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To assess the cell lines on esophagogastroduod enoscopies of children with feeding difficulty, esophageal fistula and asthma with histologic abnormality

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ABSTRACT

The purpose of this study is to evaluate the cell lines seen on esophagogastoduodenoscopy (EGD) of children who have difficulties feeding, esophageal fistula, and asthma that has some histologic abnormalities. This is a study that looked back at the medical records of 100 children whose cells had been surgically restored after being impacted by EA or TEF. A review of the instrumental tests that were carried out at our facility has been conducted in order to identify any lingering anatomic or functional abnormalities of the airways and gastrointestinal system that would explain the pulmonary clinical images. Due to neurodevelopmental sequelae and the existence of tracheostomies, only 26 sets of pre and post-bronchodilator spirometry data were available for children. 100 children cells with esophageal atresia and tracheoesophageal fistula were included in the study. The average number of weeks spent in gestation was 37.01± 2.33, and the average weight of a newborn was 2614±77.69 grammes. Twenty percent of the children's cells exhibited a syndromic appearance, and the VACTERL connection was identified in seventeen percent of the patients. In all, 80% of the children cells in the sample reported having respiratory symptoms, with 85% of patients experiencing symptoms of the lower respiratory tract and 15% experiencing symptoms of the upper respiratory tract. It is common practice to attribute children's symptoms to reflux and esophageal anomalies, despite the presence of respiratory symptoms and aberrant findings discovered by flexible bronchoscopy and CT assessment.

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Introduction

Due to the improper development of the trachea and oesophagus while the baby is still inside the uterus, children who are born with congenital esophageal atresia (also known as EA) and tracheoesophageal fistula (also known as TEF) experience persistent respiratory and digestive difficulties. It is a very uncommon disorder that only manifests itself once every three thousand people are born alive (1). The clinical manifestation of EA differs depending on the subtype. In infants born with EA, the inability to successfully swallow saliva and milk lead to the development of a condition known as gaseous expansion of the GIT tract associated with stomach reflux. Symptoms of late-onset such as coughing and cyanosis during feeding, recurring severe bronchitis, and pneumonia are seen in infants who have been diagnosed with a single case of TEF.

The major aims of therapy are to provide patients and their parents with the greatest possible quality of life, to diagnose the underlying problem as early as possible, to reduce morbidity, and to provide patients with the highest possible quality of life. The only treatment option available is surgery, however, the outlook is favorable for 95–99% of the children who undergo the procedure (2). It is of the utmost importance to maintain the patient's native oesophagus, which can be accomplished in ninety percent of all instances with primary anastomosis in conjunction with the closure of the esophago-tracheal fistula. Even if the most recommended method is to approach it from a right-sided thoracotomy (3), in the last ten years, thoracoscopic repair has established itself as the gold standard in specialist clinics for the correction of congenital and acquired TEF. A more recent meta-analysis has vouched for the efficacy of this method, which appears to have outcomes that are comparable to those of open surgery (4). The complexity of the technique, the increased risk of acidosis and hypercapnia during thoracoscopic repair (5), and the absence of randomised controlled trials that provide evidence of the technique's effectiveness and it is only used in a select few specialised centres.

Moreover, improvements in surgical methods and newborn intensive care have led to an increase in the occurrence of long-term disease-related problems, such as pulmonary symptoms. These developments have led to an improvement in survival rates. Children and their parents frequently describe symptoms such as wheezing, and dyspnea, all of which contribute to a lower quality of life during childhood, adolescence, and adulthood (1, 6, 7). Even though respiratory morbidity is more likely to decrease with age, reduced lung function can be found even in asymptomatic children and adults (8). Furthermore, long-term lung damage such as bronchiectasis can develop as a result of recurrent lower respiratory infections (9,10). This particular group of patients frequently

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experiences tracheobronchomalacia as a medical problem. There is a wide range (24% to 79%) of reported incidence rates from retrospective investigations (11–19). The prevalence of dysphagia in children with severe tracheomalacia is suggestive of a connection between the symptoms of the digestive system and those of the pulmonary system. Gastroesophageal reflux disease (GER), dysmotility, and anastomotic strictures are all risk factors for aspiration and the progression of tracheomalacia.

