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Chylothorax and chylous ascites: Management and pitfalls

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ABSTRACT

Leakage of lymph from the lymphatic ducts causes chylothorax (CT) or chylous ascitis (CA). This may happen for unknown reasons during fetal life or after birth and may also be caused by trauma after thoracic surgery or by other conditions. Fetal CT and CA may be lethal particularly in cases with fetal hydrops that sometimes benefit of intra-uterine instrumentation. After birth, symptoms are related to the amount of accumulated fluid. Sometimes, severe cardio-respiratory compromise prompts active therapy. Most patients with CT or CA benefit from observation, rest, and supportive measures alone. Drainage of the fluid may be necessary, but then loss of protein, fat, and lymphoid cells introduce new risks and require careful replacement. Low-fat diets with MCT and parenteral nutrition decrease fluid production while allowing adequate nutritional input. If lymph leakage does not stop, secretion inhibitors like somatostatin or octreotide are prescribed, although there is only weak evidence of their benefits. Imaging of the lymphatic system is indicated when the leaks persist, but this is technically demanding in children. Shunting of the lymph from one body space to another by means of valved catheters, embolization of the thoracic duct, and/or ligation of the major lymphatics may occasionally be indicated in cases refractory to all other treatments.

Introduction

Lymph is a fluid originated in the interstitial spaces of the body that contains cells, particles, protein, chylomicrons, and, sometimes, bacteria. Lymph enters the lymphatic system, a tortuous and ill-defined network of fine vessels with unidirectional valves, and gains access to the lymph nodes. These act as filters and allow treatment of the fluid by the lymphoid cells before joining the *cisterna chyli* (CC) located between the aorta and the vena cava in front of the first lumbar vertebral bodies. The lymph then reaches the thoracic duct (TD) that ascends in the posterior right mediastinum between the aorta and the azygos vein, then crosses to the left behind the aortic arch, and finally opens itself into the major circulation at the level of the confluence of the left subclavian and jugular veins.

A large share of the total amount of lymph originates in the abdominal organs, particularly the intestine and the liver. Long-chain triglycerides contained in the alimentary fat are digested in the small bowel and reduced to monoglycerides and fatty acids that are absorbed as chylomicrons and enter the lymphatic vessels. This explains why after feeds the lymph is cloudy and milk-like.

The lymphatic system develops early during intra-uterine life. At the 9th week, the CC and the TD are already present and the small lymphatic vessels run along the root of the mesentery although not following closely the main arteries and veins. At this age, the anatomy does not fit exactly that of adults.[1]

When the lymphatic system, particularly its main conduits, is severed or obstructed, the lymph leaks into the surrounding tissues and can fill the pleural or peritoneal spaces, giving rise to several conditions: pleural effusion may correspond to *lympho-thorax*, but when the cellular components of lymph, particularly cells, protein, and fat, are demonstrated, it can be properly designated as *chylothorax* (CT). When a peritoneal effusion (ascites) contains these components, it is called *chylous ascites* (CA) or *chyloperitoneum*. Obstruction and leaks of the lymphatic system can occur before birth, giving rise to threatening fetal disease: massive pleural and/or peritoneal effusions may impair venous return, cardiac output, and renal flow allowing massive exit of fluid and protein into the body tissues that become edematous. This situation is known as *hydrops fetalis* (HF) and can seriously compromise fetal life.

The present study reviews the fetal and neonatal features of chylous effusions and their diagnosis and treatment.

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Etiology

Congenital CT accounts for less than 5% of non-immune HF that is more often related to heart malformations (15%), arrhythmia (10%), twin-to-twin transfusion (10%), chromosomal anomalies and malformations (15%), viral infections (6%), congenital anemia (5%),[2,3] and more rarely, meconium peritonitis[4] or thyrotoxicosis.[5] CT should be diagnosed *in utero* only after ascertaining the lymphatic nature of the effusions. Increased pleural fluid/serum immunoglobulin G ratio may be a reliable marker.[6]

There are several causes for CT and CA. They all involve inadequate chyle transport towards the main circulation because of aplasia, hypoplasia, obstruction, or severance of the thoracic duct. Traumatic delivery or previous surgery for either correction of congenital heart disease[7] or congenital diaphragmatic hernia[8–10] can explain them. Lymphatic malformations[11] or mediastinal tumors or cysts can also cause CT, but a number of cases are "idiopathic." CA is due to organic causes in roughly 50% of cases and infectious, genetic, or idiopathic in the remaining ones.[12]

When circulation of chyle is impaired, the valvular competence is lost and reflux into enlarged lymphatic collateral paravertebral channels takes place. Lymph is redirected via bronchial, pericardial, diaphragmatic, and axillary channels to the subclavian vein. When compliance of dilated lymphatics is overcome, fluid leaks into the pleural, pericardial, or abdominal spaces. Chyle from the diaphragm drains into the lymph nodes of the tracheal bifurcation and reaches the neck via peri-tracheal lymphatics. These also drain the lungs, and this overload causes reflux of chyle into dilated lymphangiectasias that should not be confounded with congenital dilatations of the lymphatic vasculature. "Pulmonary lymphangiomatosis" or "intestinal lymphangiectasia" is not a specific disorder of the lymphatic system but rather represents different stages of the chyle reflux phenomenon into the thorax, or the abdomen. In summary, congenital CT and CA represent a kind of "lymphedema" of the trunk due to lymphatic channel malfunction.

