Factors Associated with Recurrence of Tracheoesophageal Fistula

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ABSTRACT: **Background:** Recurrence of tracheoesophageal fistula (TEF) is reported in 8–20% patients. Factors that may influence recurrence of fistula beyond the postoperative period are not clear.

Objectives: To evaluate possible factors associated with recurrence of TEF beyond the immediate postoperative period.

Methods: A single center, retrospective comparison of patients with and without recurrence of TEF was conducted. Medical records of patients previously operated for TEF who were followed in our pediatric pulmonary institute between January 2007 and December 2016 were reviewed.

Results: The medical records of 74/77 patients previously operated for TEF were evaluated. Nine patients (12%) had a recurrence of TEF and 65 did not. These groups had similar age and gender distribution and similar prevalence of VACTERL association. In addition, they had similar length of atretic gap, rates of thoracoscopic surgery, rates of prolonged need for respiratory assistance post-surgery, and frequency of gastrointestinal symptoms. Notably, the patients who had recurrent TEF had significantly more hospitalizations for respiratory symptoms ($P = 0.011$) and significantly more episodes of clinical bronchiolitis per patient ($P < 0.0001$). In addition, the patients with recurrent TEF had significantly more episodes of positive polymerase chain reaction for viruses ($P = 0.009$).

Conclusions: Hospitalizations for respiratory symptoms as well as clinical and/or viral bronchiolitis are associated with recurrence of TEF. Even though cause and effect cannot be established, these patients should undergo meticulous evaluation for the possibility of recurrence of TEF.

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Tracheoesophageal fistula (TEF) is a severe developmental malformation of the foregut. It may present as a single malformation or accompany other malformations such as the vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTREL).

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The etiology is currently unknown; however, environmental and genetic factors have been suggested [1,2]. Bronsens and colleagues [1] found that, among 275 patients with TEF, 167 genetic defects of copy number variations (CNVs) (frequency < 0.0005) were reported, suggesting that they can act as a modifier in a multiple hit model, or as the second hit in a recessive condition. The prevalence of congenital TEF is 1 patient per 2500 live births [3], with the prevalence remaining constant over the years [4]. The most common type of TEF is C type, which consists of esophageal atresia and a distal TEF connecting the lower pouch of the esophagus and the trachea [2]. Standard open repair is the most common corrective surgery conducted, with thoracoscopic repair being increasingly used. The most common short-term complication is a postoperative leak from the anastomotic site, which is more common with a long gap atresia [5].

Long-term sequelae of esophageal atresia with TEF include tracheomalacia that typically manifests as a barking cough, wheezing, respiratory distress, and cyanosis with feeding, or even apneic episodes (dying spells) [6,7]. Recurrent respiratory infections are reported in 44% of patients [6], and early esophageal stricture is a predictive factor for recurrent chest infections [8]. Gastroesophageal outcomes include dysphagia and acid reflux, esophageal strictures, and dysmotility [9]. Esophagitis, eosinophilic inflammation, esophageal gastric metaplasia, and Barrett's esophagus are frequently reported [10]. Examination with endoscopy and manometry continues to demonstrate near universal disorganized peristaltic activity.

Recurrence of TEF is a long-term complication associated with increased risk of death. The term includes recurrence of TEF in the same location as the original fistula, acquired de novo fistula in a different location, or a second TEF that may have been missed prior to the first surgery. Overall, reported rates of recurrent TEF are 8–20% [3,6,11], mostly 218 months after the initial repair [12]. Sulkowski and colleagues [13] reported that 5% of their 3479 patients required repeated TEF ligation within 2 years of discharge after their primary surgery. Recurrent TEF usually presents with cough, choking, cyanosis with feeding, or with recurrent pneumonia. Recurrence is more common in patients with a previous anastomotic leak and in patients with congenital esophageal stenosis [11]. Anastomotic leak is more prevalent with a long gap atresia [5]. Interestingly,

no differences in short-term complication rates, anastomotic leak, or anastomotic stricture were found between the thoracoscopic and open approaches [14].

