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Evaluation of Pulmonary Complications and Affecting Factors in Children for Repaired Esophageal Atresia and Tracheoesophageal Fistula

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Word count: 3591

Table and Figures: 4 tables, no figures

Funding Source: No funding was secured for this study

Conflict of Interest: All authors have no conflicts of interest to disclosesure

Abbreviations:

EA: Esophageal atresia

TEF: tracheoesophageal fistula

CCT: chest computed tomography

FB flexible bronchoscopy

BAL: bronchoalveolar lavage

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This article was a poster presentation which was examined with records of 43 patients (European Respiratory Journal 2017 50: PA4163;

DOI: 10.1183/1393003.congress-2017.PA4163

ABSTRACT:

INTRODUCTION: Recurrent pulmonary infections, wheezing and stridor due to swallowing dysfunction, esophageal dysmotility, gastroesophageal reflux, tracheomalacia and bronchomalacia are frequently seen complications after esophageal atresia and tracheo-oesophageal fistula (EA-TEF) surgeries. This study aimed to investigate the frequency and causes of respiratory problems and to evaluate the factors that affect respiratory morbidity in patients who had undergone EA-TEF repair in a tertiary referral center.

METHODS: Preoperative and postoperative records of patients with EA, TEF+EA and isolated EA were examined retrospectively. Accompanied diseases and swallowing dysfunction symptoms were questioned. Bronchoalveolar lavage results were investigated if the patient had flexible bronchoscopy.

RESULTS: A total of 71 children with EA were included in the study, and seven patients who did not have follow-up after surgery were excluded. 46 of the 64 patients continue regular follow-up visits in our department. Male sex, primary EA repair in another center, EA type C, accompanying genetic anomalies, severe tracheomalacia, late per oral feeding (1 year after surgery), and severe GER were found to cause significantly higher incidence of coughing, recurrent wheezing, recurrent pneumonia, and bronchiectasis despite surgical and medical treatments ($p = 0.048$, $p = 0.045$, $p = 0.009$, $p = 0.029$, $p = 0.025$)

CONCLUSİON: Even if anatomical anomalies are corrected by surgery in patients who underwent EA repair, precautions can be taken for GERD, laryngotracheomalacia, and swallowing dysfunction, and effective pulmonary rehabilitation can be initiated with early multidisciplinary approach before the development of respiratory tract symptoms.

Introduction

Esophageal atresia (EA) and tracheoesophageal fistula (TEF) are congenital malformations observed in 3000–3500 births[1]. Respiratory problems are common after EA-TEF repair and considered to have long-term consequences. There are several causes of respiratory morbidity in children with EA/TEF. Abnormal development of the trachea and esophagus in the early intrauterine period may lead to chronic pulmonary and gastrointestinal symptoms[1-3]. Clinical findings may vary depending on the type of EA. While early diagnosis can be made in newborns with swallowing dysfunction and gastric distension, it may take 2–3 years to diagnose isolated TEF.

Early diagnosis, prompt support in the neonatal intensive care unit, and advancement in surgical techniques positively affect the prognosis and decrease morbidity postoperatively[3-5]. Chronic cough, tracheomalacia, recurrent pulmonary infections, bronchiolitis, dyspnea, and asthma are more often reported in the infantile period; long-term bronchiectasis and scoliosis may also develop[1,6-10]. Concomitant tracheomalacia, swallowing dysfunction, and recanalization of fistula may lead to chronic cough and recurrent lung infections[9-12]. Other associated anomalies such as laryngomalacia, laryngeal cleft, and vocal cord dysfunction (VCD) may increase the risk of pharyngoesophageal aspiration[9,13-15]. Moreover, major vascular anomalies and vascular rings are more common in patients with EA-TEF. Complications such as dyspnea, dysphagia, and aspiration pneumonia may increase depending on the type of malformations and degree of compression on the esophagus and trachea[16]. Therefore, the diagnosis of vascular anomalies with accompanying malformations (right aortic arch (RAA) and aberrant left subclavian artery (ALSA); RAA with mirror image; left aortic arch and aberrant right subclavian artery (ARSA); and double aortic arch) and genetic anomalies ((VACTERL spectrum (Vertebral, Anorectal, Cardiac, TracheoEsophageal,

Renal and Limb), microcephaly, micrognathia, pyloric stenosis, duodenal atresia, a single umbilical artery, and anomalies of the genitourinary, respiratory and gastrointestinal systems) by flexible laryngoscopy, echocardiography and upper gastrointestinal series, genetic consultation etc. in the preoperative period can reduce postoperative early and late complications[17,18]. A multidisciplinary approach is recommended to avoid developmental retardation and to decrease the risk of neurodevelopmental delay[19,20].

