CASE REPORTS

Congenital chylothorax: A series of eight cases

Quilotórax congénito: Uma série de oito casos

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ABSTRACT

Introduction: Congenital chylothorax (CC) is the accumulation of lymph in the pleural space. The aim of this study was to review the cases of CC diagnosed in newborns admitted to a level III neonatal intensive care unit between January 2014 and December 2020.

Results: Eight cases of CC were identified, all with prenatal diagnosis. After postnatal confirmation of the diagnosis, supportive care and conservative therapy were initiated. Six cases underwent mechanical ventilation, two were treated with surfactant and inhaled nitric oxide, four required inotropic support, and one underwent extracorporeal membrane oxygenation. Five newborns were effectively treated with octreotide. One patient with hydrops fetalis died after birth.

Discussion: The prognosis of CC depends on the severity of the effusion and on associated abnormalities. Medical treatment is based on supportive and conservative treatment. Although the use of octreotide is not unanimous, it proved to be an effective and safe adjuvant therapy in these patients.

Keywords: chylothorax; congenital abnormality; hydrops fetalis; neonatal; octreotide; pleural effusion

RESUMO

Introdução: O quilotórax congénito consiste na acumulação de linfa no espaço pleural. O objetivo deste estudo foi analisar os casos de recém-nascidos com diagnóstico de quilotórax congénito admitidos numa unidade de cuidados intensivos neonatais de nível III entre janeiro de 2014 e dezembro de 2020.

Resultados: Foram identificados oito casos de quilotórax congénito, todos com diagnóstico pré-natal. Após confirmação pós-natal do diagnóstico, foi iniciado tratamento de suporte e conservador. Seis casos foram submetidos a ventilação mecânica invasiva, dois foram tratados com surfactante e óxido nítrico inalado, quatro tiveram necessidade de suporte inotrópico e um recebeu oxigenação por membrana extracorporal. Cinco casos foram efetivamente tratados com octreótido. Um recém-nascido com hidrópsia fetal faleceu após o nascimento.

Discussão: O prognóstico do quilotórax congénito depende da gravidade do derrame pleural e das anomalias associadas. O tratamento inicial deve ser de suporte e conservador. Embora a utilização de octreótido não seja consensual, demonstrou ser uma terapêutica efetiva e segura nesta amostra de doentes.

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Palavras-chave: anomalia congénita; derrame pleural; hidrópsia fetal; neonatal; octreótido; quilotórax

INTRODUCTION

Congenital chylothorax (CC), defined as the accumulation of lymph fluid in the pleural space, is an uncommon condition with a reported incidence of approximately 1 in 24,000 newborns.[1] It is associated with increased prenatal and postnatal morbidity and mortality, accounting for around 1:2,000 neonatal intensive care unit (NICU) admissions.[2,3]

Clinical manifestations of neonatal chylothorax can range from asymptomatic to severe respiratory distress and are related to the severity of pleural effusion/hydrops and eventual impaired lung development, which may lead to pulmonary hypoplasia and pulmonary hypertension, especially if the condition occurs during early fetal development.[2,4-6]

The management of CC is not standardized and varies among neonatal units. Published reviews and case series agree that the first-line management of CC should be conservative and include supportive measures combined with dietary changes ranging from total parenteral nutrition (TPN) to medium-chain triglyceride (MCT) formulas, provided that the neonate can be orally fed.[2,4,5,7-9] Octreotide, a second-line treatment, is a synthetic somatostatin analog that is thought to reduce lymphatic flow by causing mild vasoconstriction of splanchnic vessels.[2,10,11] Case studies have reported marked variability in its use in different clinical conditions, with no currently established treatment protocols for chylothorax.[4,6,10] A 2010 Cochrane meta-analysis reported that octreotide does not have sufficient evidence to be considered an established treatment option.[12] However, a systematic review with data from multiple NICUs reported widespread use of octreotide as an effective and safe approach.[8] Failure of medical therapy, severe metabolic and nutritional complications, and overall clinical deterioration may be indications for surgical treatment.[2]

The purpose of the present study was to review the management and clinical course of cases of CC diagnosed in a level III NICU over a seven-year period.

METHODS

A retrospective descriptive review of institutional records of newborns diagnosed with CC admitted to a level III NICU of Maternidade Dr. Alfredo da Costa, in Lisbon, Portugal, between January 1, 2014 and December 31, 2020 was performed. Patients with other known causes of chylothorax, such as trauma and surgery, were excluded. Parameters analyzed included gender, prenatal diagnosis of chylothorax and interventions, gestational age (GA), mode of delivery, Apgar score, birth weight, associated conditions, clinical presentation, characterization of pleural effusion, clinical course, treatment, and adverse effects. Inclusion criteria were based on biochemical and cultural analysis of the pleural fluid and included (i) sterile pleural fluid, (ii) more than 1,000 cells/µL, (iii) more than 80% lymphocytes, and (iv) triglycerides greater than 110 mg/dL, if feeding was enteric. Informed consent was obtained from the parents of all patients included in the study. Descriptive analysis was performed using Microsoft Excel®.

