ORIGINAL ARTICLE

Causes and manifestations of chylothorax in children in China: Experience from a children's medical center, 2007–2017

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ABSTRACT

Importance: Chylothorax is the most common cause of pleural effusion in neonates and relatively rare in children. It can cause significant respiratory morbidity. Many clinical entities may contribute to chylothorax.

Objective: To investigate the causes and manifestations of chylothorax in infants and children in China.

Methods: Case records of 107 cases with chylothorax seen in Beijing Children's Hospital from 2007 to 2017 were retrieved and analyzed; follow-up was carried out by telephone.

Results: Of 107 cases, 58.9% (63/107) were primary chylothorax (PC) and 41.1% (44/107) were secondary chylothorax (SC). Also, 36.4% (39/107) were neonatal chylothorax (NC) and 35.5% (38/107) were postoperative chylothorax. In PC with a verified lymphatic anomaly, there was one case of diffuse pulmonary lymphangiomatosis (DPL) and six cases of generalized lymphatic anomaly (GLA), which accounted for 6.5% (7/107) of cases. In most patients, chylothorax was alleviated by conservative treatment based on total parenteral nutrition (TPN); 13.1% (14/107) of cases needed further surgery. In NC, the median duration of TPN was 9 days, but 10 of 20 cases who improved had recurrence upon re-introduction of a fat-free diet, which was alleviated by further TPN. The duration of hospitalization was (23 ± 14) days for congenital chylothorax. Upon long-term follow-up, except for GLA and DPL, most patients were doing well without recurrence.

Interpretation: NC and postoperative chylothorax are the common subtypes. TPN is effective for most patients. Despite a prolonged and fluctuating clinical course, most patients had a good long-term prognosis.

KEYWORDS
Chylothorax, Etiology, Neonate, Postoperative, Lymphatic anomaly

INTRODUCTION

Chylothorax is the accumulation of chyle in the pleural space. It is the most common cause of pleural effusion in neonates. Chylothorax is a relatively rare cause of pleural effusion in children, but can cause significant respiratory morbidity, as well as malnutrition and immunodeficiency, thereby leading to prolonged hospitalization and expense. The etiologies of chylothorax include congenital lymphatic malformations, surgery, trauma, as well as tumors and infection.[1] Researchers have reported that chylothorax may be associated with birth or surgical procedures,[2, 3] but few studies have been done, especially in the mainland of China.

We investigated the causes, distribution, and manifestations of chylothorax in patients admitted to a tertiary children's hospital in northern China over one decade.

METHODS

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Beijing Children's Hospital (BCH; Beijing, China).

Diagnostic criteria

The diagnosis of chylothorax was made if the triglyceride level was >110 mg/dL (1.24 mmol/L) or chylomicrons were present in pleural effusions. A diagnosis of chylothorax could also be made if (i) a "milky" pleural effusion was observed with a monocyte percentage >80% with no evidence of infection or (ii) a high volume of the fluid from chest drains was milky, especially after starting an oral diet, in postoperative patients. [4]

Study design

This was a retrospective study. The term 'chylothorax' was used to search for cases in the medical record system of BCH from August 2007 to September 2017. The data of each case were reviewed and recorded. If the diagnostic criteria met with the medical record, then the patient was included in our analyses. Information on the demography, symptoms, examinations and treatments was recorded. Follow-up was carried out by telephone after data collection.

Etiology

Based on whether a known cause of damage to the thoracic duct was stated in the medical record, chylothorax was divided into "primary" and "secondary" types. [5] In primary chylothorax (PC), onset in newborns was described as "neonatal chylothorax (NC)" or "congenital chylothorax (CC)". If chylothorax onset was beyond the neonatal stage, then it was recorded separately.

Statistical analyses

If measurement data had a normal distribution, they are presented as the mean ± SD. If measurement data had a non-normal distribution, they are presented as median (interquartile range) values. Enumeration data are presented as percentiles.

RESULTS

Search of BCH medical records revealed a potential 110 cases of chylothorax. Of these, 107 (75 male and 32 females) cases matched the diagnostic criteria stated above and were included in the present study. Age range of these patients was from few hours after birth to 11 years of age. The course of chylothorax varied from a few hours to 2 years.

