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Neonatal Chylothorax in a Level III Neonatal Intensive Care Unit

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Abstract

Introduction

Neonatal chylothorax results from the accumulation of chyle in the pleural spaceand may be either a congenital or an acquired condition.

Objectives

To determine the etiology, clinical course and responseto treatment of neonatal chylothorax.

Methods

Retrospective observational study of all newborns with the discharge diagnosis of chylothorax between 2000 and 2015 in a tertiary neonatal intensive care unit.

Results

Seven cases of chylothorax were reported and all were preterm (gestational age 32-36 weeks):four congenital and three traumatic. One case of congenital chylothorax was idiopathic and the others were associated with hydropsfetalis (n=1), Noonan Syndrome (n=1) and Trisomy 21 (n=1).Traumatic chylothorax occurred after surgical repair of congenital diaphragmatic hernia (n=2) and esophageal atresia (n=1).

Treatment consisted of pleural taps, total parental nutrition, and respiratory support as required.

Four cases who did not respond to total parental nutrition were successfully treated with continuous infusion of octreotide. Resolution time of chylothorax ranged between 15 and 86 days.Two newborns died.

Conclusion

Clinical outcome of chylothorax is generaly good but etiology seems to be decisive in the evolution, with more prolonged course and associated morbility in congenital cases. Octreotide seems to be an important adjuvant treatment among the conservative strategies and appear to have a good safety profile in newborn. More studies are still necessary to investigate all aspects of octreotide treatment to determine the amount of its dose, initiation time and treatment duration.

Keywords: Chylothorax; Newborns; Octreotide

Abbreviations

LDH: Left Diaphragmatic Hernia

MCT: Medium-Chain Triglycerides

TPN: Total Parenteral Nutrition

TSH: Thyroid-Stimulating Hormone

Introduction

Neonatal chylothoraxis caused by the accumulation of lymphatic fluid in the pleural space. It may be either congenital or traumatic [1-3].

Congenital chylothorax, although rare, is the most common form of pleural effusion in fetus and neonates. It occurs in 1 out 10-15,000 neonates, and it is twice as common among male infants [2-4]. In half the cases, the effusion occurs at birth and in 75% of cases, in the first week, after the start of enteral feeding [2,3,5]. The etiology of congenital chylothorax is not well understood, but it is thought to occur secondary to congenital malformation of the lymphatic system. In the majority of cases, it is idiopathic, but it can occur also in association with chromosomal anomalies (Down syndrome, Noonan syndrome and Turner syndrome), *hydropsfetalis* (foetal hydrops), pulmonary lymphangiectasia, and pulmonary hypertension [2,3,6-10].

Traumatic chylothorax is, in the majority of cases, iatrogenic, arising from complications in thoracic surgery (congenital heart disease, esophageal atresia and congenital diaphragmatic hernia), chest drain insertion, or obstruction in the superior vena cava/left subclavian vein after the introduction of the central venous catheter. In these cases, it appears between seven and 14 days after surgery or drain insertion, mainly on the side where the procedure was carried out [3,11].

The clinical manifestations of chylothorax in neonates encompasses a wide spectrum of severity, depending on the volume of lymphatic fluid in the pleural space and the timing of presentation (pre or post-natal). The neonate can be asymptomatic when the effusion is small or may present respiratory difficulties of varying degrees, reduced chest expansion, reduction of respiratory sounds in chest auscultation and dullness to percussion [2,3,10,11].

Pre-natal diagnostic is based on obstetric echography, which indicates the presence of pleural effusion, and fetal thoracentesis, which confirms the diagnosis [12].

Post-natal diagnosis is based on the analysis of the pleural liquid collected in the thoracentesis: white cells count > 1000/µg with a lymphocyte fraction >80% and triglyceride levels >110 mg/dL (if enteral feeding has already been initiated), and sterile culture [1,3,13,14].

Lymphatic drainage of the pleura results in the loss of proteins, electrolytes, bicarbonate and cells (mainly lymphocytes), which may cause hypovolaemia, hypoproteinaemia, electrolyte imbalance, metabolic acidosis, malnutrition, lymphopaenia and immunodeficiency [3,11].