This study aimed to investigate the frequency and causes of respiratory problems and to evaluate the factors that affect respiratory morbidity in patients who had undergone EA-TEF repair in a tertiary referral center.

Material and Methods

Preoperative and postoperative records of 71 patients with EA, TEF+EA, and isolated EA in Hacettepe University Faculty of Medicine, Department of Pediatric Pulmonology (DPP), between 2015 and 2017 were examined retrospectively. In the postoperative outpatient records, outcomes within 1 month and 1 year after the procedure were investigated. Patients without follow-up after surgery and did not come to the outpatient clinic were excluded from the study.

Accordingly, the Gross classification of EA, frequencies of preoperative and postoperative lower respiratory tract infections, preoperative and postoperative respiratory symptoms, associated anomalies including cardiovascular system and chest wall and genetic anomalies were investigated. Moreover, swallowing dysfunction, previous tracheostomy, and asthma were recorded. Serum immunoglobulin E level, eosinophil count, and eosinophil percentage were measured during follow-up in the department of pediatric allergy. Findings of patients with complaints of grunts, wheezing, stridor, and swallowing difficulty, who were evaluated

in the department of otorhinolaryngology and who underwent flexible laryngoscopy, were recorded. In the follow-up period at DPP, weight, height, body mass index (BMI), complaints, and physical examination findings upon presentation and their management were examined. In addition, pulmonary function test (PFT), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVCI, and forced expiratory flows between 25% and 75% of the vital capacity (FEF25-75), chest radiography and chest computed tomography (CCT) results (if flexible bronchoscopy [FB] was performed), findings, and cytopathological results of bronchoalveolar lavage (BAL) culture were recorded.

Statistical Analysis and Ethics

The SPPS Statistics version 25.0 (IBM Corp., Armonk, NY) was used to evaluate data. Variables are expressed as mean ± standard deviation, percentage, and frequency. Variables were evaluated after checking normality and homogeneity prerequisites (Shapiro–Wilk and Levene tests). For data analysis, one-way analysis of variance was used for comparisons of three or more groups, and Kruskal–Wallis and Bonferroni–Dunn test, which are multiple comparison tests, were performed with the Tukey HSD test. Categorical data were analyzed by Fisher's exact test and Chi-square test. For the level of significance, p values < 0.05 and < 0.01 were accepted. For the multivariate analysis, the possible risk factors identified with univariate analyses were further entered by logistic regression analysis to determine the independent predictors of pulmonary complications. For all subgroup analyses, unadjusted OR and relative 95% CI were used as a measure of pulmonary complications. A p value ≤0,005 was considered to be significant.

Ethics committee approval was obtained from the local institutional review board.

RESULTS

A total of 71 patients with EA were included in the study, and seven patients who did not have follow-up after surgery were excluded. 46 of the 64 patients continue regular follow-up visits in our department. Of the overall population, 53.4% (n = 46) were male, and the median age was 4.7 years (1 month to 13 years). In addition, 58 (90.6%) patients were diagnosed on the first day, and the median age at diagnosis of patients with EA type E (isolated TEF) was 1.3 years (6 months to 3.7 years). Of the patients, 43 (67.2%) had undergone their first operation in another hospital but were admitted to our hospital for follow-up, need for additional surgery, and treatment of respiratory problems. The median age of the patients referred from another hospital was 6.7 years (6 months to 12 years) (Table 1).

Respiratory Symptoms

The frequency of respiratory symptoms is listed in Table 1. Most patients (n = 60, 93.8%) complained of chronic cough, wheezing, and frequent recurrent pneumonia on the first visit to our clinic.