To the best of our knowledge, later factors that may influence recurrence of TEF have not been studied. However, we have encountered several patients in whom recurrence of TEF was diagnosed concurrently or shortly after viral bronchiolitis. Such an association has not been reported.

The objective of this study was to describe the incidence and the risk factors of recurrent TEF in a tertiary pediatric hospital. In addition, we aimed to assess the possible association of recurrent TEF and bronchiolitis.

PATIENTS AND METHODS

A retrospective review was conducted of patients who underwent a previous surgery for TEF and who were followed in the pediatric pulmonary institute of our hospital between January 2007 and December 2016. The institutional board reviewed and approved the study. Patients were excluded if the information in the hospital medical record was insufficient.

Perioperative data obtained included demographic data, TEF as a solitary finding or as part of an association, open or thoracoscopic repair, need for prolonged respiratory assistance post-surgery, and length of the atretic gap. Postoperative data included recurrence of the TEF, occurrence of gastroesophageal symptoms, number of hospitalizations due to respiratory reasons, number of episodes of viral bronchiolitis, and positive polymerase chain reaction (PCR) for respiratory viruses.

We used the term "recurrence of TEF" to refer to all patients who had a fistula after a prior operation. This term includes recurrence of TEF in the same location as the original fistula, fistula de novo in a different location, or a second TEF that may have been missed prior to the first operation.

Spirometry data and main computed tomography (CT) findings were recorded when available.

STATISTICAL METHODS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics were used for the demographic variables, clinical parameters, spirometry, and CT findings. Differences between the groups with and those without recurrent TEF in the quantitative parameters were measured by Mann–Whitney U tests and Fisher's exact tests for categorical parameters. $P < 0.05$ was considered as statistically significant.

RESULTS

Seventy-seven post-TEF repair patients were identified. Three patients were excluded due to insufficient data in their medical records. Nine patients (12%) experienced a recurrence of TEF, eight of whom presented with a single recurrence. One patient (1.3%) died at 17 years of age due to respiratory insufficiency and sepsis after three episodes of recurrent TEF.

Demographic data, spirometry, and CT findings of the patients are presented in Table 1. Comparison of the groups of patients with and with no recurrence of TEF is presented in Table 2. As can be seen, the groups were similar in terms of age, gender, VACTERL association, and spirometry. Moreover, the anatomic type of TEF, length of the atretic gap, type of surgery performed,

Table 1. Patients characteristics

Patient characteristics	
Mean age, years (median; range)	8.2 ± 5.67 (8; 0.5–28)
Gender, male	41 (55%)
Concurrent anomalies VACTERL CHARGE Feingold syndrome Concurrent CCAM	 29 (39%) 1 (1.3%) 1 (1.3%) 1 (1.3%)
Recurrence of fistula	9 (12%)
Died	1 (1.3%)
FEV1 (% predicted) n=15 Mean ± SD Median (range)	 68 ± 20.7 74 (30–96)
Computed tomography (n=20) Normal lung fields Bilateral bronchiectasis Uneven ventilation and atelectasis Mediastinal collection Post lobar resection Bilateral infiltrates	 6 6 4 1 1 2

CCAM = congenital cystic adenomatoid malformation, CHARGE = coloboma, heart defects, choanal atresia, retarted growth, genital abnormalities, ear abnormalities, FEV1 = forced expiratory volume in 1 second, SD = standard deviation, VACTERL = vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities

Table 2. Statistical comparison of patients with and without recurrence of tracheoesophageal fistula

