Congenital chylothorax and trisomy 21 syndrome

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Abstract

Introduction: Congenital chylothorax is known as abnormal leakage and accumulation of chyle in the pleural space. Chyle is a lymphatic fluid of intestinal origin. Although congenital chylous effusions are relatively rare in infancy, they have serious clinical consequences and can be potentially life-threatening disorder. Some case reports including this one suggest that there may be more patients with trisomy 21 syndrome associated with congenital chylothorax. To the best of our knowledge, there are no evidence-based guidelines to support the use of octreotide in chylothorax management as first-line agent. Our case management provides an evidence that octreotide is more effective than medium-chain triglyceride (MCT) in treating chyle accumulation. We aim to provide guidance for the optimal management of congenital chylothorax in infancy.

Case summary: Here, we report a case of a premature baby born at 30 weeks gestation. Baby was diagnosed antenatally with trisomy 21 syndrome and severe bilateral congenital pleural effusions which subsequently confirmed after birth as chylothorax. Bilateral thoracenteses were performed and bilateral chest tubes were inserted soon after birth. Expressed breast milk and MCT formula was introduced in the first week of life; however, chylothoraces significantly re-accumulated. Congenital chylothorax was treated successfully after administration of octreotide infusion along with intercostal decompression of the pleural effusion and total parenteral nutrition (TPN) as adjunctive therapy. In our case there wasn’t any complication with the use of octreotide.

Conclusion: This case is of particular interest because it provides an evidence for the efficacy of octreotide usage in chylothorax management. The MCT diets have been used as first-line treatment; however, its efficacy has met with variable success in treating chylothorax. Therefore, octreotide may be used as first-line agent along with adjunctive therapy of parenteral nutrition and intercostal thoracostomy to decompress the pleural effusion. The early administration of octreotide may allow the patient to avoid invasive procedures. Some case reports including this one suggest that congenital chylothorax might be listed as one of trisomy 21 syndrome complications.
Keywords

Trisomy 21 syndrome, congenital chylothorax, chylomicrons, octreotide, thoracocentesis, total parenteral nutrition.

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How to cite


Introduction

Congenital chylothorax is known as abnormal leakage and accumulation of chyle in the pleural space. Chyle is a lymphatic fluid of intestinal origin. Congenital chylothorax is often caused by congenital lymphatic system malformation or obstruction of its main tributaries [1]. Although congenital chylous effusions are relatively rare in infancy, they have serious clinical consequences and can be a potentially life-threatening disorder [2-4]. Here, we report a case of a premature baby diagnosed antenatally with trisomy 21 syndrome and severe bilateral congenital pleural effusions which subsequently confirmed after birth as chylothorax. Some case reports including this one suggest that there may be more patients with trisomy 21 syndrome associated with congenital chylothorax. Therefore, congenital chylothorax might be listed as one of trisomy 21 syndrome complications [3]. To the best of our knowledge there is lack of evidence-based guidance to assist chylothorax management and there is no existing evidence to recommend the use of octreotide as a first-line agent. Octreotide is a synthetic, long-acting somatostatin analogue; it has the advantage over somatostatin of a longer half-life, greater potency and the option of subcutaneous administration. More recently, it has been used successfully as a second-line agent in conservative treatment of chylothorax along with total parenteral nutrition (TPN) and pleural drainage as adjunctive therapy. Somatostatin is an inhibitor of gastrointestinal tract (GIT) motility, and reduces the volume of gastric, pancreatic, and intestinal secretions. Therefore, it helps to keep the GIT empty, which in turn decreases the chyle production. It also plays a role in reduction of intestinal blood flow by vasoconstriction of the splanchnic circulation and as a result the lymphatic fluid production will be reduced. In our case octreotide administration was far more effective than medium-chain triglyceride (MCT) in treating congenital chylothorax with no significant side effects. The accumulation of chylothorax has been treated successfully, and diminished significantly with octreotide infusion. Therefore, octreotide may be used as first-line treatment along with adjunctive therapy of parenteral nutrition. The early administration of octreotide may allow the patient to avoid invasive procedures. We aim to provide guidance for the optimal management of congenital chylothorax in infancy and highlight the efficacy of octreotide in the management of chylothorax. The ultimate aim is to improve patient safety through appropriate management and improve the parents and newborns experience.

