Laryngotracheoesophageal Cleft Type IV in a Preterm Neonate. A Case Report and Literature Review

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Abstract: We present a case of a preterm neonate with a type IV laryngo-tracheo-oesophageal cleft, an uncommon congenital malformation, resulting from the failure of separation of the trachea and the oesophagus during fetal development, often associated with other deformities as well. Data in the literature shows that the long-term morbidity from the entity has declined over the last decades, even though prognosis remains unfavourable for types III and IV. This report emphasizes the complex issues neonatologists are faced with, when treating neonates with this rare disorder in the first days of life, what will raise suspicion of this rare medical entity, and that direct laryngoscopy/bronchoscopy finally depicts the exact extension of the medical condition. At the same time extensive evaluation for coexisting congenital anomalies should be performed. For all the above reasons, these neonates should be treated in specialized tertiary pediatric centers for multidisciplinary prompt management, which may improve, the outcome.

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Introduction

Laryngo-tracheo-oesophageal cleft (LTC) is a rare congenital anomaly, characterized by deficient anatomical separation of the oesophagus and the upper respiratory tract, at the level of the larynx and trachea. The incidence varies from 1 in 10,000 to 20,000 live births, with a male:female ratio of 5:3 (Griffith and Liversedge, 2014). The first reported case was made by Richter in 1792 in a newborn with feeding difficulties and recurrent aspiration (Richter, 1792; Benjamin and Inglis, 1989; Griffith and Liversedge, 2014). Laryngeal clefts comprise 0.3–0.5% of all the congenital anomalies of the larynx (Griffith and Liversedge, 2014). The classification into 4 types of clefts, as proposed by Benjamin and Inglis in 1989, is the most commonly used, as depicted in Figure 1.

Type I is a supraglottic cleft, above the vocal cords. Type II is a partial cricoid cleft, below the level of the vocal cords. Type III is a total cricoid cleft, extending through the cricoid cartilage to the cervical trachea/oesophagus. Type IV is

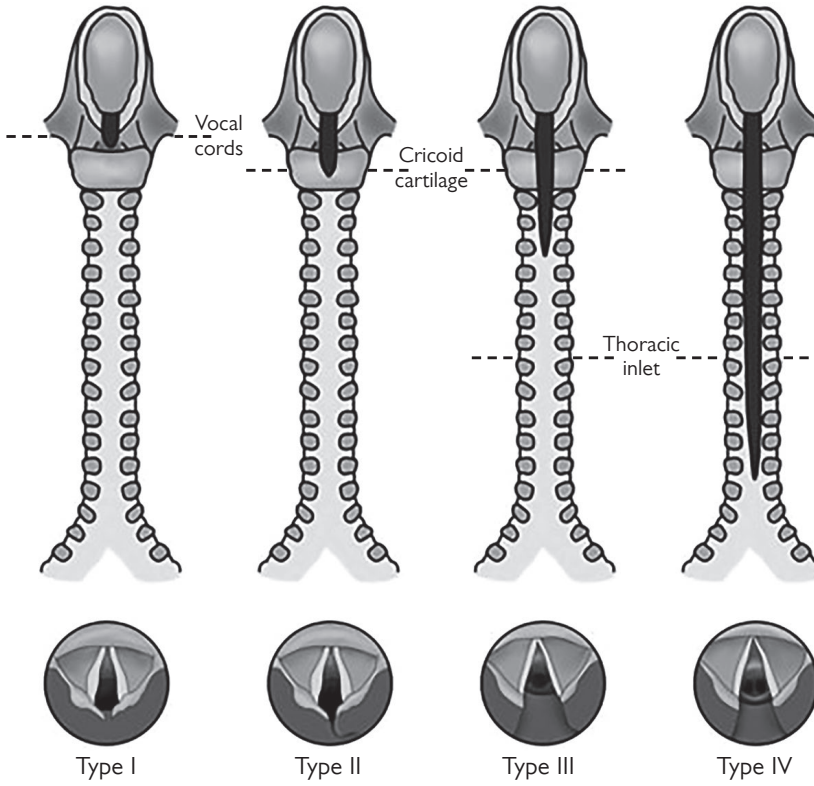

Figure 1 – Types I–IV of laryngo-tracheo-oesophageal cleft based on the classification of Benjamin and Inglis (1989).