Materials and Methods

This is a study that looked back at the medical records of cell lines of 100 children whose cells had been surgically restored after being impacted by EA or TEF. With the agreement of the institutional review board and the findings of diagnostic testing (CT scan and esophagogastoduodenoscopy) were collected via an electronic medical record review.

A review of the instrumental tests that were carried out at our facility has been conducted in order to identify any lingering anatomic or functional abnormalities of the airways and gastrointestinal system that would explain the pulmonary clinical images (Fig 1).

In order to determine the diagnosis, evaluate preoperative vocal cord motility, cannulate the fistula when necessary, and assess the presence of other associated anomalies, preoperative flexible laryngo-tracheobronchoscopy (LTBS) was performed on all of the patients as part of a standardised preoperative diagnostic assessment. All of the patients underwent this procedure. When post-operative stridor, apnea, dysphonia, or recurring lower respiratory symptoms were present, repeat flexible LTBS was performed. This was done either during the long-term follow-up phase or during the immediate post-operative period.

A preoperative screening for major associated abnormalities was performed on every newborn child. In particular, the screening consisted of the following procedures: a search for vertebral anomalies using chest and abdominal X-rays; a search for associated abnormalities using ultrasounds of the brain, kidneys, and abdomen; and an electrocardiographic and echocardiographic assessment to determine the structure and function of the heart. The thoracotomy method was utilised, regardless of whether or not TEF was present, in order to repair EA.

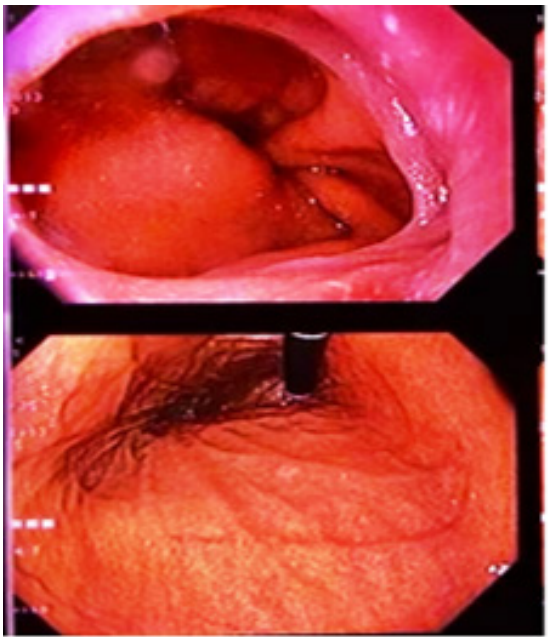

Figure 1. Esophagogastroduod enoscopies.

Weaning the patient off ventilation took four weeks, at which point tracheostomy was considered. A cough accompanied by additional symptoms such as a sore throat, runny nose, nasal congestion, and sneezing is considered to be "upper respiratory symptoms," even if it does not affect the bronchial or pulmonary systems. Common instances of lower respiratory symptoms include coughing that is accompanied by bronchitis, pneumonia, or wheezing. Cells from children who did not display apnea, stridor, or any other lower respiratory symptoms were excluded from the postoperative and long-term follow-up respiratory examination.

A positive pH impedance investigation was defined according to the NASPGHAN/ESPGHAN standard procedure. When the reflux index (the percentage of total time when the oesophageal pH is less than 4) was 11.7% in newborns and 5.4% in children cells, a positive result was determined (20). Tracheomalacia was defined as a decrease of at least 50% of the tracheal lumen with spontaneous quiet breathing during a flexible bronchoscopy conducted under anaesthesia with sevoflurane (21).