Sixty-three (58.9%) cases had PC. In 39 cases (36.4%),

onset was in newborns (NC). In the same period, 77 cases of pleural effusion in neonates were observed, so NC accounted for 50.6% (39/77) of cases. The clinical manifestations of NC are presented in Table 1. The length of hospital stay was 23 ± 14 d. Four cases had a prenatal diagnosis of pleural effusion. Hydrops fetalis was not diagnosed. In this group, only one case had a known underlying disease (mucolipidemia). All patients improved after treatment and were discharged home except for one case (the family declined further care). Long-term follow-up (0.5–8 years after hospital discharge) was done in 24 patients. Twenty-two cases were well without recurrence after hospital discharge. In one patient the disease relapsed 3 days after hospital discharge and was managed by total parenteral nutrition (TPN) and chemical pleurodesis in another hospital, after which he flourished. One case had recurrence and was re-admitted for chest drainage at 1 year of age. All patients had a normal respiratory rate and diet at follow-up.

For patients with PC, onset occurred from 1 month to 1 year of age in 12 cases, and from 1 year of age onwards for 12 cases. The clinical manifestations for PC onset beyond the neonatal period are presented in Table 2. The length of hospital stay was 23 ± 14 d. In this group, one case had underlying trisomy 21. Two cases had a history of pericardial effusion. Twelve cases had interstitial changes in lung on computed tomography; in one patient, histopathology of pleural lesions suggested that lymphangioma had been diagnosed as diffuse pulmonary lymphangiomatosis (DPL). Eight cases had extrapulmonary features: pericardial effusion; chylous ascites; chylous effusion in knee joints; bony involvement; lymphocyst in axillae; lymphangioma in the spleen; cutaneous lymphangioma; peripheral lymphedema (limbs and scrotum). Of these eight patients, six were diagnosed as having a generalized lymphatic anomaly (GLA). In these eight cases, two patients had been misdiagnosed as having tuberculosis before referral to BCH. Except for one case (the family declined further care), patients improved and were discharged home or referred to a surgical department in another hospital. Long-term follow-up (2–7 years after hospital discharge) was undertaken in 14 cases (including one case of DPL and three cases of GLA). Ten cases were cured without relapse (including two patients who had lymphatic surgery); all were on a normal diet and had a normal respiratory rate at follow-up. Three cases (including two cases of GLA) suffered recurrence; one was treated by thoracic-duct ligation, and the other two had conservative treatments, and they were on low-fat diets and could breathe normally. One case with DPL suffered a recurrence and died subsequently.

Forty-four cases of 107 patients had SC (41.1%). In 38 of the 107 cases (35.5%), SC occurred after surgery. Twenty-seven of the 107 cases (25.2%) developed chylothorax after cardiac surgery. In the other patients,

TABLE 1 Clinical manifestations of neonatal chylothorax (N = 39)

	N(%)	Description
Gestation full term	37(94.9)	
Sex male	29(74.4)	
Onset after birth<1d	24(61.5)	
Onset after birth>7d	14(35.9)	
Symptoms		
Tachypnea	29(74.4)	
Dyspnea	26(66.7)	
Hypoxia	21(53.8)	
Site	Left 20; right 14; bilateral 5	
Treatment		
Respiratory support	19	15 NCPAP; 4 intubation
Chest drainage	30	Left 19, duration 13 (10, 21) d; right 12, duration 11 (9, 29) d; (include 1 bilateral drainage)
Fat-free diet	3	2 alleviated; 1 the family declined further care on the second day
TPN	36	Duration 9 (6, 14) d; 20 improved, in which 10 had a recurrence when re-induce the fat-free diet and were alleviated by further TPN; 16 turned to other treatments as follow
Octreotide	2	1 alleviated, 1 turned to pleurodesis
Chemical pleurodesis (induced by erythromycin)	12	10 alleviated, 2 had no improvement, alleviated by further TPN
Operation	3	2 alleviated by thoracic duct ligation; 1 alleviated by thoracic duct ligation plus pleurodesis
Complications	3	Respiratory infection

Data are presented as N (%), median (interquartile range) or mean ± SD.
NCPAP, nasal continuous positive airway pressure; TPN, total parenteral nutrition.

