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Case Report

Management of Congenital Chylothorax in Intensive Neonatal Care Unit in Sfax, Tunisia: A Case Series and Review of the Literature

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ABSTRACT

Background: Congenital Chylothorax (CC) is a rare condition, which is defined as an accumulation of the chyle in the pleural cavity; moreover, it is associated with significant morbidities, including respiratory distress, malnutrition, immunodeficiency, and infections.
Case Report: The diagnosis of chylothorax was made upon count cell analysis of the pleural fluid with ≥80% lymphocytes detected before birth or within 28 days after birth. In this study, we presented five cases of CC infants. They were discharged from our tertiary center at Hedi Chaker Hospital, Sfax, Tunisia, from January 2010 to December 2018. There were three males and two females. Prenatal diagnosis was made in four cases. There were four full-term newborns and one near-term of 36 weeks. Pleural effusion was on the right side in three cases, on the left side in one case, and bilateral in one case. Four cases required mechanical ventilation. Somatostatin was indicated in one case. The treatment was successful in four cases. One case presented a dysmorphic syndrome and died of pneumothorax.
Conclusion: The treatment of CC is based on conservative management. Somatostatin or its analog octreotide is considered an adjunctive treatment of CC. However, the refractory cases are treated with chemical pleurodesis or surgical treatment. We propose an algorithm for the treatment of CC.

Keywords: Algorithm, Congenital chylothorax, Octreotide, Pleurodesis

Introduction

Congenital Chylothorax (CC) is a rare condition, which is defined as an accumulation of chyle in the pleural cavity, and it is the most common etiology of pleural effusion in the perinatal period. Its incidence is estimated from 1/10000 to 1/24000 births with a mortality rate ranging between 30% and 70% (1-2). Moreover, it is associated with significant morbidities, including respiratory distress, malnutrition, immunodeficiency, and infections. The management of CC remains controversial. It usually involves chest drainage or repeated pleural aspiration and parenteral nutrition or enteral diet based on the medium chain-triglyceride (MCT) formula (3). Recently, Somatostatin or its analog octreotide has been used with success in some cases of CC (4). In case of medical treatment failure, chemical pleurodesis with povidone-iodine, oxytétracycline, OK432, and bléomycine can be considered before surgical treatment. Recent studies suggest the use of oral propranolol for the treatment of severe CC (5).

Case report

Antenatal diagnosis was realized in four cases with pleural effusion. Three of them were born in our hospital and two were born out.

Case 1

A female infant was prenatally diagnosed with a right pleural effusion and hydramnios. She was born

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at 36 weeks of gestation (WG) by C-section because of fetal cardiac decelerations. Her birth weight was 3960g. She presented a dimorphic syndrome associated with micro retrognathism, a short neck, hexadactylia, and a unique transverse palmer crease. She developed immediate respiratory distress requiring mechanical ventilation for nine days. Chest radiography and tomodensitometry showed a small right pleural effusion. Enteral feeding by long-chain fatty acid (LCFA) formula was introduced on day 11. By day 14 of life, she developed respiratory distress and the chest X-ray showed the recurrence of the effusion. Draining of the effusion was then realized. The chest tube drained 30 ml of chylous fluid and the analysis confirmed the diagnosis of chylothorax. The patient was reintubated but she died on day 15 of life of bilateral pneumothorax.

Case 2

A male infant was prenatally diagnosed with right-side pleural effusion. He was delivered by urgent C-section at 37 WG and 5 days because of chorioamniotis. His birth weight was 3550g. The Apgar scores were 4 and 7, and the infant was intubated as a part of resuscitation and stabilization in the delivery room. The chest X-ray concluded that the pleural effusion was small. The infant was extubated on day 2 of life. Enteral feeding by LCFA formula was introduced on day 3 of life. The infant presented seizures and respiratory distress on the next day. The seizures were treated by Phenobarbital and the brain echography was normal. Chest X-ray and chest SCAN showed bilateral pleural effusion. A draining of the right pleural effusion was then realized and drained 20 ml of chylous fluid and the analysis confirmed the diagnosis of chylothorax. MCT-based infant formula was started on DOL 25. No re-accumulation of the chylothorax was noted. He was discharged on day 41 of life on breast milk only. At the time of data collection, the patient was 2 years old and had a good follow-up.