By employing inspiratory-expiratory MDCT with contrast enhancement, tracheomalacia was defined as dynamic tracheal collapse at the conclusion of exhalation (22). Due to neurodevelopmental sequelae and the existence of tracheostomies, only 26 sets of pre and post-bronchodilator spirometry data were available for children. Guidelines from the American Thoracic Society and the European Respiratory Society (23) were followed to conduct the spirometry tests. Participants were given instructions on how to do the spirometry, and the highest total score was used. The participant sat erect in an upright posture while a noseclip was used to measure lung function. Projected values of height and gender were used to generate percentages that represented the study's results.

Statistical analysis

The information that was gathered is presented in the form of numbers, means with standard deviations, and percentages. The Student t-test and the 2 analysis were used to do the statistical analysis of the data. The OR and CI for 95% were both determined using the conventional procedures for 2 by 2 contingency tables.

Results

100 children cells with esophageal atresia and tracheoesophageal fistula were included in the study. The average age was 7.55 years, with a standard deviation of 2.36 years. 55% of patients were male. The average number of weeks spent in gestation was 37.01± 2.33, and the average weight of a newborn was 2614±77.69 grammes. There were 10 patients for whom there were no accessible data on the mean gestational age, and there were 14 patients for whom there were no available data on the mean newborn weight. 53% of patients had

Table 1. Basic parameter of esophageal atresia and tracheoesophageal fistula patients

Parameters	NO.	%
Male	55	55
Female	45	45
Age	7.55±2.36	7.55±2.36
gestational age	37.01±2.33	37.01±2.33
neonatal weight	2614±77.69	2614±77.69
Malformations	53	53
Cardiac anomalies	45	45
Vascular anomalies	10	10
Genitourinary anomalies	8	8
Pulmonary anomalies	5	5
Gastrointestinal anomalies	5	5
Skeletal anomalies	3	3
Syndromes	20	20
VACTERL association	17	17
Down syndrome	2	2
CHARGE syndrome	2	2
Anophtalmia Esophageal Genital syndrome	2	2
Types of fistula		
C	85	85
B	7	7
A	3	3
E	1	1
No fistula	4	4

concomitant abnormalities, the most common of which were heart disease and vascular anomalies, which affected 45% and 10% of children, respectively. Twenty percent of the children's cells exhibited a syndromic appearance, and the VACTERL connection was identified in seventeen percent of the patients. There was no evidence of malformations or abnormalities in the cells of 20% of the children. For the 100 instances for which data were available, type C fistula was found to be the most common EA variation (85%), followed by types B (7%), A (3%), and E (1%). Table 1 provides an easy-to-understand illustration of the basic parameter. Twelve percent of children's cells showed interest in a little leak of anastomosis that occurred during the first month of life. When it came to these patients, the consumption of oral milk was limited, and they were provided with either enteral or parenteral nutrition supplementation. In 87% of patients, long-term digestive issues occurred, including 7% with esophagitis, 43% with esophageal stenosis, and 70% with gastroesophageal reflux (GER). The pH-impedenziometry test found gastroesophageal reflux 77% of the time, the swallow contrast examination detected it 22% of the time, and the gastric emptying scintigraphy detected it 1% of the time. (Figures 2, 3).

Children who had esophagitis were given medical treatment, and those who had esophageal stricture (defined as an esophageal anastomosis with a diameter of less than 5 millimetres) were given repeated endoscopic balloon dilatation while they were under general anaesthesia. In all, 80% of the children cells in the sample reported having respiratory symptoms, with 85% of patients experiencing symptoms of the lower respiratory tract and 15% experiencing symptoms of the upper respiratory tract. The beginning of respiratory issues was nearly the same in both groups, with a mean

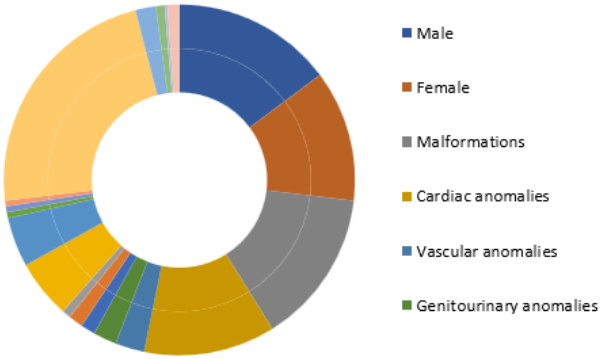

Figure 2. Distribution and Frequency of parameters.

