Congenital Chylothorax of the Newborn: A Systematic Analysis of Published Cases between 1990 and 2018

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Keywords

Congenital chylothorax · Associated anomalies · Mortality · Octreotide · OK-432 · Pleurodesis · Povidone-iodine

Abstract

Background: Congenital chylothorax (CCT) of the newborn is a rare entity but the most common cause of pleural effusion in this age-group. We aimed to find the optimal treatment strategy. **Material and Methods:** A PubMed search was performed according to the PRISMA criteria. All cases were analyzed according to prenatal, perinatal, and postnatal treatment modalities and follow-ups. **Results:** We identified 753 cases from 157 studies published between 1990 and 2018. The all-cause mortality rate was 28%. Prematurity was present in 71%, male gender dominated 57%, mean gestational age was 34 weeks, and birth weight was 2,654 g. Seventy-nine percent of newborns had bilateral CCT, the most common associated congenital anomalies with CCT were pulmonary lymphangiectasia and pulmonary hypoplasia, and the most common chromosomal aberrations were Down, Noonan, and Turner syndromes, respectively. Mechanical ventilation was reported in 381 cases for mean 17 (range 1–120) days; pleural punctuations and drainages were performed in 32% and 64%, respectively. Forty-four percent received total parenteral nutrition (TPN) for mean 21 days, 46% medium-

chain triglyceride (MCT) diet for mean 37 days, 20% octreotide, and 3% somatostatin; chemical pleurodesis was performed in 116 cases, and surgery was reported in 48 cases with a success rate of 69%. In 462 cases (68%), complete respiration was reported; in 34 of 44 cases (77%), intrauterine intervention was carried out. **Conclusion:** Respiratory support, pleural drainages, TPN, and MCT diet as octreotide remain to be the cornerstones of CCT management. Pleurodesis with OK-432 done prenatally and povidone-iodine postnatally might be discussed for use in life-threatening CCT.

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Introduction

Congenital chylothorax (CCT) of the newborn is a rare disease with high associated morbidity and mortality. CCT is defined as an effusion of lymph in the pleural cavity [1]. In contrast to the congenital idiopathic or spontaneous form of chylothorax, there exists a traumatic chylothorax, most common as a complication of surgery with iatrogenic rupture of the ductus thoracicus (surgery of congenital heart disease or atresia of the esophagus), and a symptomatic one as a result of a venous congestion (tumors, thromboses, cancers, etc.).

Fig. 1. Literature review identifying 157 case reports or case series on CCT between 1990 and 2018 according to the PRISMA criteria. CCT, congenital chylothorax.

A lot of reviews [1–30] and case reports or case series [31–187] of CCT have been published during the last 3 decades (1990–2018). The first report of CCT was published in 1917 [188], but some researchers were not sure about its congenital etiology, and thus, Stewart and Linner (1926) have often been cited as the first authors who described CCT [189]. In 1928, the first report of prenatal diagnosis was published [190]. CCT was reported to occur in one per 7,300 to 10,000 live births [26, 106, 137]. Estimations of the prevalence of CCT range between 1:10,000 [30] and 1:24,000 [173]. In severe cases with large amounts of pleural effusions, lung hypoplasia might result and consequently heart failure due to compromised vascular flow and hydrops fetalis. As a result, lymphocytes, antibodies, complement, and coagulation factors and also nutritional and fluid content and immune globulins might get lost in the pleural cavity or via drainages. These chylous fluid losses again might lead to malnutrition and dehydration and to increased risks of infec-

tious complications or bleeding episodes [30]. Additional risks included concomitant anomalies or genetic disorders that might negatively influence the prognosis of CCT. Despite modern neonatal intensive care, mortality rates reported ranged between 30 and 70% according to the literature [191]. We aimed to depicture the whole spectrum of disease by a review of cases and case series from the literature between 1990 and 2018 and to systematically analyze them with a focus on treatment strategies.