Case 3

A male infant was diagnosed prenatally with hydramnios and left pleural effusion. He was delivered by planned C-section at 39 WG. His birth weight was 3800g. He developed immediate respiratory distress requiring respiratory support with oxygen. Chest radiography showed a left pleural effusion. Pleurocentis was realized on day one of life and the analysis confirmed the diagnosis of chylothorax. On day 12 of life, the patient developed respiratory distress requiring high-frequency oscillation ventilation. Chest X-ray showed an important left effusion. A left chest tube was placed on day 14 of life and derived about 50ml/kg/day. The chest tube was accidentally removed on day 22 of life. Somatostatin was initiated on the same day at the dose of 1µg/kg/h and increased to 1.5µg/kg/h. It was discontinued on day 62 of life. The patient had additional complications of chylothorax including hypercoagulability leading to a right jugular thrombosis at the site of the broviac catheter on the day of life 19 requiring anticoagulation with low-weight molecular heparin. Enteral feeding was introduced on DOL 18 by LCFA-free formula. He was discharged on day 68 of life when the chest X-ray was normal. He was one year old at the time of data collection, and he had a good follow-up.

Case 4

A male infant was born at 37 WG by urgent C-section because of the breech presentation and spontaneous labor. His birth weight was 3300g. He was the firstborn of a twin pregnancy. He developed immediate respiratory distress requiring respiratory support with oxygen. Chest X- ray showed a small right pleural effusion. The infant was fed via gastric tube with LCFA formula and transferred to our unit care on DOL2. A thoracentesis made on day 3 of life revealed milky fluid (20ml) and the analysis confirmed the diagnosis of CC. Enteral feeding with MCT-based formula was started on DOL 4. A chest-SCAN concluded the persistent effusion, but it was well tolerated clinically. On day 20 of life, the chest X-ray showed that the effusion regressed. The patient was discharged on day 22 of life. He was 16 months old at the time of data collection, and he had a good follow-up.

Case 5

A female infant was prenatally diagnosed with right-side pleural effusion. She was delivered by urgent C-section at 37 WG because of fetal cardiac decelerations. Her birth weight was 3300g. She developed immediate respiratory distress requiring respiratory support with oxygen. The chest X-ray showed an important right pleural effusion. A right chest tube was placed on day one of life. The analysis confirmed the diagnosis of chylothorax. Then, she was transferred to our unit. The chest tube was removed on day 3 of life. She received total parenteral nutrition for three days. Enteral feeding with MCT-based formula was started on day 4 of life. The infant was discharged on day 10 of life. She was 2 months old at the time of data collection, and the pleural effusion had not recurred.

Ethical approval

The proposal for this research was presented to the Organizational Ethics Committee of the Faculty of Medicine of Sfax on the date 11/10/2023 by Prof Amel Ben Hamed. Ethics Committee of the Faculty of Medicine of Sfax certifies that this study obeys the ethical rules and regulatoryprovisions in force in this area.

Discussion

CC is often associated with abnormal lymphatic pathway development, which can be idiopathic or related to other conditions that affect the structure and or the function of the lymphatic system, such as congenital heart disease, superior vena cava obstruction, mediastinal malignancies, and chromosomal abnormalities. It produces detrimental influences on the respiratory system, nutritional and immunological consequences, and high mortality if it is not treated appropriately (2).

Prenatal interventions might improve survival in severe cases of fetal chylothorax and usually necessitate referral to an experienced prenatal care center (3). In our study, prenatal diagnosis was made in 4/5 cases. However, prenatal treatment was not possible in our center.