	No recurrence of TEF (n=65)	**Recurrence of TEF (n=9)**	***P* value**
Age, years (range)	7 (4–11)	8 (1.5–11.5)	0.97
Gender, male	36 (55%)	5 (56%)	1.00
Patients hospitalized with respiratory symptoms	32 (49%)	7 (77%)	0.16
VACTERL association	27 (42%)	2 (22%)	0.46
FEV1 % predicted, mean ± SD	69.7 ± 22.6 (n=14)	62 ± 17 (n=3)	0.51
Surgery Open Thoracoscopy	 42 (65%) 23 (35%)	 5 (56%) 4 (44%)	 0.72 0.72
Prolonged respiratory assistance	18/61 (30%)	1/7 (14%)	0.66
Gastrointestinal symptoms	40 (62%)	6 (67%)	1.00
Anatomic abnormality (C type)	60 (92%)	9 (100%)	1.00
Atretic gap, cm (range)	1.56 (0–4) n=42	1.6 (1–3) n=5	1.00

FEV1 = forced expiratory volume in 1 second, TEF = tracheoesophageal fistula, VACTERL= vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities

and need for prolonged respiratory assistance post-surgery, as well as significant gastrointestinal symptoms, were similar in the groups.

Seven out of nine patients with recurrence of TEF and 32 of 65 patients with no recurrence were hospitalized with respiratory symptoms.

All the patients with recurrence of TEF who were hospitalized had at least one episode of clinical bronchiolitis. There were 24 episodes of bronchiolitis in our group of 9 patients. Among the patients with no recurrence who were hospitalized, 19 had at least one episode of clinical bronchiolitis, and there were 30 episodes of bronchiolitis.

The details of patients who were hospitalized for respiratory symptoms are presented in Table 3. The patients who had recurrent TEF had significantly more hospitalizations for respiratory symptoms ($P = 0.011$) and significantly more episodes of clinical bronchiolitis per patient ($P < 0.0001$) than patients without recurrent TEF.

During the hospitalizations for clinical bronchiolitis, six patients with and 11 patients without recurrent TEF had a positive PCR for at least one respiratory virus. The routine PCR panel includes parainfluenza, influenza types A and B, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), and adenovirus. Adenovirus was the most frequent virus, which was identified in six patients with and three patients without recurrent TEF (data not shown).

The patients with recurrence of TEF had significantly more episodes of positive PCR for viruses ($P = 0.009$).

Table 3. Patients hospitalized for respiratory symptoms

	No recurrence of TEF (n=32)	Recurrence of TEF (n=7)	*P* value
Number of hospitalizations	57	34	
Number of hospitalizations per patient (median 25–75%)	1.5 (1–2)	3 (2–6)	0.011
Number of patients with clinical bronchiolitis	19/32	7/7	0.073
Episodes of clinical bronchiolitis per patient (median 25–75%)	1 (1–2)	3 (2–6)	< 0.0001
Episodes of positive PCR during clinical bronchiolitis	15/30	9/24	0.42
Number of positive PCR per patient (median 25–75%)	0 (0–1)	1 (1–2)	0.009

PCR = polymerase chain reaction, TEF = tracheoesophageal fistula

DISCUSSION

In this retrospective study, we assessed the factors associated with recurrence of TEF. We found that recurrence of TEF was associated with more hospitalizations for respiratory infections, more hospitalizations for bronchiolitis, and a greater rate of positive PCRs for viruses. To the best of our knowledge, such an association has not been reported.

TEF is a congenital malformation that requires early intervention for surgical correction. Over time, the prognosis has improved significantly, with survival rates of over 90% due to improved surgical techniques [9]. However, there is a high burden of residual esophageal and pulmonary pathology in patients with TEF, which require medical and surgical interventions. Continual multi-disciplinary surveillance of clinical symptoms and treatment response is warranted.

Dysfunctional esophageal activity accounts for the gastrointestinal symptoms described in the majority of children, with 50–90% of adolescents and adults reporting some degree of dysphagia. While the incidence of gastroesophageal reflux disease decreases with age, it is still described in 18–63% in adults [9].

Prolonged respiratory symptoms are described both in children and adults following TEF repair. The etiology of pulmonary manifestations following TEF repair is multifaceted. Tracheomalacia occurs in varying degrees of severity, rarely requiring aortopexy [15]. Recurrent respiratory infections are common and persist into adulthood. History reveals persistent cough, shortness of breath, and recurrent pneumonia [9]. Wheezing and physician-diagnosed asthma are reported in a higher incidence than in the general population [3]. Airway hyper-responsiveness can affect up to 78% of patients [7].

