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Respiratory morbidity in children with esophageal atresia

Abstract

Objectives: Analyze clinical and epidemiological data of patients with repaired esophageal atresia who presented with respiratory complications, and their clinical progress on follow up.

Methods: Retrospective data was gathered from charts of patients with EA who had corrective surgery in a tertiary hospital, were referred to the pediatric pulmonology clinic due to respiratory complications and had at least two appointments in the clinic, the latest between 2009 and 2016.

Results: 37patients were included, 72,9% of whom had esophageal atresia with distal tracheoesophageal fistula. Recurrent wheezing was the most common respiratory complication, present in 75,7% children in the 1st appointment, followed by recurrent pneumonia (54%) and chronic cough (45,9%). Short Action Beta Agonists was the most common prescribed medication. Spirometry results were abnormal in 66,7% of patients, with 60% presenting with obstructive disorder. Tracheomalacia was the most frequent pathological finding in bronchoscopy exams. Incidence of all respiratory complications decreased during follow up, which can be an effect of both lung growth or appropriate treatment.

Conclusions: Pathophysiology of respiratory complications of EA is still unclear. Several risk factors have been proposed, such as GERD and tracheomalacia, but do not account for all patients.

Keywords: esophageal atresia, tracheoesophageal fistula, lung diseases, children

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Abbreviations: EA, esophageal atresia; TEF, tracheoesophageal fistula; GERD, gastroesophageal reflux disease

Introduction

Esophageal atresia (EA) is a relatively common congenital malformation, occurring in one in every 2500 newborns.[1–5] The most widely used classification of EA is the Gross Classification, as follows: type A for EA without tracheoesophageal fistula (TEF), type B for EA with proximal TEF, type C for EA with distal TEF, type D for EA with both proximal and distal TEF and type E for isolated TEF without EA.[7] Type C is the most common.[1,6] Surgical treatment usually consists of fistula ligation and terminal-terminal anastomosis, except when this is not possible due to a long distance between atresia stumps and high tension of the tissues. In these cases, a cervical esophagostomy and gastrostomy may be performed, with later reconstruction via gastric or colonic interposition.[2,4,8] Early post-operatory complications are anastomotic leakage or stenosis and fistula recurrence. Late complications consist of Gastroesophageal Reflux Disease (GERD), esophageal dysmotility and respiratory complications.[1,8]

With the recent advances of neonatal surgery and intensive care there has been a significant increase in patient survival.[4,9,10] Consequently there was also an increase of late respiratory complications, previously under reported.[4,9–11] The most frequent of these are recurrent wheezing, chronic cough and recurrent pneumonia.[3,11,12] Although they are most common in the first 3years of age[4] they can persist into adulthood.[11–14]

The prevalence and pathophysiology of late respiratory complications of esophageal atresia are not yet fully comprehended. Further understanding of these matters would help to develop protocols for respiratory follow up of these patients in order to establish early diagnosis and treatment. This study will describe the clinical and epidemiological profile of EA patients submitted to surgical repair in a tertiary hospital in Rio de Janeiro, Brazil, and referred to follow up in the pediatric pulmonary clinic of the same hospital due to respiratory complications.

Materials and methods

A retrospective study was conducted following ethical board approval, with data gathered from patients' charts. Inclusion criteria were hospital admission from August 2006 to August 2016 with the diagnosis of EA; referral to the pediatric pulmonology clinic due to respiratory symptoms; and at least 2 appointments in this clinic, the last dating between 2009 and 2016. Patients were excluded if they had had surgical repair performed at a different service. Data was collected from their first appointment in the pulmonology clinic and last appointment within the study period, regarding presence of respiratory signs/symptoms, comorbidities and prescribed medications. Recurrent wheezing was defined as at least two episodes of reported wheezing in the last six months and recurrent pneumonia was defined as at least two reported physician-diagnosed episodes in the last year. Persistent cough and dyspnea were registered when mentioned as a complaint by the caregiver. Presence of GERD was

registered when diagnosed by the gastroenterology clinic. Data was also collected regarding spirometry and bronchoscopy exams, when performed.