a laryngo-esophageal cleft extending to the thoracic trachea (Benjamin and Inglis, 1989). Significant controversy surrounds the embryological origin of trachea-oesophageal anomalies. A traditional theory suggests that the separation of the foregut is the result of merging of the lateral ridges arising from the lateral foregut wall. This process begins cranially and extends caudally and thus a septum is created, dividing the foregut into a ventral component, the laryngotracheal tube and a dorsal component, the oesophagus (His, 1880; Merei and Hutson, 2002). In 1984, O'Rahilly and Müller used a "respiratory tap" analogy to describe the formation of the respiratory tract. According to their theory, the pulmonary anlage, arising ventrally from the foregut mesenchyma, extends caudally forming in the process the tracheoesophageal septum. Later Kluth et al. (1987) indicated that the respiratory diverticulum arises from the ventral aspect of the foregut and continues to elongate, forming a stalk from which the trachea will develop. In 2009 Brown and James in a systematic review of the literature proposed that the trachea and oesophagus develop from 2 completely different parts of the trilaminar embryonic disc, but due to the cephalic folding, they approximate and form a common tracheoesophageal chamber that is later divided. In other words, the respiratory primordium is formed *in situ* as a ventral component of the foregut and does not consist of a protrusion of the gut. Disruptions during the embryonic development of the tracheobronchial system and the oesophagus can lead to various anatomical deformities of the area (Jöhr et al., 2003).

Aspiration episodes and airway obstruction are the usual clinical signs of a tracheal cleft. The clinical presentation depends on the type and extend of the cleft, and on other coexisting congenital anomalies (Jorgensen et al., 2018). Infants with type I usually have non-specific symptoms, such as stridor, feeding difficulties or swallowing disorders, and may remain undiagnosed for a long period. Infants with types II and III present with pulmonary tract infections, due to significant aspiration (Leboulanger and Garabédian, 2011). Infants with type IV cleft display the most serious clinical presentation, with early respiratory distress and difficulty in maintaining mechanical ventilation.

Congenital malformation of the gastrointestinal tract (16–67%) (Leboulanger and Garabédian, 2011), such as trachea-oesophageal fistulae, oesophageal atresia or anal atresia are the most common coexisting anomalies (Roth et al., 1983). Congenital malformations from the respiratory tract (2–9%), the cardiovascular system (16–33%), the genitourinary tract (14–44%), as well as the craniofacial malformations (5–15%) are less frequent (Leboulanger and Garabédian, 2011). Laryngeal cleft may represent a congenital malformation within the context of various syndromes, such as the Opitz G/BBB syndrome (50% of children with this syndrome have a LTC [Shehab and Bailey, 2001]), 22q11 monosomy, the Pallister Hall syndrome, the VATER/VACTERL association, the CHARGE syndrome (Leboulanger and Garabédian, 2011), DiGeorge, Cayler cardiofacial and velocardiofacial syndrome (Griffith and Liversedge, 2014).

Endoscopy sets the diagnosis of LTC, makes possible the differential diagnosis for various other medical conditions, and may also reveal other coexisting malformations (Leboulanger and Garabédian, 2011).

Management of LTC depends on the type of cleft. First of all, satisfactory ventilation must be maintained, for which endotracheal intubation may be needed (Leboulanger and Garabédian, 2011). In types III and IV, adequate nutrition of the baby via a nasogastric tube or with parenteral nutrition (due to high risk of aspiration), may be required (Seidl et al., 2021). As for the closing of the cleft, various techniques have been published, both endoscopically and by open surgical approach (Seidl et al., 2021). For types III and IV an open surgical approach is the mainstay (Seidl et al., 2021).

