Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.22182

Evaluation of Clinical Findings in Children with Chylothorax: A Descriptive Study

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What is already known on this topic?

- *Chylothorax is a rare condition. There are multiple etiologies of chylothorax.*

What this study adds on this topic?

- *The most common etiologies of chylothorax were postoperative history and Gorham-Stout disease. Gorham-Stout disease should be kept in mind in chylothorax accompanied by bone lesions in patients of any age.*

ABSTRACT

Objective: Chylothorax refers to the presence of chyle in the pleural space. There are multiple etiologies of chylothorax. Our aim in this study was to evaluate the clinical manifestations, causes, and treatment of chylothorax in childhood and also to show the differences between the 2 age groups admitted to a tertiary care children's hospital. The second aim was to evaluate the clinical and radiologic features of patients diagnosed as having Gorham-Stout disease via chylothorax.

Materials and Methods: The archives were reviewed for chylothorax documented in the last 31 years. Twenty-two patients (11 girls and 11 boys) were included. Patients were divided into 2 groups: the younger group aged under 24 months and the older group aged over 24 months.

Results: A total of 22 patients had chylothorax, and 10 were aged younger than 24 months. In the younger group, etiologies were in order congenital heart surgery, congenital chylothorax, and Gorham-Stout disease. In the older group, etiologies were Gorham-Stout disease, congenital heart surgery, heart failure, heart transplantation, thrombus, intestinal lymphangiectasia, and idiopathic. The most common treatment in the younger group was the medium-chain triglyceride diet (70%), and in the older group, it was sirolimus (50%).

Conclusion: There is a wide variety of underlying etiologies in childhood, so a multidisciplinary approach is important to identify the underlying diagnosis. The common etiologies were postoperative and Gorham-Stout disease in our study. All patients with Gorham-Stout disease had a good prognosis. Gorham-Stout disease should be considered in patients of any age with a diagnosis of chylothorax who have bone lesions.

Keywords: Chylothorax, childhood, Gorham-Stout disease

INTRODUCTION

Chylothorax refers to the presence of chyle in the pleural space.[1] Any impairment or dysfunction in chylous flow that may be based on the thoracic duct or lymphatic pathways can cause chylothorax. The thoracic duct carries chyle from the intestine to the bloodstream. Chyle contains triglycerides in the form of chylomicrons, T lymphocytes, electrolytes, proteins, immunoglobulins, and fat-soluble vitamins.[1] Therefore, if chylothorax is not diagnosed and treated early, it can cause significant respiratory morbidity, malnutrition, and immunodeficiency.[2]

There are multiple etiologies of chylothorax such as lymphatic malformations, surgery, and trauma, to name a few.[3,4] The incidence of chylothorax in childhood is unknown.[3] However, the reported incidence in the United Kingdom is 0.0014%.[5] Gorham-Stout disease (GSD) is one of the complex lymphatic anomalies.[6] Lytic bone lesions and the presence of any nonmalignant

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Received: July 18, 2022
Accepted: September 4, 2022
Publication Date: December 29, 2022

Cite this article as: Nayir Büyükşahin H, Emiralioğlu N, Özcan H, et al. Evaluation of clinical findings in children with chylothorax: A descriptive study. *Turk Arch Pediatr.* 2023;58(1):28-33.

chylous effusion (pleural, pericardial, peritoneal) without other known etiology should be given attention for complicated lymphatic anomalies.[7] Chylothorax has been reported in as much as 17% of patients with GSD cases.[3]

There are few studies regarding chylothorax in childhood in the literature.[5,8] In this report, we aimed to evaluate the clinical manifestations, causes, and treatment of chylothorax in childhood and also to show the differences between the infantile period and other age groups admitted to a tertiary care children's hospital. The second aim was to evaluate the clinical and radiologic features of patients who were diagnosed as having GSD via chylous effusion.

MATERIALS AND METHODS

We conducted a retrospective descriptive study of patients with chylothorax followed by the pediatric pulmonology department between January 1990 and December 2021. Demographic features, imaging findings, and treatment protocols were recorded. The patients were divided into 2 groups based on the age of diagnosis to show the differences between the infantile period and other age groups, the younger group who were aged under 24 months and the older group who were aged over 24 months.

