OCTREOTIDE AND CONGENITAL CHYLOTHORAX. CASE REPORT AND REVIEW OF THE LITERATURE.

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ABSTRACT
Objective: To report a newborn with a congenital chylothorax treated successfully with octreotide. To review the literature on the use of octreotide in congenital chylothorax.
Case Summary: Congenital chylothorax is a rare but potentially life threatening condition. We describe a premature baby with a congenital chylothorax associated with a persistent left sided superior vena cava which failed to respond to tube thoracostomy and parenteral nutrition. The pleural drainage diminished rapidly after starting Octreotide and surgery was avoided.
Conclusion: Octreotide is emerging as a safe, effective and noninvasive option for the treatment of congenital chylothorax.
Key words: chylothorax, Octreotide, Somatostatin, vena cava

Introduction
The commonest cause of pleural effusion in the newborn period is chylothorax.1
Although a combination of thoracostomy drainage and dietary modification is the first-line therapy in the management of congenital chylothorax this is not always successful. Conventional treatment after failure of conservative measures is surgical but this is often difficult.
The beneficial effects of Somatostatin in reducing lymph production in congenital chylothorax were first described in 2003.1 Recently reports have appeared documenting the benefits of octreotide, a synthetic long-acting analogue of somatostatin, in congenital chylothorax. We report a newborn with a congenital chylothorax treated with octreotide and review the literature on this subject.

Case report
A 2.2 kilogram female infant was born by forceps delivery at 33 week gestation after spontaneous onset of labour. There were no antenatal problems. She developed respiratory distress and required mechanical ventilation for 17 hours. Chest x-ray (CXR) on day one of life showed a small right sided pleural effusion. After extubation she was established on formula feeds Nutriprem 2 (Cow & Gate®).

No dysmorphic features were noticed and her karyotype was normal. On day 21 she became tachypnoeic and repeat CXR showed a right sided pleural effusion of the same size as before. Two milliliters of milky-appearing fluid was aspirated from the right chest. Laboratory analysis of the fluid showed a lymphocytosis and elevated triglycerides. Feeds were changed to a medium chain triglyceride formula (MCT). Because of increasing tachypnoea a chest drain was inserted on day 30 of life and 40 mls of chyle was drained. A percutaneous central venous catheter was inserted via left antecubital fossa on day 37 for total parenteral nutrition (TPN). A CXR performed after line insertion

Table 1 Reported side effects of octreotide
- Transient loose stools15
- Nausea/Vomiting8
- Hypoglycemia, Hyperglycemia4
- Recurrent chylothorax8
- Necrotising enterocolitis10
- Pulmonary hypertension11
- Bloody diarrhoea19
- Abdominal distension20

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Table 2  Previous reports on the use of octreotide in congenital chylothorax