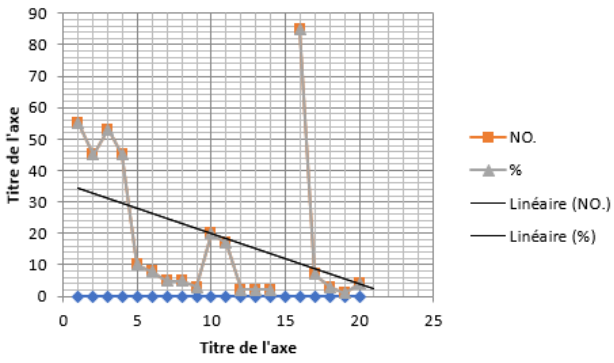

Figure 3. Basic parameter of esophageal atresia and tracheoesophageal fistula patients.

of 2.33± 1.36 years and a standard deviation of 2.33± 0.98 years, respectively.

The first evaluation of the patient's respiratory system was performed at a mean age of 4.19± 1.33 years. The lower respiratory symptoms that were reported the most frequently were recurrent pneumonia (34%) and wheezing (32%), followed by stridor (4%) and apnea (3%). Patients underwent multiple specialist evaluations throughout the follow-up period, based on the symptoms they were experiencing (Table 2 and Fig 4).

Twenty to fifty children cells, selected based on their family history of recurrent lower chest infections, underwent chest CT with contrast enhancement and flexible bronchoscopy to better understand the relationship between their blood vessels and breathing passages. In 8 patients, the CT scan revealed abnormalities, the most common of which were localised atelectasis (40%), tracheal diverticulum (35%), bronchiectasis (30%), tracheal vascular compression (20%), tracheomalacia (20%), esophageal diverticulum and bronchial stenosis (15%), and recurrent tracheoesophageal fistula (5%). Pathology was seen during flexible bronchoscopy in 50 out of 100 cases when conducted under light sedation. The most common findings were tracheomalacia (68%), tracheal diverticulum (28%), and recurrent tracheoesophageal fistula (20%) (Table 3 and Fig 5 and 6).

With the exception of vocal cord paralysis, children cells arriving from other hospitals had a higher incidence of subglottic stenosis, bronchomalacia, and various issues that can occur in the airway. The remaining two patients had CO2 laser-posterior cordotomy, however, tracheostomy was only performed in one of their cases. Endoscopic closure was successfully used to treat two different occurrences of laryngeal cleft.

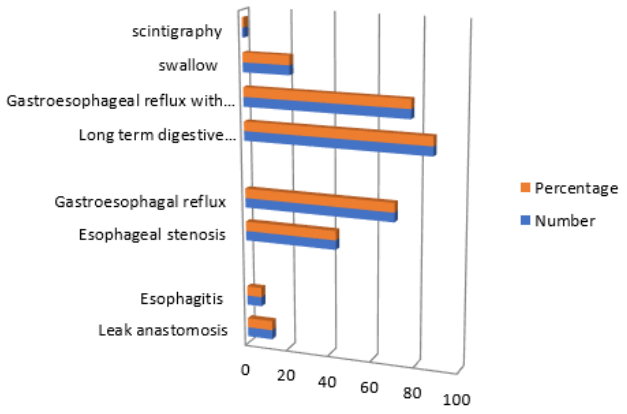

Figure 4. Digestive complications in esophageal stricture.

