciplinary program composed of physicians from gastroenterology, general surgery, cardiac surgery, anesthesia, otolaryngology, and endocrinology departments at Boston Children’s Hospital, Boston, Massachusetts, from August 1, 2009, to August 1, 2016. This database captures all patients who were seen by a surgeon from the EAT Center for a problem related to the esophagus or airway. The database includes demographic information, such as age and sex, as well as the specific procedures performed by the multidisciplinary EAT team. Patients were included if they were younger than 18 years at the time they were diagnosed with EA and/or TEF and had undergone a procedure or examination by a surgeon from the EAT Center. Patients were excluded if their primary diagnosis was an acquired airway or esophageal trauma (eg, ingestion of a foreign body or caustic ingestion). Data including demographic characteristics, primary diagnoses, dates of diagnosis, comorbidities, and airway/esophageal surgical interventions were collected and analyzed. This study was approved by the Institutional Review Board at Boston Children’s Hospital, which waived the need for patient consent.

The χ² test was used to compare the distribution of types of laryngeal cleft by types of EA/TEF. In addition, we evaluated the age at which patients were diagnosed with each condition and whether their place of residence affected the timing of their diagnosis. To compare the timing of diagnosis by residence, we used the Wilcoxon rank sum test. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc).

**Results**

Three hundred fifty-three patients were seen at the EAT Center between August 1, 2009, and August 1, 2016. Of these, 7 patients were diagnosed with acquired esophageal and/or airway conditions other than congenital anomalies and were therefore excluded from this study. An additional 76 patients did not have a diagnosis of EA/TEF and were also excluded. The remaining 270 patients with a diagnosis of congenital EA, TEF, or both were included in the data.
analysis. All patients were diagnosed in the operating room during endoscopic evaluation.

Of the 270 patients studied, 138 (51.1%) were male. The median age at diagnosis of EA/TEF was 1.0 years (interquartile range [IQR], 0.4-2.0) and at diagnosis of laryngeal cleft was 1.1 years (IQR, 0.6-2.8). Laryngeal cleft was diagnosed in 53 patients (19.6%) (95% CI, 14.9%-24.4%). Diagnosis of laryngeal cleft was likewise made in the operating room during endoscopic airway evaluation. These patients were then further assessed to analyze the association between the 2 conditions.

Laryngeal Cleft and EA/TEF Cohort
Type I laryngeal cleft was the most common type of cleft, accounting for 30 of the 53 patients (57%) with concomitant EA/TEF (Table 1). Patients with a deep interarytenoid notch were included in the type I cleft group. In addition, 18 (34%) had a type II cleft, 4 (8%) had a type III cleft, and 1 (2%) had a type IV cleft. Of the 53 patients with EA/TEF and laryngeal cleft, 16 (30%) had EA/TEF type A or B (long gap EA), 35 (66%) had type C or D (short gap EA), and 2 (4%) had an H-type fistula (Table 1).

Table 1. Demographic Characteristics of 53 Patients With EA/TEF and Laryngeal Cleft

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Age at Diagnosis, Median (IQR), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA and/or TEFa</td>
<td>Overall 53 (100)</td>
<td>1.0 (0.4-2.0)</td>
</tr>
<tr>
<td>Type A and B (long gap)</td>
<td>16 (30)</td>
<td>0.8 (0.4-1.3)</td>
</tr>
<tr>
<td>Type C and D (short gap)</td>
<td>35 (66)</td>
<td>1.3 (0.5-2.6)</td>
</tr>
<tr>
<td>H-type</td>
<td>2 (4)</td>
<td>0.9 (0.5-1.3)</td>
</tr>
<tr>
<td>Laryngeal cleftb</td>
<td>Overall 53 (100)</td>
<td>1.1 (0.6-2.8)</td>
</tr>
<tr>
<td>Type I</td>
<td>30 (57)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td>Type II</td>
<td>18 (34)</td>
<td>0.9 (0.4-2.6)</td>
</tr>
<tr>
<td>Type III</td>
<td>4 (8)</td>
<td>1.7 (0.3-10.7)</td>
</tr>
<tr>
<td>Type IV</td>
<td>1 (2)</td>
<td>0.0*</td>
</tr>
<tr>
<td>Residence</td>
<td>In stated</td>
<td>10 (19)</td>
</tr>
<tr>
<td></td>
<td>Out of state</td>
<td>43 (81)</td>
</tr>
</tbody>
</table>

Abbreviations: EA, esophageal atresia; IQR, interquartile range; TEF, tracheoesophageal fistula.

* The EA/TEF type was based on the Gross classification.

b Laryngeal cleft type was based on the Benjamin-Inglis system.

c Patient diagnosed at 1 day of life.

d Indicates Massachusetts.