Material and Methods

We performed a systematic review of the literature using “Pubmed” and searching the medical subject heading “congenital chylothorax” according to the PRISMA criteria. Included were all newborn infants younger than 29 days of life published between 1990 and 2018. The literature search and case analysis was done between August 2018 and October 2019. Within the study period, we found 467 studies; further, we used “humans” and “newborns 0–27 days” and included only German or English written articles. Thus, we reduced the number of studies to 222. These publications had to have the wording “congenital chylothorax” or “congenital pleural effusion” in the title or abstract of the study. A manual search through the references revealed the final number of 157 studies reporting cases or case series with CCT (see Fig. 1).

Inclusion criteria were more than 70% lymphocytes in the pleural fluid or presence of chylomicrons or high triglyceride levels (>110 mg/mL). Exclusion criteria were missing inclusion criteria and secondary CCT due to (cardiac) surgery or iatrogenic forms of CCT.

Perinatal data included gender, birth weight, gestational age in weeks, cesarean section or vaginal birth, presence of intrauterine drainages of the pleura, other fetal interventions, preterm birth, surgery of any kind, time of CCT resolved, any nosocomial infection, presence of fetal hydrops, associated malformations, and chromosomal anomalies. Further, we collected the age and duration of each of the following procedures: pleural drainages, pleural punctation, mechanical ventilation (MV) – either invasive or noninvasive (continuous positive airway pressure and high flow nasal cannula), total parenteral nutrition (TPN), medium-chain triglyceride (MCT) diet, somatostatin or octreotide treatment, surgery, chemical pleurodesis, and finally length of hospitalization, survival, discharge healthy, and death. In order to present the data in a reader-friendly format, we did not list all the references associated with each finding (see online supplementary data, available at www.karger.com/doi/10.1159/000518217).

Results

During the study period, 760 cases with CCT were identified for further analysis from 157 publications [31–187]. The exact inclusion criteria were fulfilled in 753 cases that comprised the study population. Seventy-one per-

Table 1. Prenatal and perinatal data of 753 cases with CCT extracted from the literature from 1990 to 2018

Parameter	Patients with data	Results
Total number of cases		753 (100)
Prenatal diagnosis		512 (68)
Age of prenatal diagnosis, weeks	324 of 512	28.8 (16–38)
Prenatal intervention		316 (62)
Age of prenatal intervention, weeks	181 of 316	29.7 (17–38)
Intrauterine death/termination of pregnancy/perinatal death		42/13/17
Polyhydramnion		96 (13)
Hydrops fetalis (nonimmunologic)		288 (38)
Survivors with follow-up		681 (90)
Cesarean section	290 of 681	159 (55)
Prematurity (<37 weeks gestation)	472	337 (71)
Gestational age, weeks	565 of 681	34.3 (26–41)
Birth weight, grams	469 of 681	2,654 (467–4,715)
Male gender	425	243 (57)
Pleural fluid with lymphocytes >70%		579 (77)
Bilateral pleural effusions	460	362 (79)

Numbers are given as *n* (%) or mean (range), CCT, congenital chylothorax.

cent of infants were preterm born; 10 studies did not report data on gestational age [31, 33, 39, 74, 78, 85, 121, 127, 138, 146]. Intrauterine death occurred in 42 cases; termination of pregnancy occurred in 13 reports.

Thus, 698 were born alive, and 17 cases died during birth or immediately after birth. Perinatal data of the total study population and the 681 newborns with follow-up are shown in Table 1. Yang et al. [155] solely reported a range of 16–29 weeks of gestational age and therefore not included. Same was done with the study of Shih et al. [150] regarding birth weights (range 780–3,110 g in 4 cases).

Diagnosis

Diagnosis of CCT confirmed by lymphocyte rates of >70% was found in 77% of cases. Two studies reported “a lot of” lymphocytes [37, 41], and in 15 cases (2%), authors solely reported that lymphocytes were dominant or predominant [38, 39, 142]. In 7 cases (1%), lymphocytes were below 70% [48, 112]. In the majority of cases, there are no specific lymphatic system studies necessary to identify the exact pathology [30]. Additionally, expertise on lymphatic studies is not universally available [30] and has been published by only one working group [91, 130].