In three patients, the submucosa of the lateral walls of the fistula was injected with fibrin glue; however, only one of these cases was effective. One patient benefited from laser therapy which was administered. In every other instance of recurrent TEF, the thoracotomy were carried out as surgical procedures.

To keep respiratory complications at bay, a conservative approach was taken to treating tracheal diverticu-

Table 2. Digestive complications in esophageal stricture.

Digestive complications	Number	Percentage
Leak anastomosis	12	12
Esophagitis	7	7
Esophageal stenosis	43	43
Gastroesophagal reflux	70	70
Long term digestive complications	87	87
Gastroesophageal reflux with pH±impedenziometry	77	77
swallow	22	22
scintigraphy	1	1

Table 3. Results of a CT scan with contrast and a flexible bronchoscopy.

Observation	LTBS= 50	Percentage	CT scan= 20	Percentage	χ^2
Tracheomalacia	34	68	4	20	1.36
Tracheal diverticulum	14	28	7	35	2.58
Lobar atelectasis	-	-	8	40	1.96
Recurrent tracheoesophageal fistula	10	20	1	5	0.58
Bronchiectasis	-	-	6	30	1.71
Tracheal vascular compression	4	8	4	20	0.69
Vocal cord paresis	5	10	-	-	0.79
Bronchial stenosis	3	6	3	15	0.33
Esophageal diverticulum	-	-	3	15	2.98
Subglottic stenosis	4	8	2	10	1.33
Pulmonary hypoplasia	-	-	2	10	0.85
Larynx cleft	3	6	-	-	0.76
Bronchomalacia	2	4	1	5	2.22
Coanal stenosis	2	4	-	-	0.14
Laryngomalacia	2	4	-	-	2.59
Vocal cord nodule	1	2	-	-	1.21

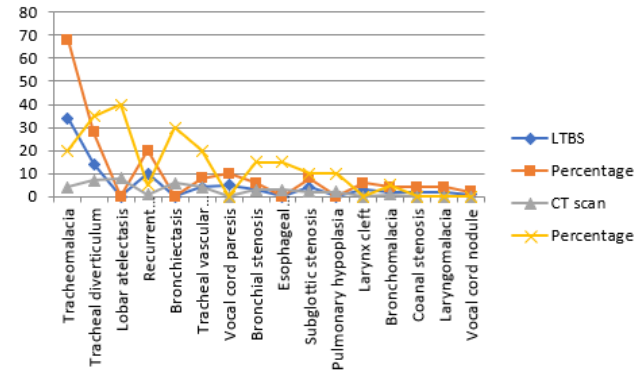

Figure 5. CT scan with contrast and a flexible bronchoscopy.

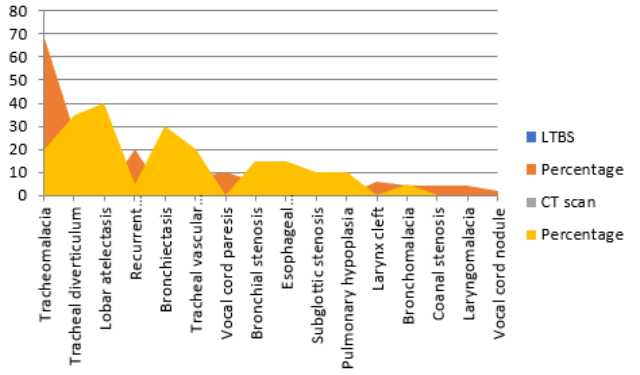

Figure 6. Percentage of flexible bronchoscopy.

lum and tracheomalacia, and measures for clearing the airways were implemented. Only two patients who still had bronchial stenosis after bronchoplasty were treated with the procedure. The above therapies were given to patients, and the parents of those patients reported an improvement in their children's "barking cough" and a reduction in the number of severe respiratory exacerbations that required antibiotic therapy that was also administered in a hospital environment. In a comparison of patients with and without lower respiratory symptoms, there was a trend associating the lower respiratory symptoms with Gender 2.22 (1.39-3.98), type C fistula 1.45 (1.11-4.77), VACTERL association 1.69 (0.59-2.22), leak of anastomosis 2.58 (2.11-4.58), and GER 2.22 (1.87-4.11); however, this association was not statistically significant. To no one's surprise, atopy was found to have a substantial association with 1.66 lower respiratory problems (1.07-2.57). The results of all statistical analyses are presented in Tables 4 and 5, and Fig 7.

