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Comorbidity and long-term clinical outcome of laryngotracheal clefts types III and IV: Systematic analysis of new cases

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Abstract

Background: Long segment laryngotracheoesophageal clefts (LTECs) are very rare large-airway malformations. Over the last 40 years mortality rates declined substantially due to improved intensive care and surgical procedures. Nevertheless, long-term morbidity, comorbidity, and clinical outcomes have rarely been assessed systematically.

Methods: In this retrospective case series, the clinical presentation, comorbidities, treatment, and clinical outcomes of all children with long-segment LTEC that were seen at our department in the last 15 years were collected and analyzed systematically.

Results: Nine children were diagnosed with long segment LTEC (four children with LTEC type III and five patients with LTEC type IV). All children had additional tracheobronchial, gastrointestinal, or cardiac malformations. Tracheostomy for long-time ventilation and jejunostomy for adequate nutrition was necessary in all cases. During follow-up one child died from multiorgan failure due to sepsis at the age of 43 days. The clinical course of the other eight children (median follow-up time 5.2 years) was stable. Relapses of the cleft, recurrent aspirations, and respiratory tract infections led to repeated hospital admissions.

Conclusions: Long-segment LTECs are consistently associated with additional malformations, which substantially influence long-term morbidity. For optimal management, a multidisciplinary approach is essential.

KEYWORDS

aspiration, home mechanical ventilation, laryngeal cleft, laryngotracheoesophageal cleft, pediatrics, swallowing dysfunction

1 | INTRODUCTION

Laryngotracheoesophageal clefts (LTEC) are rare malformations initially described by Richter in 1792.[1] Incidence ranges from 1:10,000 to 1:20,000 with a male predominance.[2–5] As most cases are sporadic, the etiology of LTEC is considered multifactorial.[4,6] Leading symptoms are neonatal respiratory distress, inspiratory stridor, hoarseness, chronic cough, recurrent aspirations, recurrent pulmonary infections, and dysphagia.[7–11] Variable mortality rates have been published over the years for long segment LTEC and declined substantially from over 90% in the early 1980s to 50% in more recent series.[12–14]

A variety of classifications for LTEC have been published. The most widely used classification was proposed by Benjamin and Inglis[8] in 1989 and is based on the caudal extension of the LTEC (Figure 1). It divides LTEC into four types: (1) type I extends to the level of the vocal cords, (2) type II extends below the vocal cords into the cricoid cartilage, (3) type III extends through the cricoid cartilage to the cervical trachea/esophagus, and (4) type IV extends to the level of the thoracic trachea.[15] To differentiate long segment LTEC types III and IV, the level of the thoracic inlet in relation to the distal cleft extension needs to be determined by endoscopy.[3] Other classifications are used less often.[6,15]

The embryological development of LTEC is not fully understood. Two contrasting theories exist explaining how the normal respiratory system is separated from the gastrointestinal tract.[16] According to these long segment LTECs may be (1) the result of apoptosis of a primary existing separation or (2) deficient separation of two primary connected tubes.[4,14,17–22]

The goal of surgical treatment is to resolve impaired feeding and minimize respiratory complications, which may be achieved only in a stepwise approach. Endoscopic or open techniques have been published.[2–4,12,17,23–25] For long segment LTEC, an open surgical approach is the mainstay. An endoscopic cleft repair can be considered when adequate visualization can be achieved,[25] tubeless anesthesia with or without spontaneous ventilation or jet-ventilation is possible[26] limiting the endoscopic approach mostly to patients with no or restricted involvement of the trachea (mostly LTEC type I or II and in certain exceptional cases LTEC III).[10,15,27]

Only small case series and single case reports have been published, focusing on various surgical procedures and mortality. To our knowledge, no comprehensive study about long-term morbidity has been published before. The goal of this analysis is to report comorbidities, morbidity, and long-term clinical outcome in a comprehensive fashion.

2 | METHODS

2.1 | Study cohort

We identified children diagnosed with long segment LTEC by going consecutively through all surgical reports of children admitted to our department from 2004 to 2020. Diagnosis and classification were made with rigid bronchoscopy by determining the distal cleft extension in relation to the thoracic inlet. Clinical information was collected retrospectively from the clinical charts. All children underwent structured evaluation by a pediatric pneumologist, gastroenterologist, nutrition expert, and cardiologist. Demographic data, information on the clinical presentation, comorbidities, time from symptom onset to diagnosis, treatment, and clinical outcome data were collected.