We aimed at presenting a premature neonate, admitted to a tertiary neonatal intensive care unit, with the diagnosis of LTC type IV, based on the classification of Benjamin and Inglis (1989). This case provides educational points on the clinical signs and conditions, that could aid the neonatologist to make a prompt diagnosis of this rare developmental anomaly. We focus on the difficulties while treating the patient and the team-oriented management that is crucial for optimizing the outcome of this uncommon, yet ominous deformity.

Case report

A 32-week of gestation female neonate with birth weight of 1,470 g was born to a healthy 38-year-old Gravida 2 Para 1 mother, via an emergency caesarean section due to non-reassuring fetal status. Pregnancy was uneventful until 28 weeks when oral glucose tolerance test (OGTT) confirmed gestational diabetes mellitus, and ultrasonography showed polyhydramnios (confirmed at the caesarean section) with absent fetal stomach. At birth the neonate was floppy, apneic with heart rate < 100 beats/min. Resuscitation with sustained inflation was provided with inadequate response, and the neonate was intubated with great difficulty by the attending neonatologist with a size 3 endotracheal tube (ET). On admission to neonatal intensive care unit (NICU), the neonate was connected on a ventilator on volume guarantee mode. The achievement of delivering appropriate tidal volume to the neonate was impossible, and large air leak of 80–90% was recorded. Due to vigorous respiratory effort of the neonate, ventilation mode was changed to pressure control. In order to confirm or to rule out oesophegeal atresia, a size 6-8FR nasogastric tube (NGT) was sited with great difficulty as well. Chest X-ray showed air in the stomach, and the tip of NGT *in situ* (Figure 2).

Early after birth, the neonate developed respiratory distress and received one dose of surfactant, maintaining adequate respiratory drive thereafter. Vital signs and physical examination were otherwise normal. The difficult intubation procedure

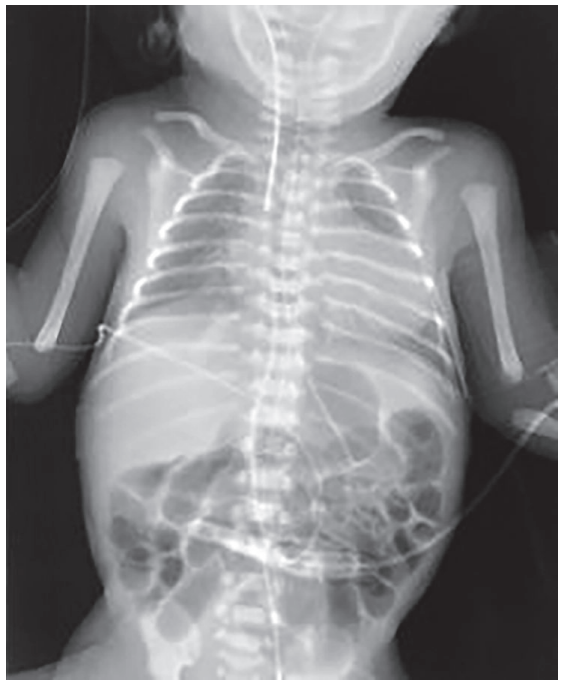

Figure 2 – Chest X-ray with nasogastric tube into the stomach.

with a large air leak, and the aspiration of gastric content during endotracheal suctioning raised the suspicion of H-type tracheoesophageal fistula. Pediatric surgical consultation was carried out, and a barium swallow study was scheduled for the next day, provided that the patient's clinical condition would be permissive. However, during the ensuing hours the neonate's pulmonary status gradually deteriorated, and the barium swallow study was deferred. Echocardiography and abdominal ultrasonography were normal, and cranial ultrasonography depicted grade II intraventricular hemorrhage. Reintubation, following accidental extubation, on the 3rd day of life proved to be a challenge. Abnormal upper airway anatomy and inability to visualize the entry of the trachea and oesophagus raised suspicion of a laryngeal cleft. The infant was transferred to a tertiary pediatric hospital for diagnostic laryngotracheobronchoscopy by pediatric specialists. The next day, after accidental extubation, the neonate developed pneumothorax, while multiple attempts for reintubation were performed. At laryngoscopy, the diagnosis of laryngeal cleft type IV was confirmed by otolaryngologist (ear, nose, throat – ENT). Unfortunately, due to the severity of the neonate's condition no documentation of the endoscopic examination was obtained. Soon after, the patient died, prior to genetic counselling that had been scheduled. Parents did not consent to postmortem examination.