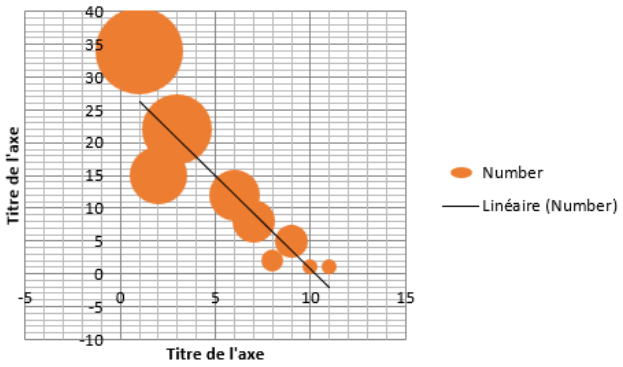

Figure 7. The percentage of patients having of airway complications.

In addition, the mean age at which respiratory complaints first appeared in patients with concomitant heart disease was 1.5± 0.36 years: the onset was premature when compared with children cells that did not have cardiac defects, and the difference was only marginally significant statistically.

Table 4. The percentage of patients having of airway complications.

Airway complications	Number	Percentage
Tracheomalacia	34	34
Tracheal diverticulum	15	15
Recurrent tracheoesophageal fistula	22	22
Lobar atelectasis	12	12
Bronchiectasis	8	8
Bronchomalacia	2	2
Vocal cord paresis	5	5
Subglottic stenosis	1	1
Larynx cleft	1	1

Table 5. Parameter related to respiratory tract symptoms

Parameter	OR(95%CI)	P value
Gender	2.22(1.39-3.98)	0.21
C type fistula[b]	1.45(1.11-4.77)	0.74
Malformations	0.87(0.66-2.57)	0.02
Heart disease	0.63(0.42-1.89)	0.007
VACTERL association	1.69(0.59-2.22)	0.41
Leak of anastomosis	2.58(2.11-4.58)	0.19
Long-term digestive complication	3.58(3.01-5.59)	0.63
Gastroesophageal reflux	2.22(1.87-4.11)	0.41
Atopy	1.66(1.07-2.57)	0.36

Discussion

The proportion of pulmonary morbidity in EA and TEF survivors is still fairly high despite breakthroughs in prenatal and surgical care, increasing knowledge of related morbidity, and more aggressive treatment options. Due to the frequent co-occurrence of respiratory morbidity as a consequence of both illnesses. The clinical complexity of patients with EA and TEF necessitates consideration of the fact that a number of variables greatly impact the respiratory morbidity of these patients. The most common occurrences of the associated congenital anomalies have been documented in males (24). Our sample includes an equal number of male and female patients with cardiac defects and the VACTERL relationship. Isolated malformations, abnormalities related to the VACTERL connection, and heart defects are not strongly linked to respiratory problems when considered independently.: This result is consistent with what Legrand and coworkers (25).

As a second point, airway abnormalities such as tracheomalacia, tracheobronchial malformations, and lung hypoplasia contribute to recurrent respiratory exacerbations by impeding mucociliary transport. The prevalence of tracheomalacia in our sample was much higher than expected (9).

Esophageal dysmotility from esophageal stenosis and GER may also negatively impact respiratory function. The prevalence of esophageal strictures and gastroesophageal reflux disease (GERD) in our patients is similar to other studies (26,27).