The management of CC at the considered NICU is based on supportive care consisting of respiratory and cardiovascular support and correction of anemia, coagulation disorders, and hypoalbuminemia, if present. In cases of metabolic acidosis with bicarbonate levels below 12 mEq/L, bicarbonate solution is used to maintain water-electrolyte balance. Thoracentesis and pleural drainage combined with pain management are performed in cases of moderate-to-severe pleural effusion or symptomatic newborns. In mild and asymptomatic cases, a MCT formula supplemented with parenteral nutrition is started and tapered according to clinical improvement. In more severe or symptomatic cases, initial treatment includes fasting and individualized prescription of TPN. After one week of TPN, octreotide therapy is used in cases where a large effusion persists. If the pleural drainage volume after birth is ≥ 50 mL/kg/day, octreotide may be considered earlier, between the third and fifth day. If the drained volume is <10-20mL/Kg/day, formulas with MCT are introduced. Intravenous immunoglobulin is used in newborns with prolonged pleural effusion and hypoglobulinemia.

RESULTS

Eight cases of CC were identified in this seven-year review, predominantly in male patients (n=5). All cases had prenatal suspicion of this diagnosis at a mean (standard deviation [SD]) GA of 27.2 ± 5.8 weeks, with ultrasound evidence of fetal pleural effusion. In addition, cases 3 and 5 had prenatal diagnosis of bilateral hydronephrosis, and case 6 had prenatal diagnosis of hepatomegaly and ascites. Case 8 was diagnosed with hydrops fetalis at 20 weeks GA and underwent pleuroamniotic shunting due to its severity. As no improvement was noted, intrauterine fetal thoracentesis twice weekly was started at 26 weeks GA. This was the only case requiring *in utero* intervention. Prenatal data are summarized in **Table 1**.

Table 1 - Prenatal findings in neonata chylothorax cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Sex	M	F	M	F	M	F	M	M
Prenatal diagnosis of pleural effusion	Yes (22 w)	Yes (27 w)	Yes (20 w)	Yes (33 w)	Yes (31 w)	Yes (32 w)	Yes (33 w)	Yes (20 w)
Other prenatal ultrasound findings	--	--	Hydronephrosis	--	Pericardial effusion	Hepatomegaly, ascites	--	Hydrops fetalis
Antenatal interventions	No	No	No	No	No	No	No	Yes (Pleuroamniotic shunt + fetal thoracentesis)

F – female; M – male; W – weeks

The median GA at birth was 35 weeks (range 30-40), and 50% of patients were born by eutocic delivery. Birth weight ranged from 1,950 to 4,595 grams. Half of cases required immediate resuscitation. Three cases were diagnosed with other conditions: cases 1 and 3 with bilateral hydronephrosis and case 5 with Down syndrome associated with septal heart defects and bilateral cryptorchidism. The demographic characterization of neonatal chylothorax cases is summarized in **Table 2**.

Table 2 - Demographic characterization of neonatal chylothorax cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
GA	35w+ 1d	40w+3d	35w+3d	33w+4d	37w+1d	36w+6d	35w+4d	30w
Delivery Mode	eutocic	eutocic	vacuum	eutocic	caesarean	caesarean	caesarean	eutocic
AS 1/5/10´	6/8/8	9/10/10	8/9/10	5/8/9	8/9/10	5/8/9	9/10/10	2/4/6
BW, g	2,668	3,540	2,735	2,130	2,740	4,595	2,600	1,950
Associated clinical pathologies	Bilateral hydronephrosis	--	Bilateral hydronephrosis	--	Down syndrome, ASD, VSD, cryptorchidism	--	--	--
Pleural effusion location	Right	Right	Bilateral	Bilateral	Right	Right	Bilateral	Bilateral

AS – Apgar score; ASD – atrial septal defect; BW – birth weight; d – days; GA – gestational age; VSD – ventricular septal defect; W – weeks

At birth, six patients showed signs of mild to moderate respiratory distress, and one (case 2) was asymptomatic. Case 8 presented with severe symptoms and died four hours after birth with severe respiratory failure despite implementation of recommended protocols.