Prenatal Treatment

Prenatal interventions were reported in 316 of 512 (62%) prenatally diagnosed cases. One hundred eighty one cases had data on gestational age. Information re-

garding prenatal punctuation was given in 128 (40%), thoraco-amniotic shunting in 137 (43%), and both in 17 cases (5%). Some of the pleural punctuations were done prior to delivery to avoid perinatal asphyxia. Mussat et al. [48] reported on 20 cases with intrauterine shunt implantation and 4 cases with intrauterine punctuation; thereafter, 16 cases reconvert with improvements regarding the course of disease and its treatment. Picone et al. [89] reported on 44 intrauterine shunted cases (thoraco-amnial) with recurrent punctuations until birth. Chen et al. [126] published 17 cases with intrauterine punctuations of pleural effusions, and some of these punctuations immediately before birth were found to ameliorate postpartal adaption of the newborn [60]. Mussat et al. [48] reported clinical improvement in 2/3 of the procedures (shunting in 20 and punctuation in 4 cases). Gonen et al. [60] reported on recurrent prenatal punctuations in 4 cases including one immediately before birth. Two centers demonstrated a lot of experience with prenatal shunting (44 and 17 cases, respectively) [89, 128]. Rates of fetal interventions including intrauterine punctuation and thoraco-amniotic shunting are shown in Table 1.

A total of 87 cases were treated with fetal intrapleural instillation of OK-432 (Picibanil, a sclerosant and immunostimulant). Tanemura et al. [73] and Okawa et al. [74] first published the method in 2001. Yang et al. [155] reported on a cohort of 45 fetuses – the largest cohort – having been treated with OK-432. Thirty-one fetuses survived the OK-432 procedure, having either a complete

Table 2. Associated anomalies and chronic sequelae* found in 216 of 753 cases with CCT of the newborn from the literature between 1990 and 2018

Lung		Lymphatics (outside the lungs)	
Congenital pulmonary lymphangiectasia	47	Lymphatic dysplasia/malformation	15
Pulmonary hypoplasia	43	Lymphangiectasia generalisata	3
BPD*	5	Anomaly of the thoracic duct	2
Sequestration of the lung	4	Primary hereditary lymphedema	1
Subglottic stenosis	2	Lymphangiomatosis	1
Right lung 2 lobes	1	Lymphodysplastic syndrome	1
Cystic adenomatous malformation	1	Sum	23
Hemorrhagic lung edema	1	Other anomalies	
Laryngomalacia	1	Hydrocele testis	4
Congenital diaphragmatic hernia	1	Hypertelorism	3
Sum	106	Myelodysplastic-monocytic leukemia	2
Heart and vessels		Congenital hypothyreosis	2
Ventricular septal defect	7	Cleft lip and palate	2
Atrial septal defect	6	Hygroma colli	2
Atrioventricular channel defect	6	Malformations, multiple	1
Heart defect (no details)	6	Hydronephrosis	1
Persistent ductus arteriosus Botalli	4	Horseshoe kidney	1
Persistent foramen ovale	3	Congenital lipodystrophia	1
Hypoplastic vena cava superior	3	Kryptorchism	1
Tetralogy of Fallot	3	Hypospadia	1
Arteriovenous malformation	2	Gastroschisis	1
Aortic isthmus stenosis	2	Mediastinal neuroblastoma	1
Pulmonary artery stenosis	2	Polydactylia	1
Hypertrophic cardiomyopathy	2	Omphalocele	1
Hypoplastic left heart syndrome	1	Cervical teratoma	1
Aplasia of pulmonary valves	1	Pyloric stenosis	1
Pericardial teratoma	1	Sum	27
Missing left subclavian artery	1	Brain	
Sinus venosus defect	1	Microcephaly	2
Missing vena azygos	1	Encephalopathy	1
Single umbilical artery	1	Agenesis of the corpus callosum	1
Ebstein anomaly	1	Intraventricular hemorrhage	1
Venous malformation	1	Intracranial hemorrhage	1
Sum	53	Ventriculomegaly	1
		Sum	7

BPD, bronchopulmonary dysplasia; CCT, congenital chylothorax. * Preterm infants with CCT developing chronic lung diseases of prematurity (BPD).