Four newborns were full term and one near term of 36 weeks. All newborns had immediate respiratory distress. One infant had a dysmorphic syndrome. The chylothorax was confirmed after pleural fluid analysis with triglyceride levels >110mg/dl, or a total blood cell count>1000/µl with a predominance of lymphocytes (>80%) (6). In our study, pleural draining was made in all cases and the chemical analysis confirmed the diagnosis of CC.

Prenatal interventions aim to reduce the mass effects of pleural effusion and the risk of pulmonary dysplasia (8). Postnatal management of CC includes supportive medical treatment (ventilator support, pleural drainage, pain management, nutritional management, intravascular volume replacement, blood pressure support, and immune support).

Initial management in these cases includes keeping the baby Nil Per Os (NPO) along with the initiation of total parenteral nutrition and monitoring of chyle output from chest drain. Keeping the patient NPO decreases the chyle formation and also the lymphatic flow (9).

Re-establishing of oral feeds was authorized if pleural effusion regressed < 20ml/kg/day and was stable over 48 hours (8). Dietary treatment of chylothorax calls for MCT-based nutrition with adequate LCFA supplementation. In fact, MCTs with enteral feeding are absorbed directly into the portal venous system and they bypass the intestinal lymphatic system. Michaela et al. proposed the use of skimmed breast milk after a defatting procedure. It has proven positive effects above all in preterm infants as optimal nutrition with protective components superior to formula feeding (10). However, the nutritional analysis of the skimmed milk and the correlation to a re-accumulation of pleural fluid need future multicenter studies.

With supportive treatment, 80% of the patients have spontaneous resolution of CC (7). In our study, four cases required mechanical ventilation. The first case was ventilated for 14 days and he died of bilateral pneumothorax. In the third case, the association between mechanical ventilation, chest tube drainage, and nutritional management did not resolve the chylothorax after 22 days, but the prompt resolution of the effusion was coincidental with the use of Somatostatin with any effects encountered.

Somatostatin and octreotide (Somatostatin analog) for the treatment of CC were first described by Goto et al. in 2003 (11). Octreotide acts by reducing the blood flow in splanchnic circulation including lymph flow, decreases the secretion of gastric and intestinal secretions, and decreases intestinal absorption ultimately, leading to reduced chyle flow (12).

Carlo Bellini performed a systematic review which included 39 articles. Octreotide was effective in 47% of patients with a slight but not a significant difference between congenital (30/57) and acquired chylothorax (9/27). Side effects were reported in 12 of 84 patients (14.3%). This review suggests that octreotide therapy should be considered an adjunctive treatment in term and preterm neonates affected by congenital and acquired chylothorax (12). In a retrospective study of 11 neonates who received octreotide therapy over 15 years, Sayed Ahmedzaki concluded that octreotide is a safe adjunct therapy for the treatment of chylothorax and chylous ascites in neonates, and the treatment with octreotide can be initiated early (13).

Octreotide was used either subcutaneously (10 to 70µg/kg/day) or intravenously (0.3 to 10µg/kg/h) (14). The dose is increased by 1µg/kg daily upon the response till the maximum dose of 10µg/kg/h. However, there are no randomized controlled clinical trials to evaluate the medication's efficacy, dose, duration, and safety profile (12-14). The major side effects related to

Somatostatin/octreotide treatment are necrotizing enterocolitis, an increase in liver enzymes, pulmonary hypertension, hyperglycemia, and transient hypothyroidism (14-16).

Recent studies concluded that octreotide is effective and safe for the treatment of chylothorax, and the side effects are mild and transient; moreover, there is no need for the discontinuation of the treatment (12,15,17,18). In our study, only the third case was treated by Somatostatin with a dose of 1.5µg/kg/h. The duration of the treatment was 40 days; it is too long, compared to the literature. This patient has right jugular thrombosis at the site of the broviac catheter. We cannot explain this thrombosis by the hypercoagulability due to the chylothorax or turbulences due to the catheter.