Case presentation

A male premature baby, born at 30 weeks gestation, was diagnosed by antenatal scans with trisomy 21 syndrome which confirmed with amniocentesis. On serial antenatal ultrasound scans, the baby was found to have worsening pleural effusions (Fig. 1A), skin oedema and polyhydramnios. In-utero drainage of the pleural effusions was performed at 28 weeks gestation. However subsequent antenatal scans showed re-accumulation of pleural effusions and intermittently absent end diastolic flow (EDF). The decision was made to deliver the baby by emergency caesarean section. Emergent resuscitation was performed successfully and the baby was ventilated immediately after birth. On examination, the baby had all physical features of Down syndrome including low-set ears, excess skin at the back of the neck, upward slanting eyes, epicanthic folds and sandal gaps. Post-natal chest X-ray (Fig. 1D) and ultrasonography (Fig. 1C) confirmed bilateral pleural effusions. Echocardiogram was performed and was reported as normal. Bilateral thoracentesis and bilateral chest tubes were inserted soon after birth (Fig. 1B) due to the large size of the pleural effusion which compromised the respiratory system. Daily quantification of drainage was used
to determine clinical improvement and also used as a guide for fluid imbalance and replacement of daily losses. TPN was commenced on the first day of life and expressed breast milk (EBM) enteral feeds was introduced on the second day via nasogastric tube. Enteral EBM feeding was stopped after three days due to significant re-accumulation of chylothoraces. An MCT formula (Monogen®) was introduced on day 7 of life; however, chylothoraces re-accumulated, which were drained by another bilateral thoracentesis and bilateral chest tubes. Enteral MCT feeding was stopped as there was no clinical improvement and the daily chyle drainage flow rate was high (> 10 ml/kg/day). Biochemical analysis of the pleural effusions was as follows: on the first day of life, protein 2.3 mg/dL, albumin 2.0 g/dL, triglycerides < 0.08 mmol/L, white blood cells (WBC) > 2,000/mm³, lymphocytes > 70% and there was no bacteria on the gram stain. Pleural effusion was diagnosed as chylothorax, on the basis of this analysis. The triglycerides level increased significantly from < 0.08 mmol/L prior introduction of enteral feed to 5.12 mmol/L after increasing the enteral feed volume of EBM and MCT.

Octreotide eventually started on day 15 of life and TPN was used as adjunctive therapy. It was started at low dose of 1 mcg/kg/hour, intravenous (IV) infusion, increased gradually to maximum of 4 mcg/kg/hour with good effect. Following introduction of octreotide, the production of pleural effusion significantly reduced. Octreotide infusion continued for a total of 10 days, gradually weaned over a course of 4 days and successfully stopped. The use of octreotide in our patient was very effective and safe. We monitored his electrolytes on daily basis (Na, K, glucose, Ca), liver function twice weekly (total protein and albumin), coagulation screen twice weekly (PT, PTT and fibrinogen, antithrombin III level) and total IgG level fortnightly. Thyroid function was monitored twice monthly (free T4 and TSH) when octreotide was used. Neither hypotension nor hyperglycemia was observed, and there was no change in inotropic doses required in our patient. He was ventilated for 15 days and required inotropic support for the same period. In view of significant protein losses via pleural effusions, he required multiple human albumin solution 4.5% (HAS) infusions. He spent 45 days in total at the neonatal unit. Prior to discharge the baby was gradually and successfully weaned onto full breast milk feeding without an evidence of re-accumulation of chylothoraces.