surgery was carried out for a mediastinum mass (six cases), retroperitoneal tumor (one case), pulmonary lobectomy (one case), posterolateral spinal fusion (one case), plication of the diaphragm (one case), and repair of esophageal atresia (one case) were also done. In cases of chylothorax that occurred not secondary to surgery, three cases were associated with trauma, two cases with malignancy, and one case with tuberculosis. The clinical manifestations of chylothorax after cardiac surgery are presented in Table 3. The length of hospital stay was 32 ± 18 d. The onset time of chylothorax was 2(2, 5) d after operation. In this group, one case had underlying trisomy 21. Twenty-six cases improved and were discharged from hospital except for one case (the family declined further care) because of a complex congenital heart disorder and postoperative infection. Long-term follow-up (0.5 – 8 years after hospital discharge) was undertaken in 14 cases. All cases are doing well eating a normal diet and breathing normally without recurrence except for the patient who died from a complex congenital heart disorder.

DISCUSSION

Chylothorax is a rare disorder. Haines et al reported the prevalence of chylothorax in the UK to be 0.0014%.[6] The exact prevalence in the mainland of China is not known.

In consideration of the complicated clinical course, susceptibility to complications, and variation in medical treatment, attention should be paid to CC and SC.[7] There are multiple causes of chylothorax in infants and children. In the present study, PC and SC accounted for about 60% and about 40%, respectively. NC (also known as CC) and postoperative chylothorax are common etiologies. Surprisingly, there were seven cases of congenital lymphatic malformations, three cases of trauma, two cases of malignancy, and one case of tuberculosis, all of which are rare causes of chylothorax, so the differential diagnoses must be undertaken carefully.

Chylothorax is the most common form of pleural effusion in neonates who have not undergone surgery; it was about 50% at BCH. Wang et al reported 38 neonates with pleural effusion in a tertiary neonatal care center over a 5-year period, in which the cause was CC in seven cases.[8] The incidence of chylothorax can vary depending on location and type of hospital. Approximately half of newborns with CC develop symptoms within 24 h of birth,[5] which tallies with our data (61.5%). In many cases, CC can be diagnosed by prenatal ultrasound.[9] However, in our study, the prevalence of prenatal diagnosis was low. This may

TABLE 2   Clinical manifestations of primary chylothorax onset beyond the neonatal period (N = 24)

	N(%)	Description
Age>1yrs	12(50.0)	
Sex male	18(75.0)	
Days with symptoms pre-hospitalisation	30(11, 60)	
Symptoms		
Dyspnea	17(70.8)	
Tachypnea	14(58.3)	
Cough	14(58.3)	
Fever	6(25.0)	
Cyanosis	5(20.8)	
Chest tightness	4(16.7)	
Cast branches-like sputum	1(4.2)	
Site	Left 10; Right 8; Bilateral 6	
Lymphoscintigraphy	7	5 had thoracic duct obstruction; 1 had lymphatic obstruction; 1 had lymphatic dysplasia
Treatment*		
Chest drainage	16	Left 11, duration 12 (6, 20) d; right 7, duration 11 (6, 13) d; (include 2 bilateral drainage)
Fat-free diet	7	4 improved; 2 improved and turn to a lymphatic surgical department; 1 failed
TPN	16	6 improved; 7 turn to thoracic duct ligation; 3 turned to a lymphatic surgical department in another hospital
Octreotide	2	1 improved; 1 failed
Operation	8	5 alleviated by thoracic duct ligation plus pleurodesis; 1 failed and alleviated by further TPN and pleurodesis in another hospital; 2 improved by thoracic duct ligation but relapse in 1month and 1 year respectively
Complications	2	1 with deep venous thrombosis；1 with electrolyte disturbances

Data are presented as N (%), median (interquartile range) or mean ± SD.
TPN, total parenteral nutrition.
*One case whose family declined further care for a second day in hospital was not included.

have been due (at least in part) to patients visiting a local hospital that did not have the latest medical technology.