Each variable was described by its absolute frequency, percentage, mean, median and standard deviation. The corrected Mc Nemar test was used for comparing respiratory complications and treatments in first and last appointments, and the Chi squared teste or Fisher's exact test were used for comparing presence of surgical and bronchoscopic complications with presence of respiratory symptoms. Results were considered statistically significant when p value <0,05. Statistical analysis was conducted through the software SAS® System, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

Results

A total of 168 patients with EA diagnosis who had a medical evaluation from any department in the hospital from August 2006 to August 2016 were identified. Of these, 54(32%) were found to have had at least one appointment in the pediatric pulmonology clinic. Eight patients were excluded because they had been submitted to surgical correction in other hospitals, 5 were excluded because they didn't have any follow up appointments and 4 were excluded because they were referred to the pulmonology clinic despite having no respiratory symptoms, leaving a total of 37patients selected. Epidemiological characteristics of the selected sample are described in Table 1. The mean age of diagnosis was 0,5 days for patients with EA (median 0days, standard deviation ±2,0 days) and 247,5days for patients with TEF without EA. Type of fistula and surgery performed are shown in Table 1. Ten patients were later submitted to a gastric transposition, and the mean age of this procedure was 56 months. Some patients also presented with acquired comorbidities. One preterm patient had perinatal asphyxia and Respiratory Distress Syndrome, as well as diaphragmatic eventration. One patient had post infectious bronchiolitis obliterans and two had suppurative lung disease, one submitted to a pneumectomy. One patient was diagnosed with eosinophilic esophagitis. Non-respiratory surgical complications are described in Table 2. Of the 24patients diagnosed with GERD, 11(29,7%) were treated with ranitidine, 4(10,8%) with omeprazole and 7(18,9%) with fundoplication.

Respiratory complications and prescribed medications on first and last appointments in the pulmonology clinic are shown in Table 3. The mean time interval between first and most recent appointments was 62months. Chronic cough, recurrent wheezing, recurrent pneumonia and GERD had a statistically significant reduction. The use of as needed SABA, LABA and inhaled corticosteroids was statistically higher at the last appointment. Presence of respiratory symptoms in the last appointment did not statistically correlate with GERD (p0,38). Nineteen patients were submitted to at least one bronchoscopy and fifteen to a spirometry, with results shown in Table 4. Mean age in the first bronchoscopy was 20,8months (mean 7months, ±19,9), and only eight patients were submitted to follow up exams. Presence of tracheomalacia did not have a significant association with persistence of symptoms in the last appointment (p0,84).

Mean age age in the first spirometry was 96,1months (median 87months, ±25,6). Only two patients, both of whom had grade I obstructive pattern, had a positive bronchodilator test. Eleven patients had at least one subsequent exam, and one patient who had a normal result in the first spirometry developed an obstructive pattern in follow up.

Table 1 Epidemiological Characteristics of patients with Esophageal atresia

Variable	n	%
Male Gender	24	64,8
Prenatal Care	36	97,3
Prenatal Diagnosis	3	8,1
Reported polyhydramnios	13	35,1
Full Term Birth	27	72,9
Associated Malformations		
Congenital Heart Defect	13	35,1
VACTER[a] Association	4	10,8
CHARGE[b] Syndrome	1	2,7
Horse-shoe Kidney	2	45,4
Anchored Marrow Syndrome	1	2,7
Diaphragmatic eventration	1	2,7
Duodenal Atresia	1	2,7
Imperforate Anus + congenital heart defect	1	2,7
No associated malformations	13	35,1
Type of EA[c] (Gross Classification)		
Type A	5	13,5
Type B	1	2,7
Type C	27	72,9
Type D	1	2,7
Type E	2	5,4
EA + Mediastinal Fistula	1	2,7

[a] vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (genetic association)

[b] coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities (genetic Syndrome)

[c] Esophageal Atresia.