($n = 8$) or a partial ($n = 23$) response, and were followed-up every 2 weeks until delivery. Sixteen of these (51.6%) survived beyond 1 month of age, while 15 (48.4%) resulted in neonatal deaths [155]. In 13 cases, time point of intervention was documented being mean 21.5 (range 16–33) weeks. In 54 cases, no details were provided, for example, Lee et al. [180] who did not describe their method but reported on 3 intervention modalities – pleurodesis, thoracocentesis, or thoraco-amniotic shunting. Parra et al. [80] uniquely instilled maternal blood into the fetal intrapleural cavity in 2003.

Anomalies and Genetics

In 217 cases (29%), associated anomalies had been reported (see Table 2). The majority were pulmonary findings and anomalies associated with the lymphatic system – 47 cases with congenital pulmonary lymphangiectasia and 43 cases with pulmonary hypoplasia and 21 malformations of the lymphatic system, in total 111 (51%). Congenital heart disease was observed in 52 cases including malformations of the arteriovenous system (24%).

Table 3. Chromosomal findings in 117 of 753 cases with CCT of the newborn between 1990 and 2018

Genetic disorder	N (%)
Down syndrome	48 (41.1)
Noonan syndrome	26 (22.2)
Turner syndrome	10 (8.6)
Anomalies regarding chromosomes, 13/14	6 (5.1)
C syndrome = Opitz syndrome	3 (2.6)
Edward syndrome	2 (1.7)
Hennekam syndrome	2 (1.7)
Klinefelter syndrome	2 (1.7)
Anomalies regarding chromosome 2	2 (1.7)
X-linked myotubular myopathy	2 (1.7)
Anomalies regarding chromosome 7	2 (1.7)
Ehlers-Danlos syndrome	1 (0.9)
Anomalies regarding chromosome 9	1 (0.9)
Alagille syndrome	1 (0.9)
Schienze-Giedion syndrome	1 (0.9)
Mitochondrial myopathy	1 (0.9)
Kabuki syndrome	1 (0.9)
Trisomy X (mosaik 47XXX/46XX)	1 (0.9)
Gorlin syndrome	1 (0.9)
XXX syndrome	1 (0.9)
Jacobsen syndrome	1 (0.9)
CDG syndrome (congenital disorders of N-glycosylation)	1 (0.9)
Cornelia de Lange syndrome	1 (0.9)
Sum	117 (100)
CCT, congenital chylothorax.	

Chromosomal aberrations were found in 118 cases (18%). Disorders are listed in Table 3. Down, Noonan, and Turner syndromes were the most common diagnosed entities (48, 26, and 10 cases, respectively).

Postnatal Course of Disease

Pleural punctation of CCT was reported in 218 of 681 newborns who had survived and been followed postnatally (32%); pleural drainage was inserted in 438 cases (64%). Indications were desaturation below 90% and increased work of breathing. Durations of pleural drainages were documented in 225 newborns with a mean of 20 (range 1–150) days. Zenker et al. [54] reported only a range of 10–44 days from a series of 17 cases. Fernandez Alvarez et al. [62] reported 6 cases with pleural drainages; they did not document the duration but the number of drainages per newborn, with a range of 1–15.

MV was reported in 381 cases (56%). Of 213 ventilated cases with data on duration of MV, a mean of 17 (range 1–120) days was documented. Seventy newborns (10%)

developed pneumothorax. In 78 newborns (11%), a diagnosis of sepsis was documented. A case of extremely long duration of MV reported by Ergaz et al. [137] with 885 days was not included in the final analysis as was not a case series by Zenker et al. [54] who reported only a range of 9–47 days.

TPN was reported in 296 cases (44%), and the duration (details from 113 newborns) was documented with mean 21 (range 2–81) days. MCT diet was given in 315 newborns (46%), and only 19 cases provided data on the duration of MCT diet (mean 37, range 5–50 days). In 13 cases, initiation of MCT diet was provided at mean 21 days (7–68). In 96 cases a prenatal MCT diet of the mother was reported.