Treating chylothorax in a neonate is initially carried out by conservative measures: ventilatory support, pleural drainage (thoracentesis /chest tube), volume replacement, metabolic and nutritional balance, total parenteral nutrition (TPN) and a diet supplemented with medium-chain triglycerides (MCT) [1,3,10,11].

More recently, in cases not resolved by conservative treatment, the successful use of octreotide in treatment has been reported [14-18].

Surgical treatment is indicated when conservative treatment after three to four weeks has failed [1,14]. Persistent drainage of large volumes (>100 ml/day for a period of five consecutive days), metabolic complications and/or severe nutritional complications, which are difficult to control, often lead medical practitioners to decide on earlier surgical treatment. Surgical options include thoracic duct ligation or pleuroperitoneal derivation. Other options include chemical pleurodesis and mechanical pleurodesis by abrasion [1,3,10].

Throughout treatment, it is important to monitor the level of immunoglobulins in the serum, coagulation factors (antithrombin III and fibrinogen) and albumin, and replace them as deemed necessary [2].

Early diagnosis and treatment of chylothorax are fundamental for a good prognosis, which may deteriorate if it is linked to other illnesses, namely fetal hydrops and genetic syndromes. The underlying chylothoraxetiology may be a factor predicting the success of response to treatment and prognosis, because cases of congenital chylothorax showed slower response to treatment, as previously reported in literature.

The aim of this study is to present and discuss seven cases of neonatal chylothorax, diagnosed over a period of 15 years in a Neonatal Intensive Care Unit, level 3, in an urban hospital in the north of Portugal.

Methods

It was performed a retrospective study, of all newborns with the diagnosis of chylothorax in neonatal period, between 2000 and 2015, in a tertiary Neonatal Intensive Care Unit.

The data were obtained by a retrospective search from the hospital computer database and medical records. Demographic data and information regarding pregnancy and delivery were recorded. Pleural effusion characteristics were also registered: congenital or acquired, laterality, clinical presentation, prenatal diagnosis, gestational age at diagnosis, duration of the effusion and biochemical, cytological and bacteriological analysis of the fluid. It was also recorded, data on treatment and neonatal morbidity and mortality.

Etiology of the chylothorax was established according to the clinical setting and medical history.

Results

Seven cases of neonatal chylothorax were identified: four of congenital etiology and three of traumatic etiology (Table 1).

In the four cases of congenital chylothorax, the pleural effusion was bilateral, and in three of these, occurrence was early the prenatal period, which required *in uteru* intervention.

Table 1 – Cases with Chylothorax Diagnosed during their Neonatal Period

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
GA	32 W	33 W	31 W	32 W	35 W	36 W	32 W
Gender	M	F	F	M	M	F	M
Delivery	CS	CS	CS	CS	Spontaneous	Spontaneous	Spontaneous
BW	1.720 g	2.385 g	975 g	2.600 g	2.175 g	2.750 g	1.860 g
Apgar index 1'/5'	1 / 4	7 / 8	5 / 8	4 / 7	9 / 10	8 / 10	7 / 7
Neonatal resuscitation	EI + IMV	–	Bag-mask ventilation with O_2	EI + IMV	Elective EI + IMV	–	EI + IMV
Antenatal sonographic changes	Bilateral pleural and pericardia effusion (21 W)	Bilateral pleural effusion (17 W)	Severe FGR	Cystic hygroma (17 W) Bilateral hydronephrosis (23 W) Mega cisterna magna (23 W) Recurrent pleural effusion (17, 26 and 31 W)	LDH (21 W)	–	Esophageal atresia
In utero fetal interventions	In utero chest tube (31 W)	In utero thoracentesis (intrapartum)	–	In utero thoracentesis (31 W and 32 W)	–	–	–
Hydramnios	Yes	No	No	Yes	Yes	No	Yes
First minutes of life interventions	Bilateral thoracentesis	Bilateral thoracentesis	–	–	–	–	–
Associated medical conditions	Nonimmunefetalhydrops	–	Post-natal trisomy 21 diagnosis	Post-natal Noonan syndrome	LDH D2 surgery	LDH D2 diagnosis D2 surgery	Esophageal atresia with endotracheal fistula D3 surgery
Pleural effusion side	Bilateral	Bilateral	Bilateral	Bilateral	Left	Left	Right
Age at diagnosis / PO day	Antenatal (21 W)	Antenatal (17 W)	D11 of age	Antenatal (17 W)	D6 of age/ D4 PO	D12 of age/ D10 PO	D13 of age/ D10 PO
Respiratory support	17 days	1 day (death on 1st day)	31 days (death on 31st day)	75 days	17 days	4 days	24 days
QT etiology	Congenital	Congenital	Congenital	Congenital	Traumatic (post-surgical)	Traumatic (post-surgical)	Traumatic (post-surgical)