Treatment guidelines specific to CC have yet to be developed, although there have been consistent trends in different reports.[2] With symptoms of tachypnea, dyspnea and hypoxia, and a plain radiograph of the chest, a diagnosis of pleural effusion can be made. A milky pleural effusion suggests chylothorax, but a high index of suspicion is required because the opalescent appearance of chyle may not occur in more than half of postoperative patients, especially if they are not receiving oral or enteral nutrition. This fluid may be turbid, serous, or bloody.[10]

A fat-free diet, medium-chain triglyceride formulas, TPN, octreotide, chemical pleurodesis, or surgical interventions are the main treatments for chylothorax.[1] In some mild cases, a fat-free diet alone can work. TPN is the foundation for most of the treatments for chylothorax. In our case series, the median duration of chylothorax was 9 days; 20 out of 36 cases improved but in about half of these patients recurrence occurred upon re-introduction of a fat-free

diet, and chylothorax was alleviated by further periods of TPN. Hence, working out the appropriate course of TPN is important.

Due to a long course and fluctuation of chylothorax, chemical pleurodesis was undertaken or octreotide was administered. The efficacy of octreotide is controversial. Systematic reviews have not shown a clear benefit of octreotide in patients with chylothorax of congenital or surgical etiologies.[9,11,12] Chemical pleurodesis has been used effectively in patients for whom medical therapies for chylothorax have failed and surgical ligation of the thoracic duct was not done,[13] which appeared to be the situation in some of our cases. Erythromycin has been reported to be an effective and safe sclerosing agent for chemical pleurodesis in patients with recurrent malignant pleural effusions,[14] but not for chylothorax. OK-432 has also been used as an effective sclerosing agent in neonates.[15,16] Despite a long and complicated clinical course, only three cases (7%) in our series required surgical intervention. At long-term follow-up, all were doing well without relapse except for one case who had

TABLE 3 Clinical manifestations of chylothorax after cardiac surgery (N = 27)

	N(%)	Description
Age<1yr	21(77.8)	
Sex male	19(70.4)	
Type of operation		
Aortic reconstruction	9	
VSD repair	5	
Glenn procedure for pulmonary stenosis	2	
Arterial switch	2	
TOF repair	2	
VSD+ASD repair	2	
PDA ligation	2	
Fontan procedure for RV-Hypoplasia	1	
Correction of TAPVR	1	
VSD repair+PDA ligation	1	
Site	Left 13; Right 9; Bilateral 5	
Treatment*		
Chest drainage	26	-
Fat-free diet	4	3 alleviated, 1 turn to TPN
TPN	23	Duration 8 (6, 12) d; 20 alleviated, in which 4 recurrence when re-induce of normal diet or fat-free diet and were cured by further TPN; 3 turned to operation
Operation	3	3 alleviated by thoracic duct ligation
Complications	6	5 with respiratory infection, 1 with cerebral infarction

Data are presented as N (%), median (interquartile range) or mean ± SD.

TPN, total parenteral nutrition; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; RV, right ventricular.

*One case whose family declined further care for complex congenital heart disease was not included.

a recurrence that might have been due to a congenital lymphatic malformation.

Congenital abnormalities of the lymphatic system do not always present in the neonatal period.[17] In our study, in cases of PC in which onset was beyond the neonatal stage, some had symptoms in the first several months that had a similar clinical course to that of NC. In other cases, the underlying lymphatic disorder seemed to be more dominant. TPN was less effective and surgical intervention needed more in these patients, which highlighted the different treatment strategies in these cases. Lymphoscintigraphy can enable a diagnosis of lymphatic dysplasia to be made.[18] In our study, seven cases of congenital lymphatic malformation were verified. One case with DPL, who had been reported previously,[19] had a poor prognosis and died subsequently due to chylothorax recurrence. Eight cases had extrapulmonary features, of which six cases had multiple-organ involvement and were diagnosed with GLA. The latter can affect the skin, superficial soft tissue, abdominal and thoracic viscera, and bone. Extrapulmonary features can include chylous ascites, protein-losing enteropathy, peripheral lymphedema, lymphopenia, hemihypertrophy, and disseminated intravascular coagulopathy.[20] The complicated manifestations and complex procedure for diagnosis and treatment are challenges to pediatricians. In our series, two patients had been misdiagnosed as having tuberculosis. At follow-up, one of the two cases had symptom recurrence that could not be managed by surgery. Furthermore, there are only a few general medical institutions in mainland China with a surgical department specializing in lymphatic surgery, lymphangiography and lymphoscintigraphy. Multi-disciplinary collaboration in the management of lymphatic malformations in children's medical centers is needed.