2.2 | Statistics and ethics statement

All data were anonymized and analyzed retrospectively. Due to the small number of included patients, for reliable results only descriptive statistics were performed. Values are indicated as median and ranges. The study was approved by the Ethics Commission at the Ludwig-Maximilians University of Munich, München (EK250311).

3 | RESULTS

3.1 | Study cohort

Between 2004 and 2020, nine children (four with LTEC type III and five with LTEC type IV) were seen at our department (Table 1a,b). Five children were male and four females. More than half (5/9) of the children were born preterm. In six patients, a prenatal polyhydramnion was reported, and seven patients were born via cesarean section. In all patients, the diagnosis was made within the first 4 weeks of life (median: 5 days, range: 2–28 days) suspected after recurrent aspirations, repeatedly misplaced tracheal tubes, or a malformed larynx seen during first intubation.

3.2 | Comorbidities

Comorbidities were diagnosed in every child. In three children an underlying genetic syndrome was identified (Opitz G/BBB syndrome, trisomy 21, and monosomy 18) and in two suspected due to the combination of LTEC IV and comorbidities, but no pathogenic variant was found. Tracheomalacia was diagnosed in every child with additional tracheobronchial malformations in four patients (3× shortened trachea or bronchus intermedius, 1× hypoplastic left main bronchus). Dysphagia and gastroesophageal reflux were present in every patient, microgastria in four patients diagnosed by barium swallow test. Additionally, a Meckel's diverticulum and intestinal nonrotation were found in two children. Every child was born with a congenital heart defect (seven children with atrial septal defect type II, four with ventricular septal defect). Two children developed hydrocephalus internus (one of unknown cause, the other after intracerebral hemorrhage III°); in two other children seizures were noted.

TABLE 1 Patient characteristics

(a)

	Patient 1	Patient 2	Patient 3	Patient 4
General information				
Gender	Female	Male	Female	Male
Cleft type[a]	III	III	III	III
Distance from carina (mm)	35.0	22.0	20.0	26
Age at bronchoscopy (days)	24	27	19	3
Neonatal history				
Polyhydramnios	No	nk	No	Yes
Cesarean section	Yes	Yes	Yes	No
Gestational age (weeks)	31 + 6	38 + 3	38 + 0	39 + 0
Postnatal respiratory support/ form of respiratory support	Yes/invasive ventilation	Yes/CPAP ventilation	Yes/invasive ventilation	Yes/invasive ventilation
Birth weight (g/z-score[b])	1735/−0.01	3150/0.54	2820/−1.12	4310/−0.17
Birth length (cm/z-score[b])	45/0.78	49/−1.06	45/−2.65	56/1.78
Head circumference (cm/z-score[b])	29.0/0.35	34.0/−0.80	nk	38.5/2.46
Comorbidity				
Genetic syndrome	No	Opitz G/BBB	M. Down	No
Bronchial malformation	Yes	Yes	No	No
Tracheomalacia	Yes	Yes	Yes	Yes
Dysphagia	Yes	Yes	Yes	Yes
Gastroesophageal reflux	Yes	Yes	Yes	Yes
Gastrointestinal tract	Microgastria	Microgastria	No	No
Structural heart defect	ASD II, VSD	VSD	VSD	ASD II
Nervous system	No	No	No	Seizure
Treatment				
Age at tracheal surgery	43 days	57 days	55 days	10 days
Tracheostomy	Yes	Yes	Yes	Yes
Jejunostomy	Yes	Yes	Yes	Yes
Outcome				
Period of follow-up	3.9 years	10.9 years	15.5 years	6.0 months
Clinical course	Clinically stable	Clinically stable	Clinically stable	Clinically stable
Relapse	Yes	Yes	Yes	Yes
Duration of invasive ventilation	24 months	Ongoing	Ongoing	Ongoing
Recurrent aspirations	Yes	No	Yes	Yes
Hospitalization due to respiratory tract infection	Yes	Yes	Yes	Yes
Body weight at follow-up (z-score[b])	−1.37	−1.28	−4.88	−0.13
Neurological development at follow-up	Normal development	Motor function and cognitive deficits	Cognitive deficits	Normal development