The diagnosis of chylothorax was made if the pleural fluid had either or both triglyceride levels > 110 mg/dL and the presence of chylomicrons.[9] Congenital chylothorax was defined as nontraumatic pleural effusion detected antenatally or within 28 days after birth.[10]

Patients were diagnosed as having GSD based on the following clinical and radiologic diagnostic criteria. The imaging criteria for GSD were defined as progressive osteolysis with cortical bone resorption.[11] All radiologic studies were reviewed by a pediatric radiologist with special attention to the extent of bone, soft tissue, effusion density, and visceral involvement. The imaging techniques used to evaluate the patients with GSD in this study included computed tomography (CT) (n = 7) and bone survey (n = 7).

The study protocol was approved by Hacettepe University's ethics committee (Number: GO 21/1354).

Statistical Analyses

Continuous variables were presented as median (interquartile range) values. Categorical data were presented as frequency and percentage.

RESULTS

A total of 22 patients had chylothorax. Of these, 10 were younger than 24 months and the others were older than 24 months. In all patients, the fluid from the chest drains was milky and the effusion's triglyceride level was >110 mg/dL. Fluid draining from one of our patients is shown in Figure 1.

In the younger group, 5 (50%) patients were male. Five patients had a postoperative history, 4 of which were congenital heart surgery, and 1 was esophagal atresia surgery. Six (50%) of the patients in the older group were male. Among these, 1 patient had congenital heart surgery. Six patients' chylothorax etiology was GSD in the older group. The etiology of chylothorax by age group is shown in Figure 2.

Figure 1. Chylothorax delineated by chest tube.

The most common manifestation in the younger group was hypoxia (60%, 6/10 patients), and dyspnea (41.6%, 5/12 patients) was observed in the older group. In the younger group, 3 patients with congenital chylothorax had bilateral effusion and the rest had unilateral effusion. In the older group, 9 patients had bilateral pleural effusion and 3 had unilateral effusion in the etiology of cardiac transplantation, idiopathic, and congenital heart surgery.

The most common treatment in the younger group was the medium-chain triglyceride diet (MCT) (70%, 7/10 patients), and in the older group, it was sirolimus (50%, 6/12 patients). In the younger group, 2 patients who had congenital heart surgery died. In the older group, 1 with congenital heart surgery, 1 with intestinal lymphangiectasia, and another with thrombus due to protein-losing gastroenteropathy died. The latest status of 1 patient is unknown because they have been lost to follow-up. The general characteristics, clinical-laboratory findings, and treatments of the study population by age group are shown in Table 1.

Clinical Characteristics of Patients with Gorham-Stout Disease

Seven (31.8%) patients were diagnosed as having GSD. All patients with GSD had bone involvement. The most common site of bone lesions was the vertebrae (n = 7) (Figure 3). Six patients had biopsies from different places, and biopsies show either vascular proliferation or dilated lymphatic. The imaging, pathologic findings, and therapies of the patients with GSD are shown in Table 2. Two patients with GSD had hydrocele.

DISCUSSION

The present study was a review of our experience of chylothorax and the clinical/radiologic features of GSD at a single