While there are multiple published articles on the key long-term respiratory concerns in EA children, no common management strategy has yet been developed. An examination of 26 primary papers that primarily addressed respiratory illness in EA survivors yielded a simplified care plan of pulmonary effects only in a newly published research (28-32). The review mainly focused on these papers. In this article, we provide a large case series that corroborates the results of many earlier, more limited investigations on the relationship between respiratory symptoms and bronchoscopic findings (9). This was done to get insight into the problems faced by these kids and improve the quality of treatment they receive. This retrospective investigation was conducted in a real-world setting, therefore we relied on patient and parent reports of clinical symptoms to inform our diagnostic approach. Here's something we think you should know about. Consistent with previous studies (10), we observed that EA with distal TEF (Gross type C) was the most common kind of EA in our population of interest.

The frequency with which EA patients encounter leaky anastomosis is not reported in the scientific literature. Our data suggest that this temporary digestive problem is twice as common among children originally treated at our facility as it is among those initially treated at other facilities. Because not enough is known about the second group of kids and the post-operative difficulties that matter to them, this observation is likely exaggerated. The mentioned anastomosis leak, which was always controlled with attention, does not seem to be related to breathing issues (33-35). If we focus just on the long-term digestive difficulties, we discover that 18% to 60% of individuals with EA suffer from esophageal stricture and gastroesophageal reflux disease (GER).

Children with symptoms such as nausea, vomiting, dysphagia, or failure to grow were examined to rule out gastroesophageal reflux disease (GER), which is often diagnosed with pH impedance. Our data shows that Nissen fundoplication is more common in children who had their first surgical procedure performed at a facility other than our own. Maybe the increased clinical complexity acquired in the postoperative period among this group of children explains why they were sent to our facility, and hence influences our findings. The fact that these kids had a harder difficulty getting well after surgery is a symbol of the prejudice they faced.

As compared to the rates normally reported in the scientific literature, we find a reduced prevalence of atopy (38). Sistonen et al. (38) found that this rate was independently linked to a greater risk of lower respiratory problems, which was in line with expectations.

Even if heart disease symptoms manifest in a kid beyond the age of three, this may be regarded as a premature onset. Reducing the threshold of the bronchial reactivity that is organically connected to the congenital malformation image, heart illness (39, 40) and atopy possibly expedites the development of symptoms. This adds to respiratory morbidity. Recurrent pneumonia and wheezing are the most prevalent respiratory symptoms in the first three years of life, with rates consistent with those described by other authors (41). The only exception is if the patient develops aspiration pneumonia right after surgery. The significant delay in sending children with breathing problems to a specialist like a pulmonologist is one of the most surprising results of our study. The delay is likely due to the incorrect diagnosis of respiratory issues as being caused by gastroesophageal reflux, a disease for which some patients were first treated with pharmaceutical treatment and subsequently had surgical surgery. When it was clear that the aforementioned measures had been exhausted without improvement, only then would a child be sent to a pediatric respiratory expert. Several studies have linked tracheomalacia, residual tracheal diverticulum, and recurrent TEF to the worsening of respiratory symptoms in the lower respiratory tract (42-45). The three factors have worked together to get this result.

The prevalence of tracheomalacia was in line with reports in the medical literature (9, 16). Little case series have shown the occurrence of a persistent tracheal diverticulum in newborns after EA and TEF treatment, making it impossible to offer an accurate assessment of the real prevalence of this complication.

In our research group, a chest CT scan with contrast enhancement may aid in the search for vascular abnormalities, tracheal compression, and esophageal diverticulum that would not be seen with flexible bronchoscopy alone. As for the second scenario, the greater mean age of the recruited patients is likely to be the driving factor behind the increased incidence of bronchiectasis, which might explain the induction of lung damage. In the second case, this was visible. Restrictive ventilatory impairment is more prevalent than obstructive and mixed kinds in patients with EA and TEF (30). Improved knowledge of impaired pulmonary function

is gained by patients with EA and TEF. Surgical trauma, frequent aspiration, or recurring chest infections may have contributed to the patient's breathing limitation by causing concurrent thoracic musculoskeletal defects. Aspiration, if done too often, may lead to restriction as well. While evaluating the provided data, it is important to remember the caveats of such a backward look

Limitations

The evaluated patients were solely surgically treated at our institution, and children who travelled from other institutions generally showed a larger clinical complexity due to complications that arose after surgery. We also cannot be sure that individuals who were not evaluated had normal findings on bronchoscopy, thorax CT, impedance testing, and spirometry, so the prevalence of abnormality we estimate is likely lower than it is.