Chylothorax can be a complication of thoracic surgery. With respect to pediatric cardiac surgery, the overall incidence of chylothorax was 2.8% in a large multi-institution database from the USA,[21] and 1.18% in a tertiary national cardiac center in Hungary.[22] This complication may be dependent upon the surgical procedure. Chylothorax usually occurs on the second postoperative

day,[22] and this was seen in our study, especially when the patients resumed oral intake. The chyle was milky or could be turbid, serous, or bloody.[10] Chylothorax is a significant problem and associated with increased mortality, cost, and hospital stay,[21] as well as pulmonary failure and prolonged mechanical ventilation.[22] In our case series, chylothorax seemed to necessitate long hospitalization; some cases had a respiratory infection but only one patient had a serious complication (cerebral infarction). Complex procedures such as atriopulmonary and cavopulmonary anastomoses, total correction of the transposition of great vessels, repair of congenital aortic-arch anomalies, repair of total anomalous pulmonary venous return, and total repair of the tetralogy of Fallot carry a high risk of chylothorax (3.4%−5.7%). Relatively simple procedures such as repair of a ventricular septal defect (VSD), atrial septal defect (ASD) and closure of patent ductus arteriosus (PDA) carry a risk of chylothorax of 0.9%−1.6%.[21] In our study, aortic reconstruction and repair of a VSD were most common due to the large number of VSD cases. Chest drainage and TPN were also basic treatments, and most cases recovered by conservative management, with only a few needing additional thoracic-duct surgery.

However, the timing for surgical procedures is controversial.[23] In a large multi-institution database in the USA,[21] of the patients who underwent post-cardiac surgery chylothorax, 196 (8.9%) had thoracic-duct ligation or chemical pleurodesis a median of 18 days after surgery. TPN, supplementation with medium-chain fatty acids, and octreotide were used in 56%, 1.7%, and 16% of patients, respectively. In our study, despite prolonged hospitalization and a fluctuating course, almost all cases at follow-up had a good prognosis, a result that is consistent with other reports.[22]

Chylothorax can be a manifestation of Down, Turner or Noonan syndromes[1] due to the involvement of the lymphatic system. In our study, only two cases of Down syndrome and no cases of Turner or Noonan syndromes were diagnosed. Noonan syndrome associated with chylothorax has been reported widely. In a prospective, nationwide epidemiologic study in Germany,[24] of 28 cases of CC, nine infants suffered from proven or suspected syndromal anomalies, most frequently Noonan syndrome (five). Only two cases of Noonan syndrome-associated chylothorax have been reported in Taiwan.[25,26] Liu et al reported that of five cases of Noonan syndrome in China, none had chylothorax.[27] The rarity of chylothorax in Turner and Noonan syndromes in China is different to that of Western countries, and the underling mechanism is not known.

In our case series, left-sided effusions seemed to be more common, and not in the right side as reported previously: chylothorax can be one-sided, either right (50%) or left (33%), or bilateral (16.66%).[28] The location of chylothorax depends on the point of duct injury; lesions above the fifth thoracic vertebra lead to left-sided pleural effusion, whereas lesions below this level lead to right-sided pleural effusion.[29] It is also associated with the side of the surgical approach. In a case series in a Taiwan hospital, of 14 cases of chylothorax after cardiothoracic surgery in children, seven were left-sided, three were right-sided, and four were bilateral.[30] Many case series of chylothorax have small study cohorts, and in some multicenter studies the side of the effusion has not been reported.[21] Given our relatively large study cohort, the prevalence of left-sided chylothorax was comparable to that of the right side.

CONCLUSIONS

Chylothorax is a complex entity of various causes. NC and postoperative chylothorax are the common subtypes. TPN is effective for most patients but the treatment plan and when to undertake thoracic-duct surgery need further study. Despite a prolonged and fluctuating clinical course, most cases had a good long-term prognosis. With regard to congenital lymphatic malformations, multi-disciplinary collaboration is important for management. Undertaking prospective, multicenter clinical studies with large cohorts and sharing clinical experiences might help to achieve evidence-based treatment of chylothorax.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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