Timing of Diagnosis
The data set was analyzed to determine when patients were first diagnosed with EA/TEF or laryngeal cleft and the period that lapsed until a secondary diagnosis was made. Forty-one of 53 patients (77%) were diagnosed on the same day or within 7 days. On one occasion, the diagnosis of laryngeal cleft was made 1 day before the diagnosis of type C EA/TEF. In all other instances, laryngeal cleft was diagnosed after EA/TEF or at the same time. Owing to the high prevalence of comorbid laryngeal cleft and EA/TEF, most patients underwent airway endoscopy to diagnose any additional conditions at the time of EA/TEF repair. All remaining patients underwent airway endoscopy at a time other than EA/TEF repair.

A significant difference was identified between patients who resided outside Massachusetts and patients who lived in Massachusetts, where our institution is located. Out-of-state patients were more likely to be diagnosed with EA/TEF at an older age than in-state patients (mean difference, 1.5 years; 95% CI, 0-2.9 years).

Discussion
Congenital EA and TEF are rare defects that typically cause symptoms of aspiration, choking, coughing after feeding, cyanosis, and potentially life-threatening complications.12 In most cases, EA/TEF is diagnosed in infancy, at which time other congenital abnormalities may also be diagnosed.13 Laryngeal cleft is a commonly reported comorbidity, likely because laryngeal cleft and EA/TEF have similar embryonic origins. However, much of the literature regarding the association between these 2 conditions is in the form of case reports or small case series.2,14-21 To our knowledge, the present study includes the largest number of patients with both EA/TEF and laryngeal cleft reported in the literature to date.

Of 270 patients with EA/TEF, 53 (19.6%) had a comorbidity of laryngeal cleft. This rate is considerably higher than the

Prevalence of Cleft Among Types of EA/TEF
We found no meaningful difference in the distribution of types of laryngeal cleft by type of EA/TEF (Table 2). Among 16 patients with EA/TEF type A or B, 9 (56%) had a type I cleft, 6 (38%) had a type II cleft, and 1 (6%) had a type III cleft. Among 35 patients with EA/TEF type C or D, 20 (57%) had a type I cleft, 11 (31%) had a type II cleft, and 3 (9%) had a type III cleft. Of the 2 patients with an H-type fistula, 1 (50%) had a type I cleft and 1 (50%) had a type II cleft.

Table 2. Association Between EA/TEF Type and Laryngeal Cleft Type in 53 Patients With Both

<table>
<thead>
<tr>
<th>Laryngeal Cleft Type</th>
<th>All Patients</th>
<th>EA/TEF Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Types A and B (Long Gap) (n = 16)</td>
</tr>
<tr>
<td>I</td>
<td>30 (57)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>II</td>
<td>18 (34)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>III</td>
<td>4 (8)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: EA, esophageal atresia; TEF, tracheoesophageal fistula.

* Laryngeal cleft type was based on the Benjamin-Inglis system.

b The EA/TEF type was based on the Gross classification.
Prevalence of Laryngeal Cleft in Patients With Esophageal Atresia

Controversy surrounds the need for further diagnostic testing before EA/TEF repair. A survey of the International Pediatric Endosurgery Group in 2013 reviewed current practice patterns in EA/TEF repair. The survey found that preoperative bronchoscopy was routinely performed by roughly 60% of 170 respondents. However, in a retrospective review of 88 patients, Sharma and Srinivas found that 20.5% of patients who underwent a preoperative bronchoscopy had additional clinical findings, including TEF and laryngotracheal cleft. These authors concluded that laryngotracheobronchoscopy should be performed before definitive surgical procedures. However, it is important to consider the detrimental effects of multiple exposures to anesthesia in pediatric patients, especially in infants as young as those in the present study. For this reason, it is common practice for the multidisciplinary team at our institution to perform laryngotracheobronchoscopy immediately before surgery, within the same episode of anesthesia. This procedure allows for thorough preoperative evaluation without incurring the risks of additional sedation.

Limitations

The primary limitations of this study include the retrospective design and the absence of complete diagnostic testing in the patient sample. More specifically, not all patients were referred to the otolaryngology department for a thorough airway assessment. Therefore, the number of patients described as having laryngeal cleft in this sample may be a conservative estimate. Future studies should include direct laryngoscopy and bronchoscopy to identify or rule out a diagnosis of laryngeal cleft before initial repair of EA/TEF.

Conclusions

Pediatric patients with EA/TEF have a greatly increased prevalence of laryngeal cleft compared with the general population. Protocols should be adopted to routinely assess patients with EA/TEF for laryngeal cleft and other upper airway anomalies. As previously reported, multidisciplinary esophageal and airway programs serve as an ideal clinical setting for management of EA/TEF. Preoperative upper airway evaluation may facilitate diagnosis of laryngeal cleft and other anomalies, preventing health complications and obviating the need for further medical attention later in the child’s life.