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Gestation age (weeks)</th>
<th>Weight at birth (kg)</th>
<th>Age chylothorax diagnosed (days)</th>
<th>Age octreotide commenced (days)</th>
<th>Duration of octreotide therapy (days)</th>
<th>Side effects</th>
<th>Dose of octreotide (mcg/kg/h) i/v</th>
<th>Successful/Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Au M[1]</td>
<td>1</td>
<td>36</td>
<td>Not stated</td>
<td>14</td>
<td>33</td>
<td>7</td>
<td>None</td>
<td>3.5</td>
<td>Successful</td>
</tr>
<tr>
<td>Goto[2]</td>
<td>1</td>
<td>26</td>
<td>0.467</td>
<td>16</td>
<td>36</td>
<td>3</td>
<td>None</td>
<td>0.3</td>
<td>Successful</td>
</tr>
<tr>
<td>Coulter[2]</td>
<td>1</td>
<td>26</td>
<td>0.96</td>
<td>65 thoracic duct ligation on day 103</td>
<td>109</td>
<td>27 initially 14 after recurrence</td>
<td>Hyperglycemia, Emesis, Recurrence</td>
<td>Started on 4mcg/kg/d s/c increased to 24mcg/kg/h i/v</td>
<td>Successful</td>
</tr>
<tr>
<td>Young[2]</td>
<td>1</td>
<td>40</td>
<td>3.7</td>
<td>1</td>
<td>2</td>
<td>17</td>
<td>None</td>
<td>40mcg/kg/d s/c increased to 70mcg/kg/d s/c</td>
<td>Successful</td>
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<tr>
<td>Sivasli[2]</td>
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<td>34</td>
<td>2.07</td>
<td>15</td>
<td>22</td>
<td>9</td>
<td>None</td>
<td>3.5</td>
<td>Successful</td>
</tr>
<tr>
<td>Rasiah[2]</td>
<td>1</td>
<td>34</td>
<td>2.5</td>
<td>1</td>
<td>32</td>
<td>10</td>
<td>None</td>
<td>0.5 raised to 10</td>
<td>Successful</td>
</tr>
<tr>
<td>Paget-Brown[2]</td>
<td>1</td>
<td>40</td>
<td>3.68</td>
<td>5</td>
<td>13</td>
<td>10</td>
<td>None</td>
<td>3.5 raised to 10</td>
<td>Successful</td>
</tr>
<tr>
<td>Cannizzaro[2]</td>
<td>1</td>
<td>Not given</td>
<td>Not given</td>
<td>1</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>None</td>
<td>Not mentioned</td>
<td>Successful</td>
</tr>
<tr>
<td>Siu[2]</td>
<td>1</td>
<td>37</td>
<td>3.28</td>
<td>3</td>
<td>19</td>
<td>4</td>
<td>Bloody diarrhoea</td>
<td>3</td>
<td>Successful</td>
</tr>
<tr>
<td>Sahin[2]</td>
<td>1</td>
<td>33</td>
<td>2.33</td>
<td>1</td>
<td>15</td>
<td>Not clear</td>
<td>Abdominal distension</td>
<td>0.5 raised to 10</td>
<td>Successful</td>
</tr>
<tr>
<td>Lauterbach[2]</td>
<td>1</td>
<td>24</td>
<td>69</td>
<td>99</td>
<td>104</td>
<td>4</td>
<td>None</td>
<td>0.3</td>
<td>Successful</td>
</tr>
<tr>
<td>Roehr[2]</td>
<td>1</td>
<td>34</td>
<td>Not given</td>
<td>2</td>
<td>53</td>
<td>21</td>
<td>None</td>
<td>10mcg/kg/d s/c increased to 40mcg/kg/d</td>
<td>Successful</td>
</tr>
</tbody>
</table>

showed the tip of the central line following an abnormal position down left side of the midline, suggesting a left sided superior vena cava (SVC). This was subsequently confirmed with a magnetic resonance imaging scan which demonstrated a persistent left SVC (PLSVC) continuing through the diaphragm as an aygpos vein which joined the left renal vein. This left-sided venous system then drained through the left renal vein and inferior vena cava to enter the right atrium. There was no obstruction in the PLSVC. No intracardiac abnormalities were noted. The right SVC was atretic.

The pleural drainage did not decline with TPN (figure 1). In an attempt to avoid surgery a continuous intravenous infusion of octreotide started at 1 mcg/kg/h and increased gradually to 3 mcg/kg/h. Blood glucose was monitored along with liver and renal function. No side effects were noted. The chest drainage stopped on day 59 and the octreotide infusion was discontinued over the next three days. The chest drain was removed on day 63. Oral feeding was recommenced after six weeks of TPN. A subsequent CXR showed a small residual collection of pleural fluid. More than six months after discharge from hospital the child is growing satisfactory and tolerating a normal diet.

**Discussion**

The cause of most congenital chylothoraces is unknown. This condition is seen in infants with Down's syndrome, Noonan's syndrome, Turner's syndrome, lymphangiomatosis and congenital lymphangiecstasy. It has been postulated that the thoracic duct is weak or anomalous in these conditions and that an increase in venous pressure (e.g.
during delivery) ruptures the duct. Mediastinal malignancies like neuroblastoma may cause a chylothorax due to obstruction or invasion of lymphatics by tumour. Congenital heart disease, SVC obstruction, lobar sequestration and H-type tracheoesophageal fistulae can also present as chylothoraces in the fetus or newborn.