Radiological Evaluation

The most common chest radiograph findings were chronic changes on the right side (n = 52, 88.1%), consolidation (n = 19, 32.2%), and atelectasis (n = 16, 27.1%). The most common CCT findings (n = 28, 43.8%) were consolidation (n = 11, 36.1%), atelectasis (n = 11, 36.1%), and bronchiectasis [n = 9, 30%; right upper lobe (n = 2), right lower lobe (n = 2), right middle lobe (n = 2), left upper lobe (n = 1), and left lower lobe (n = 2) (Table 1)]. Vascular compression was found in four (14.8%) patients.

Respiratory Function Tests

Ten (12.5%) patients were able to perform PFT, and the results of the four patients were within normal limits, four had mild restriction, and two had obstruction that responded to bronchodilator inhalation (Table 1).

Flexible Bronchoscopy

In 14 (21.9%) patients, respiratory symptoms were evaluated with FB. Tracheomalacia (n = 9, 64.9%) was the most common finding, and the median age of patients was 4.5 years (range, 6 months to 13 years). Purulent secretion in the main bronchi (n = 3, 21.4%), recanalization of fistula (n = 3, 21.4%), blind ending fistula stump (n = 13, 92.9%), and anatomical variations [n =5, (35.7%): two segment right upper lobe (n = 4) and tracheal bronchus (n =1) (Table 1)] were detected.

While BAL pathology was within the normal limits in three patients, 11 patients had abundant lipid-laden macrophages, and abundant polymorphonuclear leukocytes. Patients with significant tracheomalacia experienced chronic cough, wheezing, and frequent pneumonia (p = 0.029). None of the patients require surgical intervention such as aortopexy and stenting for severe tracheomalacia.

Laryngoscopy

In the ear-nose-throat department, 48 (75%) patients were evaluated with flexible laryngoscopy, and 10 (20.8%) were found to have laryngomalacia, 1 (2.8%) had omega epiglottis, 1 (2.8%) had bilateral VCD, and two (5.6%) had unilateral VCD (Table 1). One of the patients with bilateral VCD required surgical intervention. In the follow-up, 14 (21.9%) patients underwent repeated flexible laryngoscopy and 10 of them showed normal endoscopic findings. Chronic cough and wheezing were more common in patients with laryngomalacia (p = 0.049) (Table 1).

Swallowing Assessment

Videofluoroscopic evaluation of swallowing showed normal results in 16 (28.6%) of 55 (85.9%) patients with dysphagia symptoms. Esophageal dysmotility (n = 28, 50.9%), oral phase problems (n = 17, 30.9%), delayed swallowing reflex (n = 17, 30.9%), and recanalization of fistula (n = 1) were found following videofluoroscopic swallowing test (Table 1). Non-oral feeding was recommended to six patients. In the follow-up of 18 patients, the test was repeated, and nine of the patients showed improved swallowing function after proper rehabilitation. Significant gastroesophageal reflux (GER) was noted in 10 (15.4%) patients and medical treatment was given, and none of the patients needed fundoplication. Cough, frequent recurrent lung infections, and wheezing were observed in patients with severe GER ($p = 0.025$) (Table 1).

Accompanying Asthma

In 48 (75%) patients, repeated pediatric allergy consultations were needed due to wheezing and prolonged need for bronchodilator inhalation. Of the patients, 35 (71.4%) were followed up for asthma and 32 of them started steroid inhalation treatment. The median age at asthma diagnosis was 2 years (8 months to 6 years) (Table 1). No significant relationship was found between having asthma, atopy, eosinophilia, and high total IgE levels and frequent pulmonary infection, atelectasis, and bronchiectasis ($p = 0.897$) (Table 4).

Nutrition and Anthropometric Measurements

In 14 patients with a mean BMI of 15 (+/- 1.75, SD), their height and weight were <5th percentile and two (26%) patients had BMI <5th percentile, depending on their age. In these patients, preoperative malnutrition persisted within 1 year after surgery.