Pleural effusion was bilateral in four cases and right-sided in the remaining cases. Biochemical and cultural analysis of the pleural fluid is shown in **Table 3**. Triglyceride levels >110 mg/dL were found only in cases 2 and 5. In both cases, the newborns had already received enteral nutrition for several days.

Table 3 - Characterization of pleural fluid

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Cells (cells/µL)	1,500	16,000	9,146	4,272	7,000	7,961	13,484	1,559
Lymphocytes (%)	95.3	97	97.1	97.1	93.3	88.7	96.7	92.2
Proteins (g/dL)	25	72.2	1.89	24.5	30	40.4	24.7	16.4
Triglycerides (mg/dL)	20	1064	44	43	637	53	20	17
Culture test	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

Regarding supportive care, six patients required invasive ventilation support (**Table 4**). The median duration of invasive mechanical ventilation was 15.8 days (range 1-33). Patients 1 and 8 received surfactant due to hyaline membrane disease. Case 3 required inotropic support due to hemodynamic instability since the first day of life. On day 10, the newborn's clinical condition deteriorated, with severe persistent pulmonary hypertension refractory to aggressive ventilation with 100% oxygen, nitric oxide treatment, and inotropic support. The patient was eligible for extracorporeal membrane oxygenation, which he received for a total of 19 days, with gradual clinical improvement. Cases 1 and 7 also presented with hypotension requiring inotropic support for five and nine days, respectively. All infants required chest drains with a mean duration of insertion of 13 days (SD ± 9.9). Initial treatment for all newborns included fasting and individualized prescription of TPN. When clinically stable, oral feeding with a high MCT formula was initiated.

Table 4 - Supportive treatment of neonatal chylothorax cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Invasive ventilatory support (days)	Yes (11)	No	Yes (33)	Yes (6)	No	Yes (11)	Yes (33)	Yes (1)
Surfactant	Yes	No	No	No	No	No	No	Yes
Cardiovascular support	Yes (inotropic agents)	No	Yes (inotropic agents + ECMO)	No	No	No	Yes (inotropic agents)	Yes
Chest drainage duration (days)	13	7	33	3	13	11	27	1

ECMO – extracorporeal membrane oxygenation

Five patients did not respond to conservative treatment and were treated with continuous octreotide infusion. Octreotide administration was initiated at a median age of six days (range 5–27) and continued for a median of 29 days (range 17–46). The initial dose was 1-2 µg/kg/h, with progressive increases according to therapeutic response. Case 7 responded effectively to the maximum dose of 12 µg/kg/h. None of the most commonly reported side effects of octreotide therapy was observed. Resolution of chylothorax was achieved in all five patients. Full enteral feeding with MCT formulas was achieved at a mean age of 39 days (SD ± 15). Octreotide treatment is summarized in **Table 5**.

Complications were present in almost all CC cases (**Table 6**): pneumothorax in four, late-onset culture-negative sepsis in one, late-onset sepsis due to coagulase-negative staphylococci susceptible only to vancomycin in three, and severe hypoalbuminemia in three.

The median time to resolution of pleural effusion was 22 days (range 13–50). No patients required surgical intervention. The mean length of hospital stay was 58.1 days (SD ± 19.8). One patient did not survive (case 8).

Table 5 - Octreotide treatment of neonatal chylothorax cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Octreotide	No	No	Yes	Yes	Yes	Yes	Yes	No
Starting day	--	--	6	20	27	6	5	--
Total duration (days)	--	--	17	24	29	46	45	--
Intial dose (µg/Kg/ h)	--	--	1	2	1	2	2	--
Maximum dose (µg/Kg/h)	--	--	7	4	2,5	5	12	--

Table 6 - Complications and clinical course of neonatal chylothorax cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Complications	Pulmonary hypertension Arterial hypotension Sepsis Coagulopathy Hypoalbuminemia	--	Pneumothorax Pulmonary hypertension Hypotension Anemia Thrombocytopenia Hypoalbuminemia Hypogammaglobulinemia Acute kidney failure	PTX	Sepsis Anemia	PTX Sepsis Anemia Coagulopathy Acute kidney failure	PTX Hypotension Sepsis Hypoalbuminemia	Respiratory Insufficiency Tension PTX
Time to reach full enteral feeding (days)	24	16	39	35	42	61	49	--
Length of stay (days)	29	62	47	50	79	79	65	--
Outcome	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Death

PTX: Pneumothorax

DISCUSSION

Congenital chylothorax, defined as the accumulation of chyle in the pleural space, results from various pathologic processes or developmental abnormalities of the lymphatic vessels or lymphatic duct that damage or obstruct this system, leading to leakage in the absence of external insults such as trauma or surgery.[1,2,4] It may be idiopathic or associated with genetic syndromes, such as trisomy 21, X monosomy, or Noonan syndrome.[2-4,13] It is a rare condition, but represents the most common cause of pleural effusion during the fetal and neonatal periods.[4]

Eight neonates with CC were identified in the present NICU, corresponding to an incidence of 1:3,000 live births. However, selection bias towards more severe cases cannot be excluded, as all patients were diagnosed prenatally and referred to our tertiary hospital for intensive postnatal care.