BW – birth weight , CS –Caesarian section, D – days of age, EI – endotracheal intubation, F – female, FGR – fetal growth restriction, g – grams, GA – gestational age, IMV – invasive mechanical ventilation, LDH – left diaphragmatic hernia, M – male, PO – post-operative, QT – chylothorax, W - weeks

The three cases of traumatic chylothorax (Cases 5, 6, and 7) appeared after thoracic surgery (repair of left diaphragmatic hernia (LDH) n=2; and repair of esophageal atresia n=1). Case 6 did not present a prenatal diagnosis of LDH. It was identified through respiratory difficulty with episodes of cyanosis for 18 hours of life. Pleural effusion appeared on the fourth day (Case 5) and on the tenth day (Cases 6 and 7) after surgery on the side on which the surgery was done (unilateral effusion on the left in the LDH cases, and on the right in the case with esophageal atresia). The confirmation of the diagnosis was done by biochemical, cytological and bacteriological analysis of the pleural fluid (Table 2); triglycerides level above 110 mg/dl was found only in case 3, the one that had several previous days of enteral feeding.

Table 2 –Characteristics of Pleural Fluid

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
White blood cell count (/µg)	2.850	2.050	8.060	4.894	3.703	3.010	6.220
Lymphocytes (%)	98%	93%	80%	97.6%	92.2%	90.8%	94%
Protein (g/dl)	2,5	2.2	2.9	2.9	2.4	2.6	2.1
Triglycerides (mg/dl)	19	25	295	10	41	46	69
Culture	Negative	Negative	Negative	Negative	Negative	Negative	Negative

Given the volume and persistence of the effusion, it was necessary to place a chest tube in the four cases of congenital chylothorax and in one of the cases of traumatic chylothorax (Case 7).

With the exception of Case 2, all the neonates each had a period of TPN, with fasting in the initial phase of treatment (Table 3).

Table 3 – Clinical Course and Treatment

Cases	**TPN**	**Octreotide (days) (days)**	**Clinical course and treatment**	**Clinical complications and treatment**
Case 1	16	–	Resolution with TPN	Hypoalbuminemia (min 2.1 g/dl) Albumin iv (1x) Weekly lipid perfusion (5 W)
	7	–	First relapse (after starting SEF): Resolution with TPN	
	7	16	Second relapse (after starting MCT): Resolution with TPN and octreotide (4µg/kg/h)	
Case 2	–	–	IV fluids Death after 14 hours due to respiratory insufficiency	Bilateral pneumothorax
Case 3	20	8	Treatment failure with TPN, octreotide (4µg/kg/h) started on TPN 7th day Imagiological resolution on D26 of age Death on D31 due to multifocal pneumonia and respiratory inefficiency	Hypoalbuminemia (min 1.2 g/dl) Albumin iv (8x)
Case 4	55	48	Treatment failure with TPN, octreotide (4µg/kg/h) started on TPN 7th day	Hypoalbuminemia (min 1.7 g/dl) Albumin iv (10x) Hypogammaglobulinaemia (min 127 mg/dl) Imunoglobulin iv (4x)
	21	20	First relapse (after starting MCT): Resolution with TPN and maximum dose octreotide (12µg/kg/h) Start of enteric nutrition with MCT (3 W) Imagiological resolution on D86 of age	
Case 5	9	–	Resolution with TPN Start of enteric nutrition with MCT (2 W) Imagiological resolution on D19 of age	–
Case 6	7	–	Resolution with TPN Start of enteric nutrition with MCT (1 W) Imagiological resolution on D15 of age	–
Case 7	26	18	Treatment failure with TPN, octreotide (12µg/kg/h) started on TPN 7th day Start of enteric nutrition with MCT (3 W) Imagiological resolution on D33 of age	Hypoalbuminemia (min 2.3 g/dl) Hypogammaglobulinaemia (min 230 mg/dl) Imunoglobulin iv (1x)