Comparison According to the Center Where Primary EA-TEF Repair Was Performed

In the comparison of patients who underwent primary EA-TEF repair, 43 patients who had undergone their first operation in another hospital had more frequent chronic cough, recurrent lung infection, and bronchiectasis than those who underwent EA-TEF repair in our hospital ($p = 0.390$, $p = 0.380$, and $p = 0.480$, respectively)

Associated Anomalies

Three of the nine (14.1%) patients with genetic anomalies had Down syndrome, four had VACTERL association, and two had Di George syndrome (Table 2). No statistically significant difference was found between the groups according to the Gross classification in the frequency of congenital heart disease ($p = 0.178$) (Table 2).

Type of EA

EA patients were evaluated according to the Gross classification (Table 3).

Intraoperative and Postoperative Complications

Associated anomalies were present in 35 (54.7%) patients. Anastomotic leaks in the early postoperative period were observed in three (4.7%) patients. Anastomotic stenosis was found in 29 (45.3%) and relapse fistula in seven (10.9%) patients. Esophageal dilatation was required in 46 (71.9%) patients after surgery (Table 3). Oral intake was initiated in 37 (57.8%) patients 1 month after surgery, in 15 (23.4%) patients between 1 month and 1 year, and in 12 (18.8%) patients after 1 year (Table 3).

After surgery, 42 (65.6%) patients required short-term invasive mechanical ventilation, and four patients (6.3%) with tracheostomy were followed up. Moreover, the need for mechanical ventilation in the early postoperative period did not increase the frequency of respiratory tract problems, but chronic cough, wheezing, and recurrent pneumonia were observed in patients who developed subglottic stenosis and VCD. The frequency of pneumonia after surgery

decreased but did not change significantly (p = 0.957) (Table 3). A patient with right middle lobe bronchiectasis, who had irregular follow-up in another clinic, presented with scoliosis and underwent surgery during follow-up.

Furthermore, 46 (71.8%) patients have been followed regularly in the outpatient clinic for pediatric chest diseases. The most common symptoms were cough (n = 43, 94.4%), wheezing (n = 30, 66.7%), and recurrent pneumonia (n = 20, 44.4%). The median frequency of pneumonia was 1.31 (0–10 times/year) in the previous year. No patient required continuous or intermittent oxygen treatment within 1 year. A patient who underwent colon transposition had mediastinitis that needed oxygenation via a nasal cannula for 3 months after surgery and do not need further management.

Preoperative malnutrition persisted after surgery. However, the frequency of malnutrition showed a tendency to decrease within 1 year after surgery (p = 0.045). All cases with chest deformity and clubbing developed type A EA (p = 0.013). One patient was diagnosed with recurrent fistula by videofluoroscopic evaluation of swallowing function and two patients by FB in late postoperative period.

No statistically significant difference was noted in the frequency of pneumonia, chronic cough, and wheezing in patients before and after surgery when compared according to Gross classification; however, chronic cough and wheezing were more common in patients with EA type C (p = 0.037, p = 0.044, respectively) (Table 4).

Male sex, primary EA repair in another center, EA type C, accompanying genetic anomalies, severe tracheomalacia, late per oral feeding (1 year after surgery), and severe GER were found to cause significantly higher incidence of coughing, recurrent wheezing, recurrent pneumonia, and bronchiectasis despite surgical and medical treatments (p = 0.048, p = 0.045, p = 0.009, p = 0.029, p = 0.025) (Table 4). Patients with congenital heart disease have more

frequent respiratory problems, without any statistically significance. The frequency of respiratory tract infections was not statistically different in patients with early anastomotic complications and additional surgical anomalies (Table 4).

Discussion

Respiratory problems are common in patients with EA-TEF. This frequency may be related to many factors in the early and late postoperative period. The mean age of patients admitted to our clinic and the findings of almost all patients concerning the respiratory tract are intriguing in terms of patient follow-up. Since most patients who had preexisting respiratory problems were followed up irregularly in another hospital and most of their complaints were managed with palliative medical treatment, the mean age and frequency of symptoms increased significantly. In a study conducted with 105 patients in Italy, the mean age of onset of symptoms was 1.5 years, and the age of admission to the advanced center was 7.5 years, which was attributed to the lack of knowledge about multidisciplinary approach and long-term complications after surgery[21]. Currently, many patients are managed in our clinic after discharge but before respiratory problems have developed; thus, many complications can be prevented. Recently, the International Network of Esophageal Atresia, Respiratory Complications Working Group describes various aspects of the condition in terms of their relative importance, available diagnostic methods, and therapeutic interventions according to the age of patients with EA[22]. Regular long-term follow-up by a multidisciplinary team was considered imperative.