Discussion

According to Brescia, chylothorax was first diagnosed by Bartolet (1633) and described as an accumulation of chyle in the pleural space as a result of damage or obstruction to the thoracic duct or its main tributaries [1]. Congenital or primary chylothorax is the most common pleural effusion in neonatal period and it usually develops spontaneously; however, it is a relatively rare in infancy. Congenital chylothorax can be idiopathic due to congenital lymphatic malformation, atresia or hypoplasia of the thoracic duct or may be associated with various genetic diseases such as Noonan’s, Turner’s and Down’s syndromes. It was reported that approximately 4.9% of foetuses diagnosed with Down syndrome was associated with pleural effusions [3]. Congenital chylothorax may occur spontaneously or in association with other conditions such as polyhydramnios, hydrops fetalis, intra-thoracic mass lesions, or superior caval vein obstruction [4]. The incidence of primary chylothorax is reported as 1 in 2,000 Neonatal Intensive Care Units (NICU) admissions. If not treated appropriately, it is a potentially life-threatening disorder that can lead to serious respiratory distress, metabolic disorder, immunodeficiency and nutritional complications. Mortality rates range from 20-60% depending upon associated findings, gestational age, and the duration and severity of the chylothorax [5].

Figure 1. A. Prenatal ultrasound demonstrating the presence of bilateral large pleural effusion. B. Postnatal chest x-ray showed bilateral pleural drains. C. Postnatal trans-thoracic US image showed a hypo-echoic area representing a pleural effusion between the chest wall and atelectatic lung. D. Postnatal chest x-ray showed large bilateral pleural effusions and collapsed lungs.
Pathophysiology

The thoracic duct is the main vessel for the transport of chyle and other nutrients from the intestine to the circulation. In adults, the thoracic duct length is approximately 38-45 cm, and around 5 mm in diameter. The thoracic duct originates from the convergence of the intestinal trunk and the right and left lumbar trunks forming the cisterna chyli, which lies behind and to the right side of the aorta. It extends from the level of the 2nd lumbar vertebra to the root of the neck and ends at the junction of the left subclavian vein and left internal jugular vein, below the level of the clavicle. It collects and transports the lymph from the whole body apart from the right side of the thorax, right arm, and right side of head and neck, which are drained by the right lymphatic duct. The length of the right lymphatic duct is about 1.25 cm, and ends at the junction of the right subclavian vein right internal jugular vein. Thoracic duct normally transports around 150 mL/kg/day of fluid. The chyle flow rate is variable and depends on the duct wall smooth muscle response to vagal and splanchnic stimulation. In addition, acetylcholine, norepinephrine, dopamine, serotonin and histamine all increase thoracic duct contraction and chyle flow. The chyle production and flow rate are reduced by starvation and opiates [6].

The word “chyle” comes from the Latin word which means “juice”. The chyle is a fluid enriched with high triglycerides content secreted from the intestinal cells and often has a turbid milky appearance, in particular after ingestion of fatty meals. Chyle has a clear amber-coloured appearance in the fasting state and after ingestion of low fat diets due to low fat contents. Approximately 60% of the ingested fats are transported into the venous blood via the thoracic duct. Dietary fats consist of different fatty acid chain lengths triglycerides, which are metabolised differently. The majority of the triglycerides of the dietary fats are long-chain triglycerides (LCTs) which are extruded into lacteals from the intestinal “jejunum” mucosal cells to the circulation via the thoracic duct. LCTs require transformation into lipoprotein “chylomicron” to be transported via thoracic duct into venous blood. MCTs are more water soluble and absorbed from the GIT directly to the portal circulation, bypassing the lymphatic system, for further metabolism in the liver.

Chyle is an alkaline fluid (pH 7.4-7.8) and contains large amount of triglycerides, proteins, electrolytes, glucose, and fat soluble vitamins. Lymph is the other main constituent of chyle and made of immunoglobulins and high white cell counts, the majority of which is T-lymphocytes, which usually keep this fluid bacteriostatic (Tab. 1). Glucose level and electrolytes concentration are usually similar to plasma. The diagnosis of chylothorax is established by measuring triglycerides level in the pleural fluid. Pleural triglycerides concentration of greater than 110 mg/dL strongly supports the diagnosis of a chylothorax, with 1% chance of being non-chyloous, but triglycerides concentration of less than 50 mg/dL has only a 5% chance of being chyloous. If pleural triglycerides concentration is between 50 and 110 mg/dL, lipoprotein analysis should be performed. The gold standard test is the cytological analysis which reveals chylomicrons (protein and fat globules) that stain with Sudan III [7, 8].