Somatostatin and octreotide (somatostatin analog) for the treatment of CCT were first described by Goto et al. in 2003 [86]. Cleveland et al. [142] reported the largest case series of 13 newborns having received both drugs. Data on octreotide treatment were documented in 138 cases with a mean duration of 22 days (range 3–151 days from 76 newborns). Sixty-two case reports did not provide information on duration of octreotide treatment; 66 newborns received octreotide intravenously and 6 newborns subcutaneously. Octreotide treatment was started between days 2 and 109. Initial intravenous dosage varied between 3 and 4 µg/kg/h and maximum dosage between 6 and 12 µg/kg/h. Subcutaneous injection was given at dosages ranging between 1 and 40 µg/kg/day initially and maximum dosages between 24 and 70 µg/kg/day. In 30 cases, therapy with octreotide failed, resulting in subsequent surgery. Coulter et al. [93] reported on a case with failure of surgical ligation of the ductus thoracicus and subsequent successful octreotide therapy.

Somatostatin treatment was described in 22 cases (3%). Duration of treatment was provided in 3 cases (10, 18, and 23 days, respectively, with a mean of 17 days). In a case series of Cannizarro et al. [114], 3 newborns with intravenous somatostatin were reported. Somatostatin was started with 3.5 µg/kg/h and gradually increased to 12 µg/kg/h.

Forty-eight newborns (7%) received prophylactic and therapeutic antibiotics, 40 received steroids, and 56 surfactant. Immune globulins were given in 29 case reports (4%). Twenty-five case reports casually mentioned this information in contrast to one report with weekly immune globulin treatment and another with treatment twice a week [70, 181]. Bulbul et al. [138] described a case with postpartal immune globulin therapy at a dosage of 1 mg/kg, and Gupta et al. [167] gave immune globulins every 24 h with a dosage of 2 g/kg.

Table 4. Chemical pleurodesis and surgical procedures in CCT of the newborn from 157 out of 753 cases from the literature between 1990 and 2018

Procedure	Agents used for pleurodesis	Interventions (n)
Chemical pleurodesis		116
Intrauterine + postnatal	OK-432	87+2
Postnatal	Povidone-iodine	12
Postnatal	Minocyclin	5
Postnatal	Dextrose	2
Postnatal	Oxytetracycline	2
Postnatal	Bleomycin	1
Postnatal	Fibrin glue	1
Postnatal	Pleurodesis (unclear)	2
Intrauterine	Maternal blood (in utero)	1
Postnatal	Autologous blood	1
Surgical pleurodesis		23
Ligation of the thoracic duct		15
Pleuroperitoneal shunt		8
Partial surgical pleurodesis		2

Multiple interventions in one case possible. CCT, congenital chylothorax.

Surgery and Chemical Pleurodesis

In 157 case reports (23%), surgery including chemical pleurodesis was the final treatment to cure CCT. Time of surgery was at a mean of 39 days (range 11–150 days; data from 41 cases). An extremely late surgical intervention was reported by Bellini et al. [159] at the age of 2 years (successful pleurodesis). In Table 4, the different interventions are described that have been successful in 105 of 150 cases (67%).

Chemical pleurodesis with OK-432 was done in 62% of newborns, and prenatally used in 87 cases and in one newborn with maternal blood [80]. Successful interventions were reported in 71 postnatal and 44 prenatal cases. Successful surgical pleurodesis was reported in 20 of 25 cases (80%), ligation of the ductus thoracicus in 10 out of 15 cases (67%), and pleuroperitoneal shunting in 4 of 8 cases (50%).

Mortality

Death occurred in 138 newborns who were primarily born alive with data from 77 infants regarding time of death (mean 25, range 1–202 days). Twelve newborns died on the first day of life and 6 within 48 h. Lee et al. [180] published 13 cases who died between day 1 and 28 [133]. Thus, all-cause mortality including termination of pregnancy was 27.9%. Causes of deaths (89 cases with data) included respiratory insufficiency ($n = 26$) and pulmonary hypoplasia ($n = 24$), infectious complications and sepsis ($n = 15$), renal failure ($n = 6$), multi-organ failure ($n = 3$), lymphangiectasia ($n = 3$), pulmonary obstructive disease ($n = 3$), aspiration ($n = 2$), and rare causes includ-

ing lymphedema, Opitz syndrome, interstitial fibrosis, intra-alveolar and interstitial hemorrhage, pulmonary hypertension, pneumopericardium, and Ebstein anomaly.