Another drug used for this baby was sildenafil. Sildenafil prevents the degradation of cyclic guanosine monophosphate by selective inhibition of phosphodiesterase and could thereby facilitate lymphatic growth and/or remodeling (16). Furthermore, an important step in management is the elimination of long-chain fatty acids by administering total parenteral nutrition till the volume of chyle reduces, followed by a slow introduction of a diet containing MCTs and protein to supplement calories. MCTs are directly absorbed into the portal venous system bypassing lymphatic drainage (16). Other studies are needed to demonstrate the efficacy of sildenafil in the management of chylothorax (19).

A 2010 Cochrane review identified 19 cases of chylothorax with wide variations in octreotide timing, dose and duration, as well as inconsistent success. In total, 14 of 19 cases (73, 6%) had successful resolution of chylothorax after octreotide treatment. The Cochrane review concluded that no practice recommendation can be made, and a multicenter randomized controlled trial is needed to assess the safety and efficacy of octreotide in the treatment of chylothorax in neonates (20).

The treatment of CC with octreotide is judged effective if the response is noted after 2 or 3 weeks of drug administration. Sayed Zaki et al. and Paget-Brown et al. reported that the effusion was resolved within 3-16 days of reaching the maximum dose of octreotide infusion (21, 22). Usually, CC resolves in a few weeks (2 to 6 weeks) with conservative management. The time duration at which conservative management should be considered a failure is not well defined. Daily drainage is used by some centers as a guide for clinical improvement or failure in pediatric patients (<10ml/kg/day of pleural drainage is considered an improvement; >10ml/kg/day of pleural drainage is considered to be a failure after 4 weeks of nonsurgical management) (22).

Chemical pleurodesis is proposed as a second-line treatment after the failure of conservative management. Instillation of various agents (povidone-iodine, OK-432, bleomycin, tetracycline) can be indicated. Pleurodesis with povidone-iodine in neonates has been first described by Brissaud et al. (22). Since this report, 19 neonates have been treated with povidone-iodine (10 studies) in the literature (23-31). Furthermore, 14 chylothorax cases have been resolved (73%). Side effects (e.g., respiratory distress, renal failure, shock, and organ failure) were observed in 8 (42%) neonates. In Tunisia, Kasdallah et al. reported a case of a full-term female with a right pleural effusion. She was treated with povidone-iodine pleurodesis. A chest tube was placed and the volume was 49ml/kg/day. At day 16 of life, chemical pleurodesis with povidone-iodine was performed. The pleural effusion was completely dried during the following 48 hours after instillation. In this case, treatment by octreotide was not tried before pleurodesis (30). Povidone-iodine details are provided in Table 1.

Recently, successful treatment of prenatal and neonatal chylothorax by intrapleural instillation of OK432 has been reported by a few studies (32, 33, 34, 35). OK432 is a penicillin-inactivated and lyophilized preparation of a low-virulence strain of streptococcus pyogenes. It induces intense inflammation after administration into the intra-pleural space. Accordingly, nine neonates were treated with OK432. Chylothorax was resolved in all cases; however, there were some side effects, such as fever, tachypnea, acute respiratory distress syndrome, and hemolytic anemia. Other studies are needed to confirm the effectiveness and safety of OK432 for the treatment of CC. OK432 details are provided in Table 2.

Recent studies suggest the use of propranolol in the treatment of severe fetal CC. Oral propranolol has become the first-line therapy for the treatment of hemangiomas for its efficacy and safety (5). Roxane Handal-Orefice et al. used propranolol for four neonates: two in prenatal for pregnant women at the dose of 40mg four times daily and in postnatal for 2 newborns at a dose of 0.3 mg/kg/day which increased to 1 to 2 mg/kg/day. Prenatal treatment with propranolol led to the resolution of the chylothorax before delivery. Postnatal propranolol led to the improvement of pleural effusion. There were no complications from prenatal or postnatal

Table 1. Studies reporting treatment with povidone-iodine instillation in congenital chylothorax