Persistence of the left SVC is the commonest congenital anomaly of the venous system and occurs in 0.5% of the population. The left SVC drains into the right atrium through the coronary sinus in 92% of cases. In 20% of children with a PLSVC the right SVC is absent. We have not been able to find previous reports of an association of a PLSVC with a congenital chylothorax. We speculate that the chylothorax in our case was due to an abnormal thoracic duct associated with the venous malformation.

Congenital chylothorax is usually a transient condition which responds to pleural drainage and dietary modification. Milk formulas containing medium-chain triglycerides (MCT) are the most widely used first-line treatment. There is a significant failure rate from MCT milk which has prompted some authors to recommend TPN in all patients until the pleural effusion has resolved.

Management of a chylothorax by TPN and closed chest drainage is not problem free. Although the lymphatic leak may cease within days, it may persist for months. Prolonged use of TPN is associated with well recognised complications, including infection and liver injury. Intercostal chest tubes block and displace, often requiring multiple replacements. They are painful and increase the risk of infection. Furthermore, prolonged lymphatic drainage results in lymphopenia, hypogammaglobulinemia, hypoproteinemia, coagulopathy, sepsis and fluid and electrolyte imbalances.

If the lymphatic leak fails to settle after two to four weeks of conservative management surgery has been advised. Options include ligation of the thoracic duct, attempting to identify and suture the site of the leak, pleurodesis and pleuroperitoneal shunts. Early surgical intervention in refractory neonatal pleural effusions may reduce morbidity and shorten the length of hospital stay, when successful.

A recent addition to the conservative management of chylothorax is the long acting somatostatin analogue, octreotide acetate. The use of Octreotide in a spontaneous neonatal chylothorax was first reported in 2003. Somatostatin in its native form has limited clinical usefulness because of a short duration of action (half-life less than three minutes) and post-infusion rebound hypersecretion of hormones. To counter these problems synthetic somatostatin analogues were developed and Octreotide is the most widely available. The exact mechanism of action of octreotide is not understood but it probably acts on somatostatin receptors in the splanchnic circulation to decrease lymph fluid production and by decreasing splanchnic blood flow, with a resultant decreased portal venous pressure. Suppression of intestinal fat absorption, mainly long chain triglycerides, also appears to occur, with an increase in faecal fat excretion.

The safety profile associated with short term use of Octreotide in children is favourable. Previously reported side effects are shown in Table 1. Adverse effects in the pediatric cases published to date have been uncommon. Transient, self-resolving, hyperglycemia was reported in one
patient8. There is a theoretical risk of necrotizing enterocolitis (NEC) because of the reduction on splanchnic blood flow. Mohseni-Bod reported a neonate who developed NEC within 72 hours of commencing octreotide to treat a post-operative chylothorax10. Arevalo et al reported two premature neonates with bronchopulmonary dysplasia (BPD) in whom increased oxygen requirements developed during octreotide treatment for enterocutaneous fistula complicating NEC11. They postulated that octreotide treatment may aggravate BPD by causing pulmonary vasoconstriction and hypoxaemia.

Neither the dose nor the route of administration of somatostatin or octreotide for treating a chylothorax has been established. Data from previous case reports documenting the use of octreotide in congenital chylothorax are presented in Table 2. Octreotide can be administered subcutaneously or intravenously. Octreotide dose regimens used previously include either 20 to 70 mcg/kg/day in three divided subcutaneous doses or as a continuous intravenous infusion starting at 1-4 mcg/kg/hr, increasing to 10 mcg/kg/hr12. The duration of therapy is determined by the reduction in the volume of pleural drainage. In the cases reviewed in table 2 the duration of treatment ranged from 3 to 21 days with a mean of 11 days. Octreotide was usually weaned over a period of two to four days while the patient was monitored for reaccumulation of the effusion. Enteral nutrition will normally have been suspended prior to starting Octreotide but several authors reported continuing enteral nutrition during treatment13,2.

Somatostatin is found in high concentration in human milk16. This might have an inhibiting effect on the production of chylothorax if human milk is continued in babies with chylothorax.

**Summary**

Based upon the published literature and our experience, we recommend octreotide as a safe and effective treatment for congenital chylothorax. We recommend administration of octreotide by continuous intravenous infusion.

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**REFERENCES**