Consistent surveillance techniques and careful monitoring of these patients from birth forward are strongly recommended, in light of our findings. Nevertheless, there are currently no recommendations for the respiratory management of infants and young children with EA and TEF, despite the fact that this issue is well-recognized and deserves attention from a wide range of specialists. Patients with moderate to severe airway disease should be followed up with regularly, as recommended by the solely published algorithm (32), which recommends stratifying disease severity based on the recurrence of respiratory symptoms.

Nonetheless, beyond the first year of life, we believe that all children should be assessed in a multidisciplinary paediatric setting at least every six months up to the age of 36 to assess their clinical history, growth, and relevant symptoms.

Dietitians, cardiologists, otolaryngologists, neuropsychiatrists, orthopedists, and physiotherapists may all be consulted when dealing with conditions such as gastrointestinal distress, stunted growth, cardiac or airway abnormalities, neuromotor delay, and congenital or acquired skeletal malformations. A comprehensive assessment of the respiratory system is necessary when symptoms such as repeated bouts of pneumonia, bronchitis, wheezing, a persistent wet cough, nocturnal apnea, and exercise intolerance manifest. A pulmonologist should also be consulted for children who have had tracheostomy surgery, have severe tracheomalacia, or have abnormalities on thoracic imaging. When pneumonia is suspected or when determining a lung baseline, a chest X-ray should be taken as part of the respiratory examination. The overnight pulse oximeter and the forced oscillation method only need to be performed once a year (FOT). The first one would signal desaturations that need additional evaluation to rule out cardiac, central, or obstructive respiratory events. There is potential for using FOT to monitor pulmonary function in preschoolers since it provides concordant information on lung function compared to other conventional techniques (45). The proposed clinical evaluation seeks to reduce breathing difficulties with medication and chest physical therapy, prevent lower respiratory exacerbation with early antibiotic therapy, and collect data that will lead the clinician to suspect an underlying condition responsible for the persistence of symptoms and warrant further investigations, such as bronchoscopy and CT scan. Angiography should be performed as a follow-up to a thorax CT scan since 20% of patients will have underlying vascular abnormalities that will influence the degree to which their airway is constrained.

Past research results have shown that Feeding Difficulty is related to inflammation (46,47).

In this regard, the relationship between asthma in children and inflammation was previously reported (48,49).

Despite the prevalence of respiratory symptoms and aberrant findings revealed by flexible bronchoscopy and CT scan, it is usual practice to ascribe them to reflux and esophageal defects in children. Symptoms may be made worse by gastroesophageal reflux, although this disease cannot be blamed on reflux alone. Respiratory symptoms may return due to tracheal pouch formation, recurrent tracheoesophageal fistula, or persistent tracheomalacia (TEF). In order to decide on the best surgical or medicinal therapy to avoid respiratory exacerbations and long-term dysfunctions, it is important to first discover the underlying diseases that cause them. As high bronchial reactivity may trigger and perpetuate a "vicious loop" that further impairs respiratory outcomes, thorough monitoring of patients must be carried out at least in the first three years of life, with a particular focus on children who have heart illness and atopy status. Children in an atopy condition need to be monitored in this way. Thus, this population of patients must be treated by a multidisciplinary team that includes a pulmonologist in order to better control their condition and to harmonise their treatment, since children whose cells have EA and TEF have connected diagnoses from many systems.

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