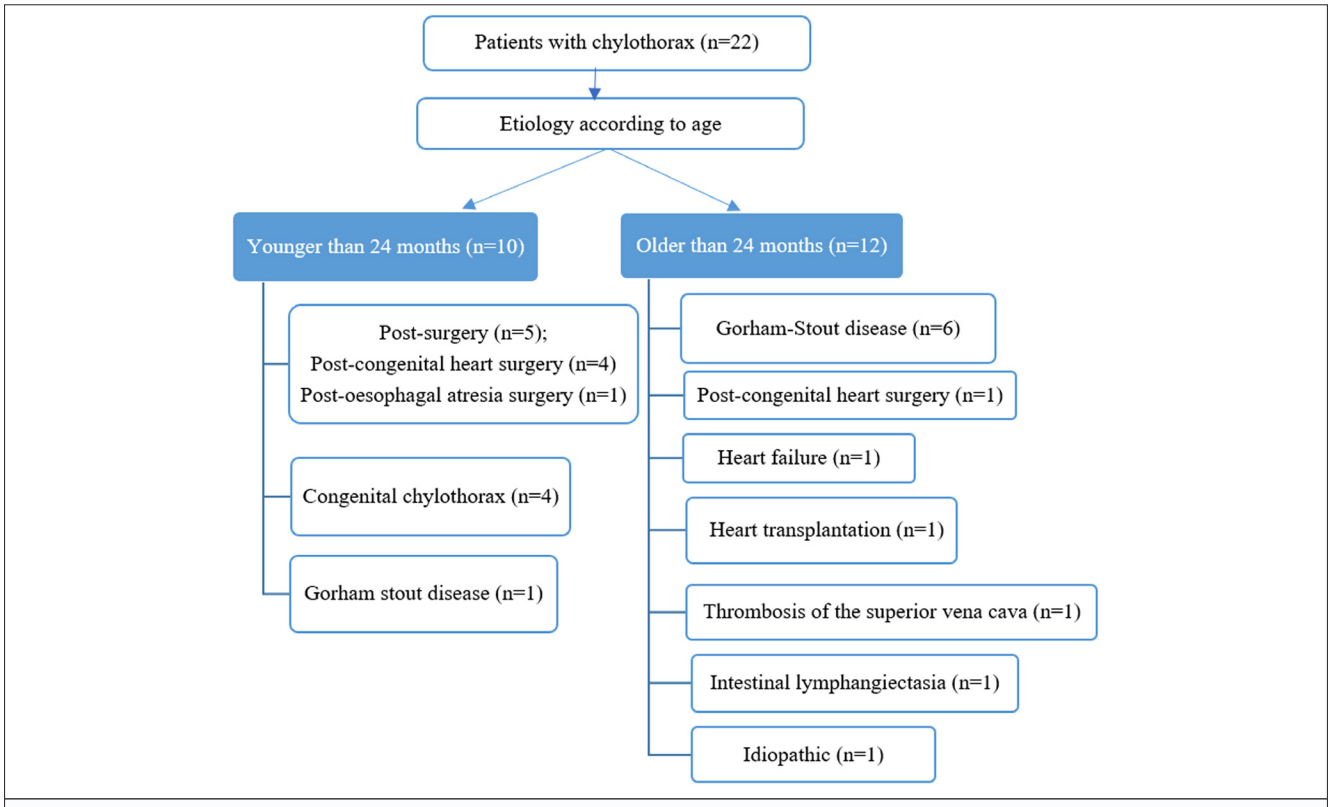

Figure 2. The etiology of chylothorax by age group and study population.

Table 1. Clinical Characteristics and Treatments of 22 Children with Chylothorax

	Patients Younger Than 24 Months (n = 10)	**Patients Older Than 24 Months (n = 12)**
Female/male, n (%)	5 (50)/5 (50)	6 (50)/6 (50)
Age at chylothorax time, months, medians (interquartile range)	1 (1-1)	72 (36-117)
Symptoms, n (%)		
Tachypnea	3 (30)	1 (8.3)
Dyspnea	1 (10)	5 (41.6)
Hypoxia	6 (60)	2 (16.6)
Chest discomfort	0 (0)	4 (33.3)
The site, n (%)		
Left	5 (50)	1 (8.3)
Right	2 (20)	2 (16.6)
Bilateral	3 (30)	9 (75)
Level of triglycerides in pleural fluid, mg/dL, median (interquartile range)	680 (270-1769)	476 (298-993)
Treatment, n (%)*		
Total parenteral nutrition	1 (10)	0 (0)
Medium-chain triglyceride diet	7 (70)	3 (25)
Ligation of the thoracic duct	2 (20)	0 (0)
Sirolimus	1 (10)	7 (70)
Propranolol	1 (10)	0 (0)
Intravenous octreotide/somatostatin	5 (50)	2 (16.6)
Steroid therapy	0 (0)	3 (25)
Chemical pleurodesis	1 (10)	0 (0)
Interferon alpha	0 (0)	4 (16)
Latest status, n (%)		
Survival	7 (70)	9 (75)
Exitus	2 (20)	3 (25)
Unknown	1 (10)	0 (0)

*Multiple treatment strategies are possible for each child; hence, percentages do not equal 100%.