Regression of CCT and Hospitalization

In 462 cases (68%), complete restitution was reported; in 34 of 44 cases, following intrauterine intervention; and in 81 cases, the outcome was unknown. Time of complete regression of CCT was at a mean of 28 (range 1–148) days. In those cases treated prenatally (8 cases), pleural effusions were reported to have resolved at 24 weeks of gestation (range 19–26). Chen et al. [126] reported 12 of 17 cases treated successfully intrauterine. Bellini et al. [159] reported 26 of 33 cases having had survived and been discharged with MCT diet. Only rare and mild cases of CCT are managed by a wait-and-see strategy [5, 22, 26, 37]. Length of hospitalization was documented in 223 newborns with a mean of 41 (range 4–386) days.

Follow-Up

The mean duration of follow-up of 133 newborns (29%) was 14.7 (range 1–144) months. The longest follow-up was reported by Resch et al. [158] including 6 cases followed up to the age of 12 years. Recurrence of pleural effusions has not been reported [34, 37, 48, 158]. Long-term observations revealed 2 cases having interstitial infiltrations, one asthma bronchiale, one pulmonary obstructive disease, and finally one having pleural fibrosis. Dutheil et al. [58] described one case having prolonged pleural fluids lasting over months that resolved at the age

Table 5. Summary of postnatal treatment, complications, and outcomes of 681 cases with CCT published between 1990 and 2018

Treatment modalities	N (%) or mean (range)
MV	381 (56)
Duration of ventilatory support, days ¹	17 (1–120)
Pleural punctuation	218 (32)
Pleural drainage	438 (64)
Duration of drainages, days ²	20 (1–150)
TPN	296 (44)
Duration of TPN (days) ³	21 (2–81)
MCT diet	315 (46)
Duration of MCT diet (days) ⁴	37 (5–50)
Octreotide	138 (20)
Duration of octreotide treatment (days) ⁵	22 (3–151)
Somatostatin	22 (3)
Duration of somatostatin treatment (days) ⁶	17 (8–23)
Antibiotics	48 (7)
Surfactant	56 (8)
Steroids	40 (6)
Immune globulins	29 (4)
Surgical interventions including chemical pleurodesis	157 (23)
Time at intervention (day of life) ⁷	39 (11–150)
Successful intervention	105 (67)
Complications/associated anomalies/genetic disorder	
Pneumothorax	70 (10.3)
Sepsis	78 (11)
Associated anomalies	217 (29)
Chromosomal aberrations, genetic disorders	118 (16)
Outcomes	
Discharged healthy	462 (68)
Discharged with unknown health status	81 (12)
Duration of treatment ⁸	28 (1–148)
Deaths	138 (20)
Time at death (day of life) ⁹	25 (1–202)
Duration of hospitalization, days ¹⁰	41 (4–386)
Follow-up of 133/543 cases (25%), months	14.7 (1–144)

CCT, congenital chylothorax; TPN, total parenteral nutrition; MV, mechanical ventilation; MCT, medium chain triglyceride.

¹Data from 213 cases. ²Data from 225 cases. ³Data from 113 cases.

⁴Data from 19 cases. ⁵Data from 76 cases. ⁶Data from 3 cases.

⁷Data from 41 cases. ⁸Data from 79 cases. ⁹Data from 77 cases.

¹⁰Data from 223 cases.

of 1 year. Al-Tawil et al. [68] reported 17 cases being healthy between the age of 6 months and 7 years; one case with Down syndrome died at the age of 7 months due to congenital heart disease. One case with eosinophilic pulmonary vasculitis was discharged at day 104 of life and reported to be healthy at the age of 2 years [79]. A summary of the postnatal course of CCT from 681 live born cases is shown in Table 5.

Treatment Algorithm

In Table 6 we provide a management algorithm of CCT as a consequence of our systematic review of published cases from the literature including a timeline that might be necessary in severe cases to avoid further complications (nosocomial infections, prolonged TPN and subsequent cholestasis, and MV and ventilator-associated pneumonia). Chemical or surgical pleurodesis and surgical interventions certainly are the last choice of treatment in severe and otherwise untreatable cases of CCT.