Table 1. Chyle composition and characteristics (from van Straaten et al. [8], modified).

<table>
<thead>
<tr>
<th>Character reference</th>
<th>milk-like, serous, or sanguineous appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odour</td>
<td>odourless</td>
</tr>
<tr>
<td>Culture</td>
<td>sterile</td>
</tr>
<tr>
<td>pH</td>
<td>7.4-7.8</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.012-1.025</td>
</tr>
<tr>
<td>Total fat</td>
<td>0.4-6.0 g/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>65-220 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt; 80 mg/dL</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>present</td>
</tr>
<tr>
<td>Total protein</td>
<td>2.2-6.0 g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.2-4.2 g/dL</td>
</tr>
<tr>
<td>Globulin</td>
<td>1.1-3.1 g/dL</td>
</tr>
<tr>
<td>Sodium</td>
<td>104-108 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.8-5.0 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>3.4-6.0 mEq/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>85-130 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>8.0-17 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>48-200 mg/dL</td>
</tr>
<tr>
<td>Fibrogen</td>
<td>16-24 g/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>5.0-21.0 (U/mL)</td>
</tr>
<tr>
<td>AST</td>
<td>22-40 (U/mL)</td>
</tr>
<tr>
<td>Amylase</td>
<td>50-83</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>2,000-10,000/mm³</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>400-6,800/mm³</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.
In the investigations section, it was explained that a chest X-ray should be performed to identify pleural effusion. Ultrasonography will determine whether there is free fluid in the pleural space or organized as seen in empyema. Chest CT scans and lymphangiography can be helpful to identify the site of chyle leakage and to ascertain the cause of chylothorax. Echocardiogram and venogram are essential to value for thrombosis in the left jugular, subclavian, innominate veins, or superior vena cava.

In the Conservative therapy section, it was noted that the conservative treatment includes thoracocentesis, intercostal chest tube insertion for pleural drainage, dietary modification and somatostatin. Non-operative management of chylothorax in children is successful in approximately > 80% of reported cases. The response to conservative treatment will be indicated by a reduction of lymphatic flow rate and is usually evident within 3-6 days after initiation of treatment. It may take up to 3-6 weeks before surgical procedures will be considered.

The initial approach to conservative management of chylothorax is to relieve the thoracic pressure on the lungs by thoracocentesis, which allows re-expansion of the partially collapsed lungs and obliterates the pleural space, and this will permit an accurate measurement of chyle production. The first thoracocentesis is usually used for diagnostic purposes; however, if size of the pleural effusion is large and compromises lungs function then an intercostal chest tube should be inserted for continuous drainage. Careful monitoring of chyle flow rate and replacement of daily fluid losses are essential during the continuous pleural drainage, as well as monitoring serum albumin concentration, electrolytes level, and lymphocyte count. Quantification of daily chyle flow is imperative to determine clinical improvement. Chyle flow rate of less than 10 mL/kg/day indicates improvement, chyle flow rates of more than 10 mL/kg/day means failure, after 4 weeks of conservative management [9, 10].

Administration of MCT as a source of fat has been recommended as first step in conservative treatment; however, its efficacy have met with variable success in treating chylothorax. This is because any oral enteral feeding increases lymph flow [11]. MCTs are mainly water soluble and absorbed from the GIT directly to the portal circulation, rather than the lymphatic system. Monogen® is the most popular MCT-based enteral formula used for children with lipid and lymphatic disorders. MCT is the major constituent of Monogen® fatty acids and is provided by fractionated coconut oil, while the LCT constitutes only 7% and is provided by walnut oil. Monogen® also has a substantially higher energy level than alternative feeds, which is important for patients with chylothorax as they have high energy requirements due to increased metabolic demand from the chyle loss. Some studies have recommended stopping enteral feeding and initiating TPN at the time of chylothorax diagnosis to reduce the chyle flow and allow healing of the thoracic duct.

Comparison of enteral versus parenteral nutrition shows that the thoracic duct closure occurs faster with TPN and without enteral feeding in the setting of chylothorax [12].