Pulmonary function tests demonstrate restrictive patterns in a significant proportion of patients. Multiple potential predisposing factors include congenital or acquired vertebral or chest wall abnormalities (i.e., scoliosis or postoperative rib fusions), surgical trauma, aspiration, and/or recurrent chest infections. Obstructive or mixed patterns also have been described. At lung imaging, a few studies detected bronchiectasis and irregular cross-sectional shape of the trachea, whereas diffuse bronchial thickening, consolidations, and pleural abnormalities were the main chest X-ray findings [7].

Recurrence of TEF manifests with respiratory and gastrointestinal complaints, often mimicking the aforementioned symptoms. As mentioned earlier, persistent symptoms following repair can be severe, and a high index of suspicion is needed to diagnose the recurrence. Early detection of recurrent TEF is required to prevent life-threatening events, decrements in pulmonary function, and serious long-term complications. Recurrence of fistula is not always easy to diagnose and establish. Barium swallow and various techniques, such as a dye study, during bronchoscopy are required [16]. In a recent retrospective study of 65 patients with recurrent TEF, 77% of TEF was categorized as recurrent, 26% as acquired from esophageal leaks, and 6% as persistent or missed. Seven patients in this series had multiple TEFs [17].

The recurrence is usually located in the pouch of the original TEF [3] and usually requires additional corrective surgery, although a few alternative methods, such as injections of fibrin glue [18] and bio-absorbable patches [19], have been developed over the past few years. The rate of recurrent TEF in our study was 12%, which is consistent with previous reports.

This study is the first to evaluate the possible association between recurrence of TEF and viral bronchiolitis. As noted

earlier, known risk factors for such recurrences include previous anastomotic leak and congenital esophageal stenosis. No differences in short-term complication rates, anastomotic leak, or anastomotic stricture were found between the thoracoscopic and open approaches [14].

In the current evaluation, the only factors associated with recurrent TEF were respiratory hospitalizations and diagnosis of viral bronchiolitis. Remarkably, we found more episodes of positive PCR for viruses per patient in the patients with recurrent TEF. PCR for viruses is not always sent for every patient with clinical bronchiolitis. Moreover, the panel contains six viruses, and it is possible that a patient had clinical bronchiolitis caused by other viruses, such as rhinovirus and bocavirus.

An association between de novo TEF and infectious agents has been reported in immunosuppressed patients: in a renal transplant patient following Mycobacterium tuberculosis infection [20], in a patient with human immunodeficiency virus-1 who had necrotizing candidiasis of the trachea that resulted in the formation of a TEF [21], and in a patient with aplastic anemia and invasive pulmonary aspergillosis [22]. The exact mechanism for the development of these TEF complications is unknown. The patients in our study who developed recurrence of TEF were immunologically intact. We postulate that, following TEF repair, the tracheoesophageal area might be more vulnerable to additional insults, such as viral infections.

This study has several limitations. The main limitations are the relatively small sample size and the retrospective nature. Not all patients underwent bronchoscopy prior to the first surgery; hence, we could not clearly categorize the TEF. The study was based in a pediatric pulmonology institute at a tertiary center to which patients with more complicated health issues are referred. Finally, as it is merely a descriptive study, we were unable to establish the cause and effect relationships. It is impossible to determine whether the bronchiolitis itself increases the risk of recurrence of TEF, or whether patients who develop recurrence of fistula are more vulnerable to common infectious agents in the process or have more hospitalizations with respiratory symptoms mimicking bronchiolitis.

CONCLUSIONS

Even though cause and effect cannot be established, patients with a history of TEF and hospitalizations for viral bronchiolitis should be carefully evaluated for the possibility of recurrent TEF. In light of this data, we also suggest that vaccinations against RSV and influenza for patients with a history of TEF may be beneficial. Further larger prospective studies should be conducted to better understand the association between viral bronchiolitis and recurrent TEF.

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