(b)

	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
General information					
Gender	Female	Male	Male	Female	Male
Cleft type[a]	IV	IV	IV	IV	IV
Distance from carina (mm)	2.5	0.7	8.0	8.0	8.0
Age at bronchoscopy (days)	11	1	4	3	3

TABLE 1 (Continued)

(b)

	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Neonatal history					
Polyhydramnios	Yes	Yes	Yes	Yes	Yes
Cesarean section	Yes	Yes	Yes	No	Yes
Gestational age (weeks)	36 + 2	30 + 4	37 + 1	32 + 2	35 + 5
Postnatal respiratory support/ form of respiratory support	Yes/invasive ventilation	Yes/invasive ventilation	Yes/invasive ventilation	Yes/invasive ventilation	Yes/invasive ventilation
Birth weight (g/z-score[b])	2720/−0.22	1680/0.37	2716/−0.94	1350/−1.23	2100/−1.58
Birth length (cm/z-score[b])	48/−0.29	42.5/0.4	52/0.70	40/−0.93	45/−1.42
Head circumference (cm/z-score[b])	34.0/0.35	30.4/0.68	34.0/−0.32	29.5/−0.29	31/−1.62
Comorbidity					
Genetic syndrome	No	Suspected	No	Monosomy 18	Suspected
Bronchial malformation	Yes	nk	Yes	No	No
Tracheomalacia	Yes	nk	Yes	Yes	Yes
Dysphagia	Yes	nk	Yes	Yes	Yes
Gastroesophageal reflux	Yes	Yes	Yes	Yes	Yes
Gastrointestinal tract	Microgastria	Microgastria, pancreas aplasia	Microgastria, Meckel's diverticulum	No	Intestinal nonrotation
Structural heart defect	ASD II	ASD II	ASD II	ASD II	ASD II, VSD
Nervous system	Hydrocephalus internus	Seizures	No	ICH III° with hydrocephalus internus	Enlarged subarachnoid space
Treatment					
Age at tracheal surgery	13 days	3 days	9 days	38 days	7 days
Tracheostomy	Yes	Planned	Yes	Yes	Yes
Jejunostomy	Yes	Yes	Yes	Yes	Yes
Outcome					
Period of follow-up	3.2 years	34 days	6.9 years	9.2 months	6.4 years
Clinical course	Clinically stable	Deceased	Clinically stable	Clinically stable	Clinically stable
Relapse	Yes	–	No	Yes	No
Duration of invasive ventilation	Ongoing	Until death	Ongoing	Ongoing	Ongoing
Recurrent aspirations	Yes	Yes	Yes	Yes	Yes
Hospitalization due to respiratory tract infection	Yes	Yes	Yes	Yes	Yes
Body weight at follow-up (z-score[b])	−1.97	−11.3	−0.3	−2.69	−1.18
Neurological development at follow-up	Delayed neurological development	Normal development	Delayed neurological development	Motor function and cognitive deficits	Motor function and cognitive deficits

Abbreviations: ASD, atrium septum defect; CPAP, continuous positive airway pressure; ICH, intracerebral hemorrhage; nk, not known; VSD, ventricle septum defect.
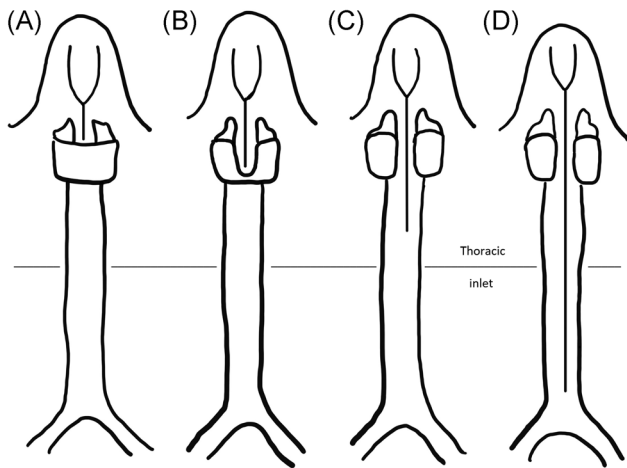
[a]According to Benjamin and Inglis.[8]

[b]The data for z-scores were taken from Fenton et al.[29]

3.3 | Treatment

Due to respiratory insufficiency, all patients needed respiratory support after birth: eight invasive and one non-invasive ventilation. For long-term mechanical ventilation, tracheostomy was planned for all children but only performed in seven, as one child died before the intervention. Due to gastrointestinal comorbidities (dysphagia, gastroesophageal reflux, and microgastria) in all children a jejunostomy was placed to ensure adequate nutrition.