D - day, iv – intravenous, MCT – medium chain triglycerides, min – minimum, SEF – semi-elemental formula, TPN – total parenteral nutrition, W – week

Four did not respond to conservative treatment (Cases 1, 3, 4 and 7) and were effectively treated with a continuous perfusion of octreotide. Octreotide perfusion was started with an initial dose of 1 µg/Kg/h and increased progressively depending on therapeutic response up to 12 µg/Kg/h. Cases 1 and 3 responded effectively to a minimum effective dose of 4µg/kg/h, while Cases 4 and 7 to a maximum dose of 12 µg/kg/h (Table 3). There were no secondary effects linked to the use of octreotide. Although surgery is indicated when conservative treatment fails after three or four weeks, in Case 4, it was decided to maintain conservative treatment with octreotide perfusion due to the unstable clinical profile of the patient.

The period for treating chylothorax varied from 15 to 86 days, with traumatic chylothorax cases showing earlier improvement.

There were complications in all cases of congenital chylothorax and in one of the cases of traumatic etiology: hypoalbuminaemia (Cases 1,3,4 and 7), hypogammaglobulinaemia (Cases 4 and 7) and bilateral pneumothorax (Case 2). There were two deaths (Cases 2 and 3), and in both, the cause was attributed to an underlying illness.

Discussion

Although rare, chylothorax is the main cause for pleural effusion in neonates. Whether it is of congenital or acquired etiology, treatment is initially conservative and includes various pre and post-natal therapeutic measures [1,18,19].

In utero intervention should always be considered to treat fetalchylothorax of larger dimensions and/or with signs of decompensation. Some researchers propose the positioning of a pleuro-amniotic shunt in effusions appearing before 24 weeks of gestation. Others prefer decompressive thoracentesis as the technique of first recourse, although it is a procedure that is limited to rapid re-accumulation of pleural fluid. In effusions of a small volume or those that appear in the third trimester, the risk of lung hypoplasia is low and the spontaneous resolution is observed many times, with sufficient ecography vigilance [12,20].

After birth, conservative treatment consists of pleural drainage for lung expansion and replacing nutritional losses. Ventilatory support is frequently required. Repeated thoracentesis can be carried out, however the introduction of a chest tube is preferable in effusions of greater volume [1]. Some authors advocate the use of TPN with fasting from the initial phase of treatment. To maintain nutritional status without significantly increasing lymph volume, other researchers use diets with fat, from the start, in the form of MCT which, in theory, are directly introduced into the portal venous system, without increasing the production and flow of lymph through the thoracic duct [1,13,14].

In cases not resolved through conservative treatment, the successful use of octreotide in treatment has been reported [15,17,21]. Octreotide is a long-acting somatostatin analog, with properties which inhibit the growth hormone, glucagon, insulin and the thyroid-stimulating hormone (TSH). Its effects on the gastrointestinal system are responsible for effectively reducing the production of lymph once the blood flow is reduced, and other hormones like serotonin, gastrin, vasoactive intestine peptide, secretin, motilin and pancreatic polypeptide are inhibited [1,21]. It can be administered intravenously (1-4 µg/Kg/h up to 12 µg/Kg/h) or subcutaneous injections (20 to 70 µg/Kg/day in 3 doses) [15]. If there is improvement, treatment can be continued for eight to 12 days with a minimum effective dose.

In our sample octreotide has proven to be effective and safe for the treatment of neonatal chylothorax without any secondary effects observed when it was administered. However there are studies that show that there was no clear and consistent effect of octreotide treatment on pleural effusions. Systematic clinical research is needed to establish treatment efficacy and to develop a safe treatment protocol [22,23].

The decision on when is the best time to introduce octreotide treatment, the best dosage to be used and how long the treatment should last is still under discussion. The rarity of these incidents and the scattering of published cases, to date, do not allow protocols of practice to be drawn up, but their need should encourage multicentric studies to be carried out, in order to optimise outcomes and to enable standards of practice to be drafted.

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