

Analysis of Intractable Chylothorax Treatments during Consultations from Other Hospitals: A Treatment Strategy for Central Lymphatic Diseases

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Background: Lymph flow disorder in the central lymph pathway is referred to as central lymphatic disease. This disorder can be intractable and can present as postoperative chylothorax. Although novel concepts and treatments have been reported, some specialists were generally asked about ideas beyond their specialties. Hence, the current study aimed to validate the ideas that emerged from these consultations.

Material and Methods: We analyzed the consultations handled by our team from May 2016 to May 2020. All data about the location and characteristics of the consulted hospitals, specialty of the consulting physician, and aim of the consultations (operation request, treatment plan, testing details, and nutrition) were retrospectively assessed.

Results: In total, 38 consultations were evaluated. We observed an annual increment in the number of cases. The majority of questioners were in the Kanto region, university hospitals, and pediatric cardiologist, about postoperative chylothorax. Notably, the consultations primarily aimed to discuss treatment plans rather than operative requests.

Conclusion: A standardized therapeutic strategy for central lymphatic disease should be established. Thus, a proposal for such a treatment approach was presented in our strategy flowchart.

Keywords: postoperative chylothorax, central lymph disease, lymphatic venous anastomosis, interventional radiology, treatment strategy

Background

Lymphatic vessels are part of an important organ system spread throughout the body with roles in the immune system and in fluid homeostasis. Lymphatic fluid merges to flow into the central pathway, such as the cisterna chyli and thoracic duct, eventually flowing out to the venous system at the venous angle. Along the pathway could be lymphatic effusions, and this condition is called central lymphatic disease. This disease can lead to various severe symptoms with intractable general conditions such as post-operative chylothorax, chylous

ascites, or protein-losing enteropathy.

Recently, radiological diagnosis has advanced to enable visualization of lymphatic flow, and several novel approaches have been developed for central lymphatic diseases, such as the flow-oriented concept to understand its pathophysiology. Following this novel concept, and taking advantage of our expertise as plastic surgeons, we reported the results of therapeutic interventions for this disease by focusing on lymphatic vein anastomosis under a microscope. However, the pathophysiology, examination methods, and treatment strategies have not yet been generalized. There have been increasing cases

Received: January 7, 2021; Accepted: April 21, 2021

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Original published in *Pediatric Cardiology and Cardiac Surgery*, Vol. 36 (2020), No. 4, pp. 287–293

doi: 10.24509/jpcscs.21-001

of consultations to out-of-hospital specialists like us, by telephone or e-mail, regarding treatment strategies for intractable cases.

The present study aims to clarify the consulter types and clinical problems of central lymphatic diseases, by analyzing previously received consultations from other hospitals, as a step to standardize the treatment.

Materials and Methods

The subjects were those who were consulted to our team by doctors from other hospitals about lymphatic disease May 2016 to April 2020. Only central lymphatic disease consultations were included, with symptoms of chylothorax, chylous ascites, pericardiac effusion, and protein-losing enteropathy. Those limited to peripheral lymphatic disorders (lymphedema and/or lymphangioma) were excluded. A series of exchanges were counted as single consults; however, different cases or other questions from previous consultants were counted as independent consults. Detailed non-trackable consults were excluded, such as phone calls that were not recorded.

We classified consultant regions (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, Shikoku, Kyushu-Okinawa), characteristics of consulting hospitals (University hospital, Specialty hospital, General hospital), consultant physician's specialty, cases (age, anomalies, genetic diseases, symptoms, previous surgeries), contents of the consult (operation request, treatment plan, testing procedure, medical treatment, nutrition), and our responses. The contents of the consults were counted individually when they included more than two questions in the first e-mail, but the additional questions in the following e-mails in the series consult were not included.

Results

A total of 47 consults were collected during a period of 4 years (48 months). Nine consults were excluded from this study because they were not linked with central lymphatic disease; therefore, 38 cases were included. The number of consults increased every year, with 19 consults (out of 38 consults, 50%) in last year, 2019 (Fig. 1).

Consultants were affiliated to 20 hospitals. Regional distribution showed that more than half of the hospitals were in Kanto region (13 of 20 hospitals, 65%), but there was at least one hospital from all regions west to Chubu. Hospital type classification indicated that university

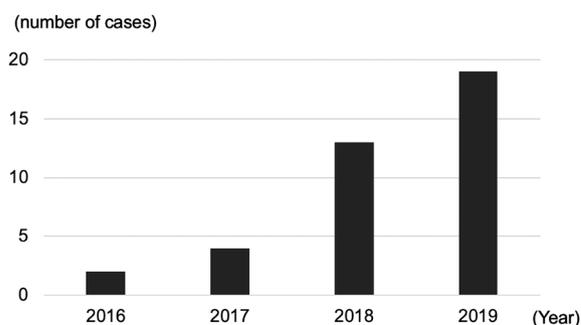


Fig. 1 Yearly change of consult cases
Number of cases increased over years, from 2016 to 2019 (12 months each, started in May).

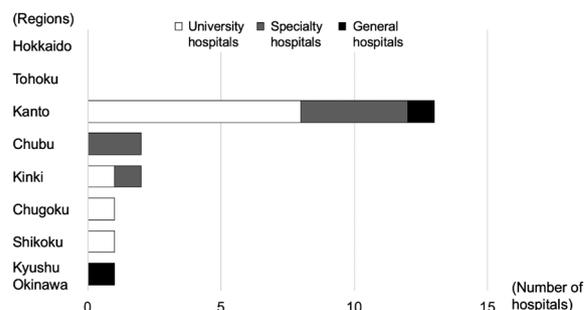


Fig. 2 Characters and regions of consulter hospitals
Although, the majority was in Kanto region, hospitals distributed 6 regions out of 8 in Japan.

hospitals were the most common (11 out of 20, 55%), followed by specialty hospitals (specialized for pediatric hospitals or cardiovascular hospitals) (7, 35%), and general hospitals (2, 10%) (Fig. 2).