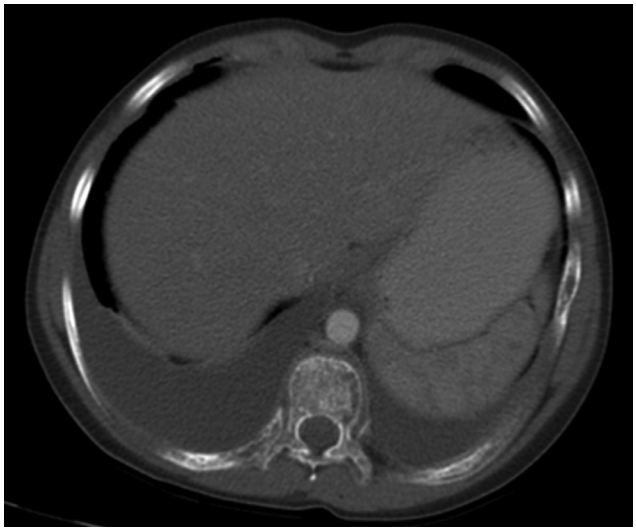

Figure 3. Axial chest computed tomography image shows bilateral pleural effusion and lytic lesions of the vertebrae and ribs.

tertiary care center. There are multiple causes of chylothorax in childhood. In this study, the most common etiologic causes were postoperative history in the younger group and GSD in the older group. The remaining etiologies were congenital chylothorax, heart failure, heart transplantation, thrombus, and intestinal lymphangiectasia.

Chylothorax has been reported after congenital heart disease surgery due to trauma, increased central venous pressures, and central venous thrombosis.[12,13] Here, 4 of the younger group and 1 of the older group's patients had a history of surgery due to congenital heart disease. The etiology of congenital chylothorax is often unclear.[10] Associations with Down, Turner, or Noonan syndromes owing to the involvement of the lymphatic system have been reported.[2] In our study, no patients were diagnosed as having any syndromes.

Although there is no standard of care for the treatment of chylothorax including congenital chylothorax, the most suggested is to start with dietary modification, followed by octreotide, and lastly surgical intervention.[14,15] Diet modification mainly includes MCT, which is directly absorbed into the portal system, and total parenteral feeding to reduce the chyle flow. Also, octreotide is a synthetic, long-acting somatostatin analog and, in general, is considered to be a safe drug. These agents reduce intestinal chyle production, thereby reducing the volume flowing through the injured thoracic duct. In infants and children, most physicians start with a dose of 0.5 μg/kg/h and escalate as needed.[16] The optimal timing of introduction and duration of octreotide treatment is unknown. Surgery is also recommended if there has been a rapid decline in nutritional status despite conservative management.[1] However, sometimes conservative treatments take time to be effective so other treatments have been put forward. Propranolol, which is frequently used in the treatment of infantile hemangiomas, is of interest as a treatment for chylous effusions. One theory proposes that a cascade of events via inhibition of the β2 adrenergic receptors leads to decreased expression of proangiogenic factors.[17,18] Indeed, pleurodesis with povidone-iodine is well tolerated when classic management fails.[19] In terms of

Table 2. Imaging, Pathological Findings, and Therapies of Patient's with Gorham-Stout Disease

Case	Age at Diagnosis (Years)/Sex	Bone Retained in Bone Survey⁺	Computed Chest Tomography					Biopsies	Therapies
			Atelectasis	Effusion Density (R/L)*	Bone Involvement	Mediastinal Edema	Splenic Lesions		
1	1/M	-	+	-/23	Vertebrae, scapula	-	-	Lung: dilated lymphatic lumens	MCT, sirolimus, propranolol, surgery
2	6/M	Femur	+	28/24	Vertebrae, ribs	-	-	Skin: dilated lymphatic lumens	MCT, interferon, sirolimus, steroid therapy
3	9/F	Humerus	+	30/30	Vertebrae, ribs	-	-	-	Steroid therapy, sirolimus
4	10/F	Scapula, clavicula	+	38/36	Vertebrae, ribs	+	-	Lung, rib: vascular proliferation	Interferon, sirolimus, steroid therapy
5	9/M	-	+	17/17	Vertebrae	-	Cyst	Lymphadenopathy: vascular proliferation	Sirolimus, MCT, interferon
6	2/M	Femur	+	21/25	Vertebrae	-	-	Lung: dilated lymphatic lumens	Sirolimus
7	10/M	-	+	16/15	Vertebrae, scapula, ribs	-	-	-	Sirolimus, interferon