Table 2 Non respiratory complications of patients with esophageal atresia

Surgical Complications	n	%
Gastroesophageal Reflux Disease	24	64,9
Fistula Reopening with clinical treatment	7	18,9
Fistula Reopening with surgical Treatment	3	8,1
Anastomotic Leak with clinical treatment	2	5,4
Anastomotic Leak with surgical treatment	1	2,7
Esophageal Stenosis	18	48,6
Esophageal Perfuration (due to stenosis dilation)	3	8,1
No Complications	6	16,2

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Table 3 Respiratory Complications and Prescribed Medications in 1st and last appointments

Clinical Variable	1ª appointment		Last Appointment		p value[2]
	n	%	n	%	
Age (months)[1]	34,3±45,0	(1-177)	96,1 ± 60,1	(6-216)	
Respiratory Complications					
Chronic Cough	17	45,9	6	16,2	0,003
Recurrent Wheezing	28	75,7	14	37,8	0,003
Recurrent Pneumonia	20	54	6	16,2	0,001
Dyspnea on Exertion	2	5,4	2	5,4	1,3
Stridor	2	5,4	0	0	0,50
Asymptomatic	0	0	17	45,9	-
Prescribed Medication					
Regular SABA[3]	9	24,3	6	16,2	0,58
As needed SABA[3]	15	40,5	24	64,9	0,019
LABA[4]	0	0	6	16,2	0,031
IC[5]	12	32,4	23	62,1	0,027
Azithromycin	0	0	1	2,7	1
No prescribed medication	16	43,2	7	18,9	0,077
GERD[6]					
GERD[6]	18	48,6	9	24,3	0,022

[1] mean±standard deviation (minimum - maximum)

[2] Mc Nemar Test

[3] Short Acting Beta Agonists

[4] Long Acting Beta Agonists

[5] Inhaled Corticosteroids

[6] Gastroesophageal Reflux Disease

Table 4 Bronchoscopic and Spirometric Findings in 1st and last exams

Variable	1ª Exam	
	n	%
Bronchoscopy (n=19)		
Thracheomalacea	6	31,6
Patent Fistula	2	10,5
Glotic Stenosis	1	5,2
Vocal chord paresis/paralysis	2	10,5
Normal Exam	8	42,1
Spirometry (n=15)		
Obstructive Pattern	9	60
Grade I	6	40
Grade II	1	6,6
Grade III	1	6,6
Grade IV	1	6,6
Grade V	0	
Restrictive Patten	1	6,6
Normal spirometry	5	33,3

Discussion

In this study epidemiological and clinical characteristics of patients with repaired EA were analyzed in two moments, their first appointments in the pediatric pulmonology department and last appointment in the study period, in order to access ongoing status. The study sample was epidemiologically similar to that in other studies, showing a prevalence of class C EA,[6,15,16] male gender and full term births.[4,6,17] The most common associated malformation was cardiovascular, as also found by other authors.[9,15] There was a low amount of prenatal diagnostic suspicion and reported polyhydramnios. It is important to note that several patients were born in other hospitals and transferred to this tertiary center for surgical repair, and so prenatal and birth information on polyhydramnios may have been under recorded and underestimated in the study. Age of diagnosis was considerably older for E type fistulas, as compared to other types of EA. Even though this delay is expected, it was greater than the findings of other studies, suggesting a low level of diagnostic suspicion for this condition. Esophagostomy and gastrostomy with later esophageal replacement by gastric pull up was more common in our population then other studies.[6,16] On the other hand there were no colonic interpositions, a procedure adopted by other centers.[3,17]

Respiratory complications are described to occur in over two thirds of the children with EA in the first 5years of life.[11,13] Presence