The authors believe that prenatal diagnosis of fetal pleural effusion is of great value in determining the severity of the effusion, associated abnormalities, and the need for *in utero* intervention. Prenatal intervention by thoracentesis, pleuroamniotic fluid drainage, or amniotic shunting depends on the GA at diagnosis, the volume and recurrence of the chylous effusion, the degree of pulmonary compression, and the presence of hydrops.[2,4,12] Infants with large or progressive pleural effusion or two or more fluid collections (ascites, pleural or pericardial effusion, generalized subcutaneous edema) -without other major congenital anomalies should be considered for fetal treatment to decompress the pleural space, allow normal lung development, and restore fetal hemodynamics.[2] It is also important

to schedule delivery at a tertiary perinatal center with experienced neonatal staff, as most of these patients may require intensive resuscitation and ventilation.[4,5]

All cases in this series had a prenatal diagnosis of CC, but only one (the case with hydrops fetalis) was considered for antenatal intervention. The initial treatment approach was conservative and consisted of supportive measures combined with nutritional management.

Respiratory support was required in 75% of cases and inotropic support in half, similar to what has been described in previous case series.[4,5,9,14]

Pleural drainage was performed in all cases, and albumin replacement due to protein loss XXX, a commonly described complication, was also performed in three patients.[1,5,9,13,14] In some cases, dietary modification is effective and allows complete resolution of the chyle effusion.[4,5,9,13] In other cases, failure of conservative treatment requires additional treatment options, as seen in this study in five of the seven surviving cases. Octreotide was used in these patients following previous reports of treatment success with this agent.[4-6,9,11,13,15] A 2010 Cochrane meta-analysis suggested a wide dose range of 20–70 µg/kg/day administered subcutaneously and 0.3–10 µg/kg/hour administered intravenously. Studies show a wide variation in the optimal timing, dose, duration, efficacy, and safety of octreotide, suggesting that there is insufficient evidence to support it as an established treatment option.[12]

The most commonly reported side effects of octreotide are arrhythmias, injection site pain, nausea, vomiting, constipation or diarrhea, hyperglycemia, hypoglycemia, transient liver dysfunction, transient hypothyroidism, and necrotizing enterocolitis.[5,12,14] In the present series, octreotide was shown to be safe and effective for the treatment of neonatal CC, even over long periods of time, as all treated cases responded effectively and without side effects. This is consistent with previous case series that have also reported no side effects associated with this agent.[1,9,15] Conversely, Bialkowski A *et al.* reported hyperglycemia and bloody stools in two of 28 infants treated with octreotide.[14]

Although surgical treatment is indicated when medical treatment fails after four to five weeks, conservative treatment with octreotide infusion was maintained in cases 6 and 7 in this study because clinical improvement was observed without recurrence of effusion . Although some case series reported successful treatment with octreotide, others described lack of response and recurrence of effusion with the need for surgical treatment.[5,9]

In conclusion, this study confirms the previously reported very low incidence of CC and documents the clinical approach to this condition in the study NICU. The authors emphasize the importance of prenatal diagnosis to assess the severity of the disease and associated conditions and to plan for possible fetal intervention. The management approach in this NICU is based on descriptions of other case series and algorithms proposed in other NICUs. Although implementation of guidelines is difficult due to the rarity of this condition, the need to optimize the therapeutic approach should prompt the development of multicenter studies.

AUTHORSHIP

Joana Antunes - Conceptualization; Data curation; Investigation; Methodology; Writing – original draft

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Sara Brito - Supervision; Validation; Writing – review & editing

Célia Neves - Supervision; Validation; Writing – review & editing

Eduardo Fernandes -Supervision; Validation; Writing – review & editing

Eunice Vieira - Supervision; Validation; Writing – review & editing

Filomena Pinto - Supervision; Validation; Writing – review & editing

Leonor Ferreira - Supervision; Validation; Writing – review & editing

Teresa Tomé - Supervision; Validation; Writing – review & editing

José Nona - Supervision; Validation; Writing – review & editing

LEGENDS

CC – Congenital chylothorax

GA – gestational age

MCT – medium-chain triglycerides

NICU – neonatal intensive care unit

TPN – total parenteral nutrition

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