FIGURE 1 Proposed classification for laryngeal clefts by Benjamin and Inglis.[8] (A) Type I extends to the level of vocal cords, (B) type II extends below vocal cords into cricoid cartilage, (C) type III extends through cricoid cartilage to cervical trachea/esophagus, and (D) type IV extends to the level of thoracic trachea.

In the children diagnosed with LTEC type III tracheal surgery was performed within the first 2 months of life, in children with LTEC type IV within the first 4 weeks. In six patients, a stepwise surgical approach for the repair of the tracheal cleft was undertaken. First, the tracheoesophageal cleft was repaired up to the larynx; 6–20 weeks later, after the patients had gained weight and were in a cardiorespiratory stable condition, the laryngeal cleft was closed. In three patients, a complete cleft repair was performed during one surgical intervention. In two patients where a stable respiratory situation was difficult to achieve, jejunostomy was performed in combination with a gastric inlet ligation as a first surgical intervention to exclude gastroesophageal reflux and reduce gas leakage complicating mechanical ventilation. The gastric ligation was removed later during the final repair of the tracheal cleft.

3.4 | Clinical course and outcome

In all except one case, the long-term courses were reported as clinically stable at the last follow-up visit. One patient died from multiorgan failure due to sepsis at the age of 43 days. Follow-up data of eight surviving patients were available (median: 5.2 years, range: 0.51–15.7 years). Relapses of the cleft restricted to the larynx occurred in all but two patients. Due to severe tracheomalacia at the time of the latest follow-up visit all children except one (duration of invasive ventilation 24 months) were still on home mechanical ventilation due to tracheomalacia and in some cases additional bronchial malformations. For all but one child recurrent aspirations were reported and repeated hospitalizations due to recurrent respiratory tract infections and pneumonias were necessary for all patients. Except in two patients, poor weight gain was noted in every patient (median z-score for weight at the last follow-up: −1.67, range: −11.3

to −0.13) despite high-calorie nutrition via jejunostomy tubes. At the last follow-up, three children were reported with a normal neurological development, two children with delayed psychomotor development, and four with motor function and cognitive defects. Of note, in half of the patients, obstruction or dislocation of the tracheostomy cannula led to resuscitation events without further sequelae.

4 | DISCUSSION

In this study, we have analyzed a cohort of children diagnosed with long segment LTEC types III and IV. Key findings were that (1) all patients had additional tracheobronchial, gastrointestinal, or cardiac malformations, (2) almost half of the patients were diagnosed with a genetic syndrome, (3) mortality rate decreased compared to previous reports, (4) long-term morbidity is substantial although (5) a good clinical long-term outcome can be achieved in the majority of cases. Additionally, we have reviewed and compiled all cases reported in the literature up to now (Table 2) and compared those data to the findings of the present report (Table S1a,b). Overall there was good agreement of our findings with the published data. However, there were several areas of interest and novelty.

In our cohort we found a strong association between long segment LTECs and additional comorbidities (Table 2). This is in line with previously published data reporting an absence of additional malformations in only a small proportion of patients. Although a coincidental association of these different conditions cannot be excluded, this seems unlikely due to the rarity of the single diseases. We were able to identify a genetic syndrome more often than published before. Taken together, it may be speculated that long segment LTEC could be the cause or consequence of a more extended developmental disturbance and not an entity in itself.