Investigation of genes involved in lymphangiogenesis, like vascular endothelial growth factor receptor type 3 (VEGFR3), integrin 9 (ITGA9), tyrosine-protein phosphatase non-receptor type 11 (PTPN11), and forkhead box protein C2 (FOXC2) in patients with chylous disorders, could not find much evidence of their specific involvement in congenital malformations of the TD.[13] Mutations of in ITGA9 could be prognostic of bad response to chemical pleurodesis.[14] Oligonucleotide comparative hybridization with special arrays (KaryoArray® v3.0, Agilent) and SNP-array (HumanOmni1S-8 BeadChip, Illumina) is under course in newborns with lymphatic disorders.

Clinical features

Fetal disease

Congenital CT or CA can occur during fetal life due to early leakage of lymph into the pleural and/or peritoneal spaces. The lung is compressed and the cardiovascular performance of the fetus is impaired. Cardiac output decreases, the venous return is obstructed, and generalized edema develops. Loss of protein decreases oncotic pressure within the vascular compartment and water leakage to the interstices is increased. This situation of non-immune HF can cause fetal demise in a large proportion of cases[4] that is higher when the diagnosis is made before the 24th week of gestation.[12]

Neonatal disease

Most patients with neonatal pleural effusions are prenatally detected. Cases with HF or massive effusions are identified because of generalized edema, poor cardiovascular function, and severe respiratory distress. When the lungs compressed during fetal life are hypoplastic, the respiratory insufficiency may be extreme. Neonates with CT have decreased respiratory bruits upon auscultation and weak cardiac tones. X-rays and ultrasonography reveal the cause and the magnitude of the effusion. In cases of CA, the abdomen and the scrotum are distended and edematous.[15]

Chyle leak in a newborn can be temporary or not depending mainly on his or her ability to establish lymphovenous communications through collateral channels or mediastinal, lumbar, renal, or hepatic lymph nodes. The sooner the chyle regains access to the general circulation, the milder will be the associated morbidity. The effects of chyle accumulation into the pleural, pericardial, or abdominal spaces can range from being unnoticed to becoming fatal. CT or chylopericardium may cause respiratory failure requiring ventilatory support or cardiac tamponade, respectively. CA is better tolerated, and respiratory insufficiency due to abdominal distention is rarely seen. A newborn with occluded thoracic duct needs weeks to months for developing alternative lymphatic routes. Understanding of the variable individual ability to develop those alternative pathways for chyle is necessary for an interpretation of the clinical features in order to decide the opportunity and the timing of active treatments. Delay in their establishment can be as dangerous as overtreatment.

Once percutaneous evacuation of accumulated chyle is started in both CT and CA, depletion of fluids, proteins, immunoglobulins, and lymphocytes (particularly T-cells) involves a permanent risk of immunosuppression and infection[16] and prompts the use of central venous lines and antimicrobial support that in turn aggravate the risks of infection.

Diagnosis

CT and CA are readily detected by imaging soon after clinical onset. The next diagnostic step is to puncture the pleural space for obtaining fluid and verify that it is indeed lymph. When a neonate has been fed, lymph is easily identifiable because of its milk-like aspect. If not, it is necessary to measure protein and triglycerides and count and characterize the cells. Triglycerides above 1.2 mmol/L or 200 mg/dL and more than 1000 cells/mL with a predominance of lymphocytes, protein levels above 2.5 g/dL, and lactate dehydrogenase above 110 IU/L confirm the diagnosis.[17,18] If the fluid is characterized as lymph, lymphatic malformations in the area should be suspected and investigated by MRI because different management attitudes are in order.[6]

If the fluid is chyle, additional diagnostic tests should be indicated only if the clinical status and the severity of the leak make it advisable. If symptoms are not alarming, no more tests should be performed since spontaneous resolution will intervene in most cases. If this does not happen, identification of chyle leak is desirable in order to plan further steps. In contrast with arterial and venous disease, investigation of lymphatic circulatory disorders evolved quite slowly. For many years, bipedal direct lymphangiography was the method for imaging the CC and TD and eventually for identifying chylous fistulas.[19] But the use of this test, difficult to apply in newborns and small babies, declined since cross-sectional imaging was introduced.[20] Recently, TD obstruction, chylous reflux, and chylous leaks were imaged even in young infants by intranodal lymphography.[21] A simplified technique of injection of 0.5–4.5 mL of ethiodized oil into a lymph node to opacify the lymphatic system in children is currently the alternative to conventional lymphangiography. Unfortunately, this technique is still being introduced in pediatrics and no reports of its use in newborns are available to this day.

Recently, other methods of study of the lymphatic system became available. Non-invasive lymphangio-MRI allows precise