Octreotide is a synthetic, long-acting somatostatin analogue; it has the advantage over somatostatin of a longer half-life, greater potency and the option of subcutaneous administration. Octreotide can be given as a continuous IV infusion, IV bolus twice daily or can be also given subcutaneously (SC). It starts at a low dose of 0.5 mcg/kg/hour and increase gradually to a maximum of 10-12 mcg/kg/hour according to the patient’s response. Side effects of octreotide include hyperglycaemia, hypothyroidism, nausea, diarrhoea, renal and liver impairment [13-17].

In the Surgical therapy section, it was explained that surgical intervention is considered if chyle accumulation is persistent or if reduction of chyle flow failed for more than 2 weeks despite conservative treatment. It may also be considered in patients who are malnourished and those who become immunologically challenged.

Lampson (1948) reported the first successful surgical intervention of supra diaphragmatic thoracic duct ligation. Thoracotomy surgical ligation of thoracic duct is successful in around 90% of patients when performed just above the right hemi-diaphragm, between T8-T12 [18]. There is usually some obstruction to lymph flow distal to the ligated site until new collateral channels develop later to redirect the chyle around the ligation point [19].
Video-assisted thoracic surgery has been used recently and considered as a less invasive approach. Thoracoscopy thoracic duct legation has the advantages of less post-operative pain, a quick recovery and a shorter hospital stay. Endoscopic clips or fibrin glue are used at the site of thoracic duct leak [20-22]. Fluoroscopic percutaneous embolisation (FPE) has also been used recently as an alternative method to open surgery and offers a minimally invasive procedure. One of the advantages of FPE is being safely performed at an earlier time even in debilitated patients [23-25].

Milsom (1985) recommend pleuroperitoneal (PP) valved shunting in refractory chylothorax after failure of conservative therapy. PP shunting is an external communication between the pleura and peritoneum, which allows the fluid to be drained into the peritoneal cavity. This approach prevents further loss of chyle and its nutritionally important constituents, as the fluid in the peritoneal cavity will be absorbed by lymphatic vessels into the right thoracic duct. This method has the advantage of minimising the immunological and nutritional deficits which is common in chylothorax. One of the disadvantages of the PP shunting is possible occlusion with fibrinous debris which may require replacement. Contraindication to PP shunting includes presence of ascites and liver failure where a pleurovenous (PV) shunt will be considered as alternative method [26-30].

Conclusion

Congenital chylothorax is the most common pleural effusion in neonatal period. It is a relatively rare in infancy; however, it is a potentially life-threatening disorder. Some case reports including this one suggest that there may be more patients with trisomy 21 syndrome associated with congenital chylothorax. Therefore, congenital chylothorax can be listed within the complications of trisomy 21 syndrome. Management of chylothorax requires the physician to individualise the work-up because of diversity of pathogenesis. Treatment of congenital chylothorax includes conservative and surgical managements. Conservative management in children is successful in approximately > 80% of reported cases and should be tried for at least 3-6 weeks before surgical intervention will be considered. Initial conservative therapy includes intercostal drainage of the pleural effusion, along with nutritional support in the form of TPN. MCT and somatostatin have been used for reduction of chyle formation. The MCT diets have been used as first-line treatment; however, its efficacy has met with variable success in treating chylothorax. Octreotide is a synthetic, long-acting somatostatin analogue; it has the advantage over somatostatin of a longer half-life, greater potency and the option of SC administration. To the best of our knowledge, there is lack of existing evidence to use octreotide as a first agent in management of congenital chylothorax. However, our case showed that octreotide is a relatively safe drug, and far more effective than MCT in resolving the chylothorax. It allows the patient to avoid invasive procedures, such as reinsertion of intercostal drainage tubes and potential other surgical interventions. Therefore, octreotide may be used as first-line agent along with adjunctive therapy of parenteral nutrition and thoracostomy tubes to decompress the pleural effusion. Further studies assessing the efficacy of octreotide in the management of chylothorax are warranted.

Declaration of interest

The Author declares that there is no conflict of interest.

References