Discussion

As stated in a recent review, interventions include thoracostomy drainage and attempts to decrease chyle flow using a stepwise approach as far as evidence-based treatment choices are still lacking [30]. Our systematic review mainly confirmed this management strategy. We found the majority of infants being born premature with a predominance of male gender. The majority of newborns had bilateral effusions. The most common associated congenital anomalies were pulmonary lymphangiectasia and pulmonary hypoplasia, and the most common chromosomal aberrations were Down, Noonan, and Turner syndromes. MV was reported in 381 cases for a mean of 17 days, and pleural punctuations and drainages were performed in 32 and 64 %, respectively. Forty-four percent received TPN, 46% MCT diet, 20% octreotide, and 3% somatostatin. Chemical pleurodesis was performed in 116 cases, and surgery was reported in 48 cases with a success rate of 69%. In 462 cases, complete restitution was reported; in 34 of 44 cases, it was reported following intrauterine intervention. Length of hospitalization was a mean of 41 days, and long-term follow-up until 12 years revealed no recurrence of pleural effusions and was in general good including neurodevelopmental follow-up, provided there were no associated anomalies. The mortality rate was 28%.

Prenatal interventions might improve survival in severe cases of fetal chylothorax and usually necessitate referral to an experienced prenatal care center. Interestingly, fetal drainages (pigtail catheter) and subsequent pleurodesis with OK-432 seemed to be promising with a 67% survival rate. The male to female ratio was found to be 2:1.5, slightly different from the commonly reported ratio of 2:1 [30]. The large majority of neonates had bilateral pleural effusions; thus, our data do not support the reports that CCT presents preferably right-sided [30]. Extrating data for optimal management of CCT is difficult.

Table 6. Management of CCT of the newborn

Prenatal intervention**Prenatal finding of pleural effusions**

Associated anomalies; chromosomal aberrations?

Active or palliative treatment

Consider prenatal thoraco-amniotic shunting with a pigtail catheter in an experienced center

OK-432 instillation for pleurodesis is a more experimental but nevertheless successful approach

Birth

Active treatment or palliative care

Respiratory support (MV, CPAP, and HFNC)

Pleural drainage and/or replacement of pigtail catheter

Diagnosis of CCT

Percentage of lymphocytes of pleural fluid >70%

Lymphocytes >70%: high triglyceride levels?

Consider milk feeding to find chylomicrons in the pleural fluid

Document fluid losses to estimate fluid balance and electrolyte and protein (and immune globulins) losses

Week 1–4**Treatment strategies in case of confirmed CCT**

Start with total parenteral nutrition (TPN)

Consider removing (if present) the pigtail catheter (and in the same session – using a guide wire – setting a new drainage)

Initiate MCT diet very slowly (dependent on pleural fluids and maintain drainages)

Cave: even some tea might increase pleural fluids

If pleural fluids increase, back to TPN

Week 5–6

MCT diet until full enteral nutrition is reached; thereafter, switch to normal toddler diet

If not possible, consider octreotide treatment by either parenteral or subcutaneous injection/infusion; start with 4 µg/kg/h up to 12 µg/kg/h iv or up to 40 µg/kg/d s.c

If not successful, consider pleurodesis or surgical ligation of the thoracic duct or both

Consider antibiotics (even prophylactic) and immune globulins every 2–4 weeks

Prognosis

No infectious complications, no excessive fluid losses: In general, good; no long-term sequelae

Complications, no resolution: serious prognosis; late death possible

MV, mechanical ventilation; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannulae; CCT, congenital chylothorax; TPN, total parenteral nutrition; MCT, medium chain triglyceride.