Authors	Year	Number of cases	Gestation (Weeks)	Povidone-iodine solution (%)	Dose (ml)	Instillation (B, L, R)	Time of resolution (days)	Side effects	Evolution
Brissaud (21)	2003	4	31, 35, 36,40	3 cases : 4 1 case : 10	N/A	3B 1L (lymphangiectasia)	6, 7and 16 1 failure	General oedema Renal failure	3 survived, 1 died
Mitchansez (22)	2006	1	35	10	5	1L (lymphangiectasia)	1	Renal failure	Survived
Murki (23)	2010	1	40	4	4	B	N/A	None	Survived
Le Nué R.(24)	2010	4	35, 35, 33,33	N/A	N/A	1B ; 2R 1N/A	4 cases : failure	2 cases :RD	3 Survived 1 Died
Hmami (25)	2014	1	36	4	5	R	1	None	Survived
Scottoni (26)	2015	4/5	40, 35, 41,28	10	2ml/kg	B	4	3cases : RD	4 Survived 1 Died
Resh (27)	2015	1	29	10	5		2		Died (Failure of all visceria)
Maoulainine (28)	2016	1	40	4	5		1	None	Survived
Kasdallah (29)	2016	1	39	4	5	R	2	None	Survived
Kathleen (30)	2018	1	33	4+ propranolol (2mg/kg/day)	6	B (lymphangiectasia)	11	None	Survived

B: bilateral; L: left; R: right; N/A, not avalable;

propranolol use (5).

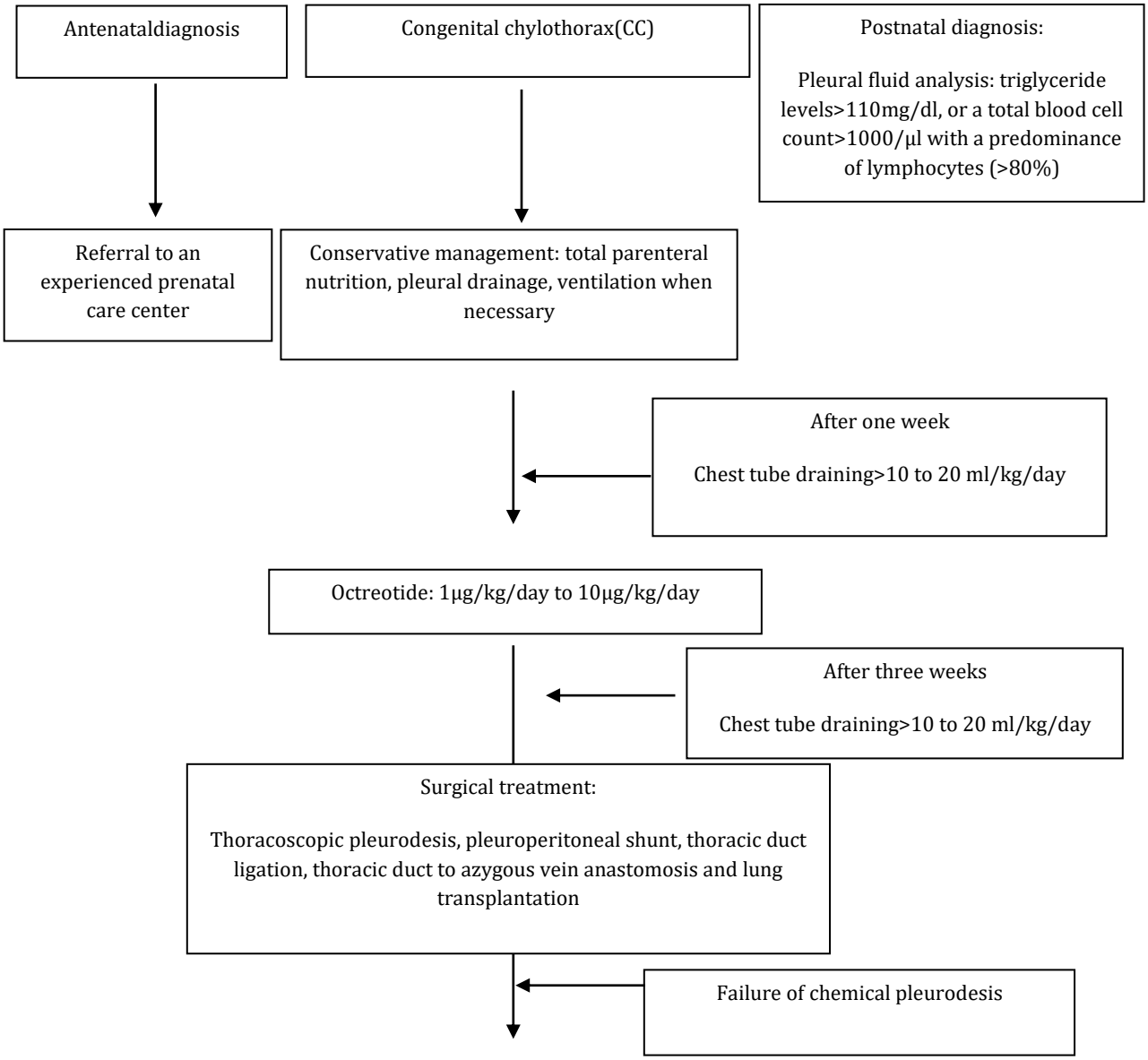
Less than 10% of neonates require surgery after failure of conservative management or because of the development of complications either of the prolonged chyle leak or of the treatment by itself. There is no consensus on the timing of surgery. Daily drainage has been suggested to be used as a guide for clinical improvement or failure (<10ml/kg/day of pleural drainage is considered to be an improvement; >10ml/kg per day of pleural drainage is considered to be a failure after four weeks of non-surgical management). Surgical options include thoracoscopic pleurodesis, pleuroperitoneal shunt, thoracic duct ligation, thoracic duct to azygous vein anastomosis, and lung transplantation (lymphangioleiomyomatosis). Successful surgery can shorten hospitalization and reduce the risks of malnutrition and immunosuppression (36).