In the longitudinal follow-up of patients who underwent EA repair, a slight decrease in the mean values of FEV1, FVC, and TLC in terms of age can be observed in the respiratory function tests[23,24] compared with the healthy control group in a retrospective study. In 59 patients, positive bronchial hyperreactivity test was found in patients who underwent EA repair. No significant difference was noted between groups in terms of exhaled NO level, atopy, and high serum total immunoglobulin levels[7]. In two studies examining infantile and childhood periods, plethysmography showed that restriction becomes evident over time[25,26]. GER disease, frequent lower respiratory tract infections, and accompanying costal and vertebral deformities can also increase the restriction[21]. In our study, few patients were able to cooperate for spirometry; however, asthma, atopy, eosinophilia, and high total IgE levels were not found, and the diagnoses of frequent recurrent lung infection, atelectasis, and bronchiectasis were compatible with those in previous publications.

Despite successful surgery, EA/TEF patients have anatomical compression and malformations in the tracheal rings circumference of the fistula leading to malaise from the intrauterine period. In patients with significant laryngotracheomalacia, swallowing dysfunction is also present; this condition is associated with chronic cough, wheezing, and frequent pneumonia[27-29]. In our study, the frequency of tracheomalacia is compatible with those presented in previous studies. Effective pulmonary physiotherapy is employed because patients do not present for follow-up unless they have postoperative complaints and are referred late to the department on pediatric chest diseases; late complications such as frequent bronchiectasis and recanalization of fistula can result from mucus plugs and unresolved atelectasis. In our study, the frequency of atelectasis and bronchiectasis were comparable with those in previous publications, whereas the frequency tracheal vascular compression was slightly lower[27-29].

In all types of EA, 20%–63% of GER were observed in the postoperative period in patients aged 1–10 years[12,30]. In their study of 61 patients, Koivusalo et al. reported that GER

prevalence increases from 16% to 56% from age 6 months to 5 years and reaches 44% at 10 years; no new presentation is seen after 3 years[31]. In these patients, pan-esophageal pressure and peristaltism were found less frequently, and correlation was found with acid reflux episodes and chronic cough attacks, so antireflux therapy was recommended[32-34]. In children with respiratory symptoms and patients with GER with pronounced acid reflux, the finding of inflammation in BAL samples was more common in those with neutrophilic alveolitis and lipid-laden macrophages[35-36]. Respiratory tract complaints were higher at the first admission, and the presence of lipid-laden macrophages and neutrophils in BAL samples of our patients supports inflammation in the airway[36,37]. Recently, glutathione and miRNA-21 levels were significantly lower in exhaled breath condensate of patients with EA, showing that airway inflammation may lead to many respiratory symptoms[38,39].

Long-term esophageal motility disorders and swallowing dysfunction are observed in 50.3% of the patients who underwent surgery due to esophageal anomalies[11,30-34]. Many studies have shown that the frequency of chronic cough, frequent pneumonia, and malnutrition increased due to swallowing dysfunction and aspiration. In 2013, Ramsay et al. highlighted the importance of follow-up and appropriate rehabilitation for swallowing dysfunctions as multidisciplinary impression of these patients[41]. In the present study, 55 (85.9%) patients showed swallowing difficulty, swallowing inability, and coughing while feeding at first admission. The high incidence of swallowing dysfunction in our clinic, which is a tertiary diagnosis and treatment center, may be due to the late admission of most patients.