Every single case might differ extremely from each other. The first step is confirmation of diagnosis of CCT. In case of uncertainty regarding diagnosis of CCT during TPN and in case of drainages, feeding of small amounts of human milk will lead to the finding of chylomicrons, and the clear fluid of chylus will become creamy or milky. The lymphatic system is responsible for the transport of lipids and the lipophilic vitamins A, D, E, and K, and enterocytes transform the lipids to chylomicrons with drainage via the capillary system into the blood circulation. Further functions include fluid and extravasal protein uptake from the interstitial space [5]. High fat intake increases the lymphatic flow dramatically, and long-chain triglycerides will be transported as chylomicrons by the lymphatic system in contrast to medium- and short-chain triglycerides that get metabolized via the portal vein in the liver [5–7]. The chyle is characterized by high triglyceride

levels >1.1 mmol/L (>110 mg/dL) and >1,000 cells/L with 80–100% lymphocytes, mainly T lymphocytes [1, 5, 8–10, 159, 169]. Electrolytes, glucose, and protein levels of the chyle are comparable to those of blood plasma; additional chylous components are albumins, globulins, prothrombin, and fibrinogen [5, 20].

The first step in the treatment of CCT is respiratory support as far as needed (mainly noninvasive ventilation with continuous positive airway pressure or high flow nasal cannula), pleural fluid drainages, and TPN with nothing per mouth. If CCT resolves, MCT diet might cautiously be initiated until full enteral feeding volumes are reached; thereafter, diet might be switched to human milk (even breastfeeding) or formula diet over several days decreasing the amount of MCT diet steadily. In case of fluid losses over 3 weeks of age, octreotide might be used on a try-and-error basis, starting with 4 µg/kg/h, thereafter dou-

bling the dose if necessary (if there was no treatment effect within 24 h) and no higher dose than 12 µg/kg/h. If CCT does not resolve, surgical intervention might be necessary using either ligation of the thoracic duct and/or surgical and/or chemical pleurodesis. Chemical pleurodesis with povidone-iodine was more recently reported [179]. Our own experience in one case was promising regarding nearly complete resolution of CCT, but unfortunately the infants died some days later [179]. From 12 reported cases between 2003 and 2014, the success rate of povidone-iodine pleurodesis was 58%, and the survival rate 75% [179]. Surgical intervention should be discussed at week 4 and at least be done at the age of 6 weeks. Prophylactic antibiotics can be considered, and immune globulins might be beneficial every 2 weeks in cases of prolonged fluid losses as are coagulation factors. A recent case series of 5 cases with confirmed CCT reported on the necessity of careful management of total body fluid balance and the successful replacement of chylous fluid losses with colloid infusions [192]. Chylous effusions usually last long; however, after 6 weeks, the majority of the effusions (74%) had ceased according to Buttiker et al. [7]. Late surgical interventions reduced the number of thoracotomies substantially, but led to very long hospitalization times. In contrast, early surgical interventions (after <3 weeks), which lead to a higher number of thoracotomies, might reduce the length of stay at the hospital [7]. Others confirm the stepwise procedure in the management of CCT [4, 30]. Initial treatment consisting of drainage, dietary modifications, and TPN is followed by somatostatin or its preferred analog octreotide [4]. Surgery should be considered for patients who fail these initial steps or in whom complications such as electrolyte and fluid imbalance, malnutrition, or immunodeficiency persist [4].

Conclusion

We analyzed the largest cohort of cases with CCT from the literature covering 3 decades. First-line treatment remains supportive with stepwise proceeding from respira-

tory support, pleural drainages, and nothing per mouth to octreotide and chemical or surgical pleurodesis. Fetal chemical pleurodesis with OK-432 and postnatal chemical pleurodesis with povidone-iodine seem to be promising in life-threatening cases. Otherwise, standard care and treatment did not change markedly during the last years.

Statement of Ethics

This study protocol was reviewed and the need for approval was waived by the Ethics Committee of the Medical University of Graz (Head Prof. J. Haas, personal communication).

Conflict of Interest Statement

The authors declare to have no conflicts of interest associated with this study.

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Author Contributions

B.R. was responsible for study design, conceptualization, supervision of data extraction, and wrote the final manuscript. G.S.Y. did all the literature search and data extraction and wrote the tables and the first draft. F.R. supervised the study and edited the manuscript. All the authors approved the final version of the manuscript.

Data Availability Statement

Raw data are available as online suppl. file.

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