MCT, medium-chain triglyceride diet.
*Right/Left, Hounsfield units.
⁺All had diffuse osteopenia.

treatments, 1 patient had chylothorax after heart transplantation and was successfully treated with octreotide. One patient who had heart failure due to myocarditis had chylothorax and he was successfully treated with octreotide. Later, he had a heart transplantation and he is currently aged 6 years. One patient with protein-losing gastroenteropathy had thrombosis of the superior vena cava, which led to chylothorax. She was treated successfully with octreotid and discharged. Unfortunately, she was lost to follow-up and we learned that she died. One of the patients in our cohort with congenital heart disease needed thoracic duct ligation. An infant who after being diagnosed as having GSD used propranolol finally needed thoracic duct ligation. One patient with congenital chylothorax was treated with chemical pleurodesis with povidone-iodine, and he is aged 14 years currently. He lives without any respiratory support at the last visit. Unfortunately, he has hypothyroidism thought to be related to this treatment. A patient whose chylothorax etiology was unknown used a ketogenic diet for childhood epilepsy. She was aged 5 years, and she was hospitalized due to pneumonia. Dyspnea developed on the fifth day of her hospitalization, and effusion was seen on the chest x-ray. Thoracentesis showed milky pleural effusion, and the triglyceride level was 1467 mg/dL. First, when we stopped feeding, pleural effusion drainage decreased by 83.3% per 24 hours. She had no bone lesions on CT. Also, thrombus was not detected in imaging methods. Therefore, we thought that a high-fat diet may lead to chyle leakage. This may be the first case in the literature of chylothorax induced by a ketogenic diet.

Gorham-Stout disease was first reported by Jackson in 1838 and may develop at any age in life.[20] The incidence is higher in males.[20] Several pathways and etiologies have been proposed for the mechanism of GSD.[20] The accepted trigger of the disease is lymphatic overgrowth.[21] A clinical feature of GSD is osteolysis of any bone.[22] Ozeki et al[23] showed that bone lesions, which is a diagnostic criterion, were present in all patients diagnosed as having GSD. If the physician cannot diagnose the disease through radiologic examinations, a biopsy of the lesion is the next diagnostic step.[22] Extra-osseous involvement in GSD as splenic involvement is also known.[24] The role of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin(mTOR) pathway has been found in the development of blood vessels and lymphatic tissues.[22] Sirolimus, which is an mTOR inhibitor, has been reported to be effective in the treatment of vascular anomalies.[25,26] Sirolimus and prednisolone combination therapy has been suggested in the literature.[27] Also, interferon, which inhibits the proliferation of blood and lymphatic vessels, is used for patients with bone or generalized lymphatic lesions.[28,29] Here, 62.5% of patients with GSD were male. One patient of the younger group who had chylothorax in the first month of life was later (in the fourth month of his life) diagnosed as having GSD. All patients with GSD (n = 7) had bone lesions. Thoracic lesions were the most common. Bone surveys (n = 7) showed diffuse osteopenia in the GSD patient group. Biopsies (n = 5) showed either or both vascular proliferation and dilated lymphatics. One of the patients had cystic lesions in the spleen. All patients with GSD used sirolimus and achieved good clinical improvement. Three patients used steroid therapy, and 4 also used interferons.

The limitations of this study include the following: our sample was from a single institution and our study was retrospective. Also, there may be patients who were not enrolled and therefore not included in the study, which may lead to an underestimation of patient numbers.

In conclusion, there is a wide variety of underlying etiologies in childhood, so a multidisciplinary approach is important for identifying the underlying diagnosis. Postoperative chylothorax and GSD were the common etiologies. All patients with GSD cases had a good prognosis. Gorham-Stout disease should be kept in mind in patients of any age with a diagnosis of chylothorax who have bone lesions.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hacettepe University (Approval No: GO 21/1354, Date: 21.12.2021).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.N.B., N.K.; Design – N.E., N.K.; Supervision – D.D., E.Y., U.O., N.K., T.K, N.O.; Data Collection and/or Processing – H.N.B., D.A., İ.G., M.A.E., B.S.; Analysis and/or Interpretation – H.N.B., N.E., N.O; Literature Review – H.N.B., N.K.; Writing – H.N.B.,N.E.,N.K.; Critical Review – H.N.B., N.E.,N.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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