Discussion

We present a case of a premature neonate, with type IV laryngo-tracheo-oesophageal cleft, a rare congenital malformation which to the best of our knowledge, is the first to be reported in Greece.

Laryngo-tracheo-oesophageal cleft is often associated with other congenital anomalies, such as tracheobronchial, gastrointestinal and cardiac malformations (Seidl et al., 2021). Seidl et al. (2021) reported that half (4 patients out of 9) of their cohort, were diagnosed with a genetic syndrome. Unfortunately, in our case, no genetic counselling was performed. Type IV LTC is the rarest form of laryngeal clefts and carries the worst prognosis. Martha et al. (2021) in a literature review of laryngeal cleft studies from 2010 to 2021, reported only 3 (0.32%) out of 1,033 patients with clefts, to have type IV.

No specific pathognomonic prenatal findings associated with laryngeal clefts exist. The polyhydramnios, observed in the index patient, is a very common finding described in many cases of airway clefts (Carr et al., 1999; Alnemri et al., 2010; Seidl et al., 2021), and is attributed to impaired fetal swallowing. Absent stomach bubble, as reported in our case, is also a prenatal fetal finding in LTCs. Kawaguchi et al. (2005) reported that polyhydramnios was noted in 5 of 6 fetuses, and absent stomach bubble in 2 others on prenatal sonography. The association between LTCs and premature birth, supported by the literature, is also exemplified in our case, as the neonate was born at 32 weeks of gestation (Moungthong and Holinger, 1997; Seidl et al., 2021).

The diagnosis of laryngeal cleft is difficult to establish, especially early postnatally, and several other entities must be included in the differential diagnosis. A LTC may imitate clinically oesophageal atresia or a tracheoesophageal fistula. Passing a NGT into the stomach rules out esophageal atresia. Barium swallow study, although it can provide adjunct information, may not be able to differentiate between tracheoesophageal fistula (TEF) and severe forms of LTC (III and IV), as contrast medium will be present in the trachea in both cases. Additionally, the 2 entities are often encountered in the same patient, with 20–37% of LTCs being complicated by TEF (Mahour et al., 1973; Fraga et al., 2015; Londahl et al., 2018). Definite diagnosis is set with endoscopy. Additional imaging, such as magnetic resonance imaging (MRI), is not needed to assess the severity of LTC, but it is only used for adjunct information regarding associated malformations (Leboulanger and Garabédian, 2011).

Difficult intubation, repeated displacement of the ET, inadvertent extubation (Moungthong and Holinger, 1997) and inability to achieve appropriate tidal volumes during mechanical ventilation, should raise suspicion for this rare malformation. In our case, neonatologists set suspicion for the malformation clinically, and thus reinforcing the fact that the laryngeal cleft type IV can be identified early postnatally, during endotracheal intubation, by an experienced neonatologist (Jorgensen et al., 2018).

Data in the literature suggests that, in the apnoeic patient, even if upper airway appears normal, a LTC may be present, because the arytenoids are not spontaneously separated. In these cases, widening of the airway can be achieved with rigid bronchoscopy or with positive airway pressure and a flexible bronchoscope (Jöhr et al., 2003). We presume that this was the case in our neonate, who was non-vigorous, floppy and apneic on the 1st day of life, and it would explain why the malformation was not visible during the first intubation attempt. All neonates with severe forms of LTC (types III and IV) face difficulties maintaining mechanical ventilation, and accidental extubation is a common event. An uncuffed ET can easily slip into the oesophagus through the cleft. This situation along with multiple attempts for reintubation, can lead to pneumothorax, as is reported in our case.