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of the three most common respiratory complications, chronic cough, recurrent wheezing and recurrent pneumonia, significantly decreased from the 1st to last appointments, but since the study was retrospective and observational it is not possible to estimate what percentage of this improvement was due to growth or appropriate treatment. It is also important to note that even though the amount of patients who were asymptomatic in the last appointment increased, so did the amount of patients on respiratory medications. Most common respiratory symptom in both 1st and last appointments was recurrent wheezing (75,7% and 37,8% respectively), similar to other studies.[6,9] Recurrent wheezing is often diagnosed as asthma in this population, even into adulthood.[5,14] Nevertheless, patients with EA have a low prevalence of allergic rhinitis and family history of asthma, findings usually common in asthmatics.[14] Furthermore, Malmstrom e Cols did not find bronchial remodeling and continuous inflammation in lung biopsies of patients with repaired EA and bronchial hyper responsiveness to histamine. It is believed that this response may be caused by chronic subclinical aspiration and not atopy.[13] The study's spirometric findings corroborate this, as even though obstructive disorder was the most common result, most patients did not present with a positive bronchodilator test, which would be expected in asthma.

Chronic cough and dyspnea on exertion may have been underestimated by our study for not being an active complaint by many patients or their parents, and we could only count on retrospective analysis of charts. Respiratory complications were historically attributed exclusively to digestive complications such as GERD, fistula recurrence, esophageal stenosis and swallowing defects that caused micro aspirations.[3,11] New studies, however, have questioned this premise. Legrand e Cols did not find a significant association between respiratory symptoms or abnormal pulmonary function tests and GERD, esophageal dilatations and dysphagia[6]. Moreover, Peetsold e Cols did not find a high prevalence of obstructive pattern in respiratory function tests in patients with GERD.[9] Likewise, our study showed that 35,1% of patients with respiratory symptoms had no history of GERD, and 16% of patients had no history of any other surgical complication, and there was so statistically significant relationship between presence of GERD and persistence of respiratory complications in the last appointment.

The most commonly used medication in both appointments was SABA, followed by IC. Use of all medications increased with follow up. LABA was used by 17,1% patients in the last appointment and none in the first, which can be partly due to younger age of patients in this group (LABA is only released for use over 4years of age). As for spirometric findings, 66,8 % of patients had an abnormal spirometry, a proportion close to the findings of Beucher et al.,[4] (67,8%) and Legrand et al.,[6] (75%). Most studies in EA patients found restrictive pattern as the most common alteration in spirometry.[3,4,9,13] It is postulated that this can be a result of poor lung growth in early infancy due to recurrent infections, micro aspirations due to GERD, congenital or acquired vertebral and chest wall abnormalities and surgical trauma.[9,12] Our results, in contrast, as in Legrand et al.,[6] found obstructive disorder as the most common finding. These can be attributed to several mechanisms including small airway disease, proximal obstruction due to tracheomalacia, epithelial damage caused by GERD or repetitive pneumonias, and decreased lung growth during infancy.[12,18]

Tracheomalacia was the most common pathologic finding in bronchoscopy, and has been described as a possible contributor to respiratory complications,[12,19,20] since it can worsen secretions clearance contributing to atelectasis and recurrent pneumonias.[11,19] Moreover it can cause a slower recovery time from infections and predispose to the formation of bronchiectasis.[4] However, in our population there was no significant relationship between tracheomalacia and persistence of respiratory complications. The study's main limitation was that, being retrospective, not all children were submitted to the same appointments and exams at the same age, which can be an important confounding factor. Furthermore, the time between the appointments assessed varied between patients. To conclude, the study corroborated the high prevalence of late respiratory complications in EA patients, particularly recurrent wheezing. It is essential that these patients have appropriate clinical follow up, as the study suggests that timely treatment and identification of complications may reduce respiratory morbidity in follow up. The pathophysiology of these complications is still unclear. Even though several risk factors have been identified, such as GERD, esophageal stenosis and tracheomalacia, they don't account for all patients presenting with respiratory symptoms. Prospective studies with follow up exams are still necessary to determine the impact each of these factors may have in the development of respiratory complications.

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Conflicts of interest

The authors declared there is no conflict of interest.

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