After the literature review and analysis of our own experience, we propose an algorithm for the treatment of this entity (6, 16, 21, 37), which is represented in Flowchart 1.

Table 2. Studies reporting treatment with OK432 in congenital chylothorax

Authors	Year	Number of cases	Gestation (weeks)	Location (B, R, L)	Octreotide (DOL)	Dose (KE) (DOL)	Frequency	Resolution (days)	Side effects	Outcomes
Matsukima (Japan) (31)	2009	2	33+6	B	23 15	0 ,5(R) 0,5(R)	1 1	3	Tachypnea, fever	Survived Survived
Jeong kim (Korea) (32)	2012	2	33 29+6	B B	26 NONE	0,1 (46L ;48 R) 26L		4 4	none	1 case: Died: Renal failure, peritonitis 1 case: Survived
Qing wang (Chine) (33)	2016	4	38 40 38 39	L L R L	NO YES YES YES	34 0,5-0,75 22 0,5-0,5 24 0,5-0,5 28 0,5-0,5	2 2 2 2	yes	RDS	4 cases: Survived
Steve.Sze (Chine) (35)	2016	1	35	R	YES 1 DAY	0,5 13-19	2	1	Hemolytic anemia	Survived

B: bilateral/L: left/R: right



Flowchart 1. Congenital chylothorax approach of management

Conclusion

CC is rare, but it is associated with a high mortality rate. The treatment is based on conservative management. Octreotide is an adjunctive, safe, and effective treatment. However, refractory cases require chemical pleurodesis or surgical intervention. Universally guidelines are important for the use of medications in this condition. Early antenatal diagnosis is essential in reducing the morbidity and mortality of this disease.

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Conflicts of interest

WE declare that there is no conflicts of interest

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