According to the relevant literature, the mean height and weight percentiles were below 3% in all age groups during follow-up[11,40-43]. In a study examining the nutritional status of 59 patients aged 9 months to 31 years who underwent EA repair, chronic malnutrition decreased from 22% to 7.7% after age of 13[43]. Similarly, in our study, the height and weight of 14 (21%) patients were below the 3rd percentile according to their age, and in these patients,

preoperative malnutrition persisted within 1 year after surgery. Malnutrition was thought to occur because our patients were referred from many centers for surgical complications, such as esophageal strictures, nutritional difficulties, and respiratory problems, and most of them did not have regularly follow-up.

Patients with EA-TEF most commonly have EA type C, which accounts for 75% in our study. Early complications of EA are multifactorial. Although most complications may develop due to surgical complications (stricture, secondary fistula development, and stump leakage), the frequency of surgical complications increases with concomitant genetic and cardiac anomalies[7-10].

Since anastomosis leaks can be often resolved with conservative treatment in minor cases, there is no data on long-term respiratory problems of these patients. In a single-center study in Italy, anastomosis leakage was determined as the only variable in the development of respiratory problems; however, as in our study, this result was not considered significant due to the insufficient enrollment of patients who underwent surgery operation outside the hospital. Long-gap anastomosis leakage was observed, and 58 (89%) patients recovered with conservative treatment[31]. In our study, fistula recurrence was recorded in 7 (10.9%) patients in the early postoperative period, but reconstruction was not required. Anastomosis stenosis was observed in 40% of 884 cases in a meta-analysis and 43% in another study[3,12]. In our study, anastomotic stenosis, which is one of the most common postoperative complications, was found in 29 (45.3%) patients, and 46 (71.9%) patients required esophageal dilation. In patients who underwent their first operation in another hospital, detailed information about complications related to early anastomosis leakage was not obtained due to the lack of registration; thus, comparison with our data was difficult. Of the 21 patients who underwent surgery our hospital, anastomotic leakage was observed in three patients in the early

postoperative period, and no significant increase was noted in the frequency of respiratory problems during follow-up.

In our study, chronic cough, wheezing, and recurrent lower respiratory tract infections were observed more frequently in patients with type C fistula after surgery, as shown in the literature[20,21]. In the follow-up, the need for mechanical ventilation in the early postoperative period did not increase the frequency of respiratory tract problems, but chronic cough, wheezing, and recurrent lower respiratory tract infection were observed in patients who developed subglottic stenosis and VCD. Chronic cough, recurrent wheezing, swallowing dysfunction, laryngomalacia, and bronchiectasis are more common in male patients with EA type C, severe GER, additional surgical anomalies, accompanying malformation, and genetic anomalies. Although concomitant genetic malformations and congenital heart diseases are more common in male patients, they do not increase the frequency of respiratory problems. Similar results have been seen in studies by Legrand C. and Porcaro F. et al.[21]

This study had some limitations. First, two-thirds of our patients have underwent surgery in another hospital and detailed information about their previous follow-up was not available. Most of our patients were >6 years old and could not perform spirometry due to associated complications. CCT and FB were not performed to all patients; therefore, other airway pathologies could not be ruled out.

Conclusion

Male sex, primary EA repair in another center, EA type C, accompanying genetic anomalies, severe tracheomalacia, late per oral feeding (1 year after surgery), and severe GER are shown to cause significantly higher incidence of coughing, recurrent wheezing, recurrent pneumonia, and bronchiectasis despite surgical and medical treatments. Even if anatomical anomalies are corrected by surgery in patients who underwent EA repair, precautions can be taken for

GERD, laryngotracheomalacia, and swallowing dysfunction, and effective pulmonary rehabilitation can be initiated with early multidisciplinary approach before the development of respiratory tract symptoms.

Author contributions

Dr Tugcu, Soyer, Emiralioglu and Ozcelik contributed to the study design, analysis, interpretation of the results and drafted the manuscript. Tugcu, Eryılmaz Polat and Hızal were working in Hacettepe University Faculty of Medicine, Department of Pediatric Pulmonology (DPP), between 2015 and 2017 and records of this tertiary center examined retrospectively. Dr Tugcu contributed to data collection and interpretation of the results and Tugcu, Soyer, Emiralioglu, Ozçelik contributed to revision of the manuscript. All authors critically revised the manuscript and approved the final version.

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