Minor clefts, such as type I and II require minimal endoscopical management with usually good prognosis. Type III and IV clefts are much more serious and require early surgical management. Long-term mortality is high in the latter types, due to cleft relapse, pulmonary infections and repeated hospitalizations, but it has dropped from 93% in 1983 (Roth et al., 1983) to 50% (Martha et al., 2021; Seidl et al., 2021). Shehab and Bailey (2001) reported only 10 (33%) cases of type IV successfully treated. Although the survival rate has increased, it is not possible to draw conclusions for the quality of life of these patients. 71% of types III and 89% of types IV required tracheostoma, and about 60% of them needed prolonged ventilation (Seidl et al., 2021). Seidl et al. (2021) reviewed studies until 2020, and reported that 97% of these children had recurrent aspirations, 80% tracheostoma, 80% percutaneous endoscopic gastrostomy, 33% percutaneous endoscopic jejunostomy and 61% survived on mechanical ventilation, with failure to thrive. All 9 patients that were reported in the same study, had sequelae as mentioned above. Shehab and Bailey (2001) reported that severe tracheomalacia was present in 2 out of 6 patients they treated, requiring prolonged positive pressure ventilation. Walker et al. (2017) reported that many patients with a cleft had a coexistent neuromuscular dysfunction, explaining the observed dysphagia and the repeated aspiration episodes. Unfortunately, in our case, the patient died in the 1st week of life immediately after diagnosis was confirmed and before any medical or surgical treatment was attempted. Any neonate with respiratory and feeding problems in the early days of life, should be evaluated for possible laryngeal cleft by an experienced paediatric ENT. A high index of suspicion for the presence of laryngeal cleft in a newborn with a difficult intubation during resuscitation, and inability to achieve appropriate tidal volume delivered with a large air leak, is needed for early detection of such abnormalities. Laryngoscopy or bronchoscopy should be performed to reveal the extent of the malformation. For optimal long-term outcome, a multidisciplinary team, of neonatologists, pediatric ENTs, pediatric surgeons and anesthesiologists, should manage these patients.

Overall, the management of LTC is difficult. Early diagnosis, satisfactory ventilation, protection of the respiratory tract from aspiration and endoscopic or surgical repair are needed. The time from diagnosis to treatment is vital and minimizes the degree

of esophageal tracheitis caused by reflux and the recurrent respiratory infections due to aspiration. Prompt diagnosis of coexisting cardiac malformations, which are very common, is equally important. LTC is often associated with genetic syndromes, and therefore, each case should be evaluated by a geneticist. When all evaluations are completed the best approach for each case should be planned. Nutritional status should be a priority in the preoperative and postoperative management. Increased caloric and protein intake has been linked to optimal growth in these neonates, and also speeds up the wound healing process. Optimizing early nutrition in critically ill neonates and especially those born very preterm and with very low birth weight, reduces mortally, growth failure, adverse neurodevelopmental outcomes and long-term health consequences (Moltu et al., 2021; Gounaris et al., 2022).

Regardless though, to early identification of LTC, the prognosis is still ominous, because of the recurrent pulmonary aspiration that causes repeated respiratory infections, such as pneumonitis and tracheitis, leading to high mortality rate.

Conclusion

This case raises several points. Laryngo-tracheo-oesophageal cleft is a rare congenital malformation of the upper respiratory and gastrointestinal tract. In order to maximize favourable outcome of these infants, a multi-disciplinary approach of specialized physicians is needed. Effective ventilation, early management of gastric reflux, adequate nutrition and endoscopic or surgical management are mandatory. Neonatologists when treating neonates with symptoms of respiratory distress in need of mechanical ventilation support with difficulties to manage, and with additional congenital abnormalities, should keep in mind this rare anomaly. The aim of this case report is to underline that increased awareness is needed for an early diagnosis, especially in long segment LTC types III and IV, which have the highest morbidity.

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