Compared with published cases, children in our cohort were more often preterm. Furthermore, in our cohort only one patient died during the neonatal period following sepsis with multiorgan failure, whereas much higher mortality rates are published. We assume that a multidisciplinary team with improved intensive care, advanced surgical procedures, and increased awareness of associated malformations contribute most to reduce the previously reported high mortality rate in the neonatal period.[12–14]

All patients suffered from severe tracheomalacia, making a tracheostomy for long-term mechanical ventilation necessary, although we did not notice severe chronic lung disease or neuromuscular weakness. The tracheomalacia remains significant after surgery due to the abnormal tracheal wall structure and often-occurring redundancy of the surgically created posterior tracheal wall.[14] Due to cleft relapse and pulmonary infections, repeated hospitalizations were necessary. We think that persistent gastroesophageal reflux found in every patient of our cohort might be a major contributing factor and therefore should be treated early. Furthermore, every patient of our cohort was diagnosed with dysphagia and almost half of the children with microgastria. It has to be noted that yet failure to thrive was present in seven of the children despite jejunostomy,

TABLE 2 Studies on laryngeal clefts types III and IV until 2020

	Type III	Type IV	Type III + IV	This study
Published cases	36	60	96	9
Sex	76% male	62% male	67% male	56% male
	24% female	38% female	33% female	44% male
Birth	26% preterm	38% preterm	33% preterm	56% preterm
Outcome				
Clinically stable	71%	34%	46%	89%
Deceased	29%	66%	54%	11%
Disease associated	75%	88%	87%	100%
Surgery associated	25%	12%	13%	0%
Recurrent aspirations	94%	100%	97%	100%
Tracheostoma	71%	89%	80%	100%
Long time ventilation	43%	81%	61%	100%
Gastrostomy/PEG	67%	90%	80%	100%
Jejunostomy/PEJ	20%	45%	33%	100%
Genetic syndromes	19%	10%	13%	44%
No malformations	4%	1%	2%	0%
Gastrointestinal malformations	24%	32%	29%	55%
Micorgastria	50%	79%	58%	80%
Bronchial malformations	19%	28%	25%	88%
Cardiovascular malformations	13%	16%	15%	100%
CoA	0%	40%	33%	0%
VSD	50%	20%	25%	44%
ASD	0%	20%	17%	77%
Urogenital malformations	12%	7%	9%	0%
Deficient neurological development	13%	8%	10%	77%
Skeletal malformations	14%	7%	10%	0%
Diaphragmatic hernia	3%	4%	3%	0%

Abbreviations: ASD, atrial septal defect; CoA, coarctation of the aorta; PDA, patent ductus arteriosus; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; VSD, ventricular septal defect.

high-calorie nutrition, and absence of intestinal problems. A recent study found coexisting neuromuscular dysfunction or dyscoordination in patients with LTECs contributing to dysphagia and aspiration.[28] This is in accordance with our findings reporting normal neurological development in less than half of the patients. Finally, congenital heart defects were reported more often in our cohort. Therefore, echocardiography should be performed early.

Our patient cohort indicates that a stable long-term clinical outcome can be achieved. Morbidity was mostly influenced by (1) aspirations and recurrent respiratory tract infection and (2) often-occurring relapses of the cleft.[2–4,23,25]

We did not find relevant differences regarding additional malformations between LTEC III and IV (Table 2). As other authors have noted,[15] the LTEC III patients in our series may confirm the heterogeneity of this group where more extensive type III lesions show substantial more comorbidity than type III lesions with less distal extension of the cleft.

This study has several limitations. The data were collected retrospectively, therefore the clinical management was variable. Furthermore, although we report severe morbidity caused by additional malformations and often occurring relapses, it is not possible to draw conclusions to the quality of life as we did not analyze patient or caregiver-reported outcomes. Recommendations for optimal medical care derived from this study should be handled carefully as the sample size of only nine patients is small. Nevertheless, our findings were put into the perspective of a review of all published cases and focus on morbidity and long-term outcomes in contrast to previous publications, mainly concentrating on various surgical procedures.

In summary, long segment LTECs are mostly associated with additional tracheobronchial, gastrointestinal, and cardiac malformations that have a major influence on morbidity, although low mortality can be achieved. We suggest that for optimal long-term outcome, patients should be followed carefully by a multidisciplinary team.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization, data curation, and writing (original draft): Elias Seidl. *Conceptualization and writing (review and editing)*: Karl Reiter, Jochen Hubertus, Dietrich von Schweinitz, Matthias Griese, Matthias Kappler, Florian Hoffmann, and Carola Schön. *Supervision*: Karl Reiter. *Data curation*: Johanna Kramer and Karl Reiter. *Conceptualization*: Diana Di Dio, Christian Sittel and Carola Schön.

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