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
Laryngotracheoesophageal clefts (LTEC) are rare malformations initially described by Richter in 1792. Incidence ranges from 1:10,000 to 1:20,000 with a male predominance. As most cases are sporadic, the etiology of LTEC is considered multifactorial. Leading symptoms are neonatal respiratory distress, inspiratory stridor, hoarseness, chronic cough, recurrent aspirations, recurrent pulmonary infections, and dysphagia. 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.

A variety of classifications for LTEC have been published. The most widely used classification was proposed by Benjamin and Inglis 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. 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. Other classifications are used less often.

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. 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. For long segment LTEC, an open surgical approach is the mainstay. An endoscopic cleft repair can be considered when adequate visualization can be achieved, 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).

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.

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

| **(b)**                          |                        |
| **General information**          |                        |
| Gender                          | Female | Patient 5 | Male | Patient 6 | Male | Patient 7 | Female | Patient 8 | Male | Patient 9 |
| Cleft type<sup>a</sup>           | IV  | Patient 5 | IV  | Patient 6 | IV  | Patient 7 | IV  | Patient 8 | IV  | Patient 9 |
| Distance from carina (mm)        | 2.5 | Patient 5 | 0.7 | Patient 6 | 8.0 | Patient 7 | 8.0 | Patient 8 | 8.0 | Patient 9 |
| Age at bronchoscopy (days)       | 11  | Patient 5 | 1   | Patient 6 | 4   | Patient 7 | 3   | Patient 8 | 3   | Patient 9 |
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.

| TABLE 1 (Continued) |
|----------------------|
| **Neonatal history** |
| Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 |
| 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) | 2720/−0.22 | 1680/0.37 | 2716/−0.94 | 1350/−1.23 | 2100/−1.58 |
| Birth length (cm/z-score) | 48/−0.29 | 42.5/0.4 | 52/0.70 | 40/−0.93 | 45/−1.42 |
| Head circumference (cm/z-score) | 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) | −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.

*According to Benjamin and Inglis.8

*The data for z-scores were taken from Fenton et al.29
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.

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. 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,
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. 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. We did not find relevant differences regarding additional malformations between LTEC III and IV (Table 2). As other authors have noted, 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.
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**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% female |
| 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.
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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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