Consultation numbers from each hospital varied; there were single consultations from 11 hospitals (out of 20, 55%), while nearly half 9 hospitals (out of 20, 45%), consulted twice or more. Of the hospitals that consulted more than twice, the majority were in the Kanto region (7 hospitals out of 9, 78%), and one hospital each was in Chubu and Kinki.

A total of 17 consulters (out of 38, 45%) specialized in the cardiovascular field (pediatric cardiology, pediatric cardiovascular surgery), with pediatric cardiology being the most common (14 consulters, 37%), followed by specialists in the intensive care field (intensive care unit, neonatology) (10, 26%) and pediatric field (pediatrics, pediatric surgery) (9, 24%), with consulters from plastic surgery being the least (2, 5%) (Fig. 3).

Consultations were done for a total of 37 cases, with one case in each of the 38 consults except for one. The majority of the cases were infants; almost half were less

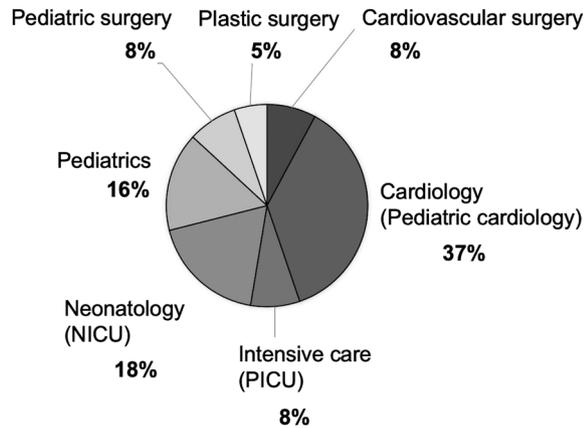


Fig. 3 Specialty of consulters
Cardiology was the majority, however various other specialists consulted.

than 3 months old (18 cases out of 38, 49%) (overall range was from 2 days to 18 years old, mean age was 2 years 6 months).

Chylothorax was the major symptom in the consults, seen as the presenting symptom in 33 cases out of 37 (89%), followed by chylous ascites (6 cases, 16%), and general edema (4 cases, 11%). Several cases showed chylous pericardial effusion and protein-losing enteropathy. Background conditions of congenital heart diseases were seen, with hypoplastic left heart syndrome being the most common (11 cases out of 37, 30%), followed by total anomalous pulmonary venous return and coarctation of aorta (4 cases, 11%). Many cases underwent cardiovascular surgery prior to the consult (28 cases out of 37, 76%); however, some cases did not undergo previous surgeries or did not have congenital anomaly (Table 1).

Notably, the major aim of the consultation was the formulation of a treatment plan (23 out of 38, 61%) followed by operative treatment request (19, 50%). Only one consult (out of 38, 3%) was aimed at nutrition advice. Most of our responses to each consultation were in line with the original consultation questions, such as providing an operative treatments, formulating a specific treatment plan, and details of the examination procedure (34 out of 38 consults, 90%). In the remaining four cases (21%), treatment was not actually carried out, since by the time the operation request came there was sudden deterioration of the patient's general condition, leading to a major shift in the treatment plan (Table 1).

Discussion

Physicians who treat chylothorax are facing difficulties in deciding priorities because several novel approaches are available leading to current testing methods and treatment options for central lymphatic disease being updated. In the present study, we aim to organize the consenter types and clinical problems of central lymphatic diseases by analyzing previously received consultations from other hospitals.

As a result, the majorities were in Kanto region, university hospitals, consult from pediatric cardiologists, infantile cases, and aimed specific treatment plans. On the other hand, the types of consultation were similar across regions, hospital types, and specialties. This result indicates that a standardized treatment strategy is necessary for central lymphatic diseases.

Patients with central lymphatic diseases can be diagnosed immediately after as fetal edema,¹⁾ but can occasionally occur (6%) posterior to Fontan related cardiac surgery.²⁾ Spontaneous improvement and preservation therapy could be effective; therefore, the treatment plans were decided by the hospitals. However, when it became intractable, treatments could be difficult due to limited therapeutic options, eventually led to prolonged hospitalization and developmental disorders.³⁾

General treatment strategies for this disease include nutrition therapy (Medium chain triglyceride milk or fasting),⁴⁾ medical therapy (octreotide or steroids),⁵⁾ symptomatic surgeries (drainage or thoraco-abdominal shunting), and/or radical surgeries (pleural adhesion or thoracic duct ligation). However, the invasive radical surgeries listed above could be unsuccessful.^{6,7)}

On the other hand, several novel treatments have been developed based on the concept of normalizing the lymph flow owing to the progression of methods for evaluation of lymph flow.⁸⁾ Various imaging methods are now in practice to enabled detailed visualization of lymph flow, such as lymphography with inguinal lymph node access.⁹⁾ The same is also applied to assess deep dynamic lymph flow. Other techniques include dynamic magnetic resonance lymphangiography (MRL),^{10,11)} to overcome the low resolution of classical lymphoscintigraphy.¹⁾ Some reported novel treatments following to those evaluations such as thoracic ductal embolization by interventional radiology (IVR),¹²⁾ or lymphatic venous anastomosis (LVA) to create bypass for lym-

Table 1 List of consult cases

No	Age	Malformations	Genetic disorder	Symptoms	Surgeries	Consult purpose
1	0M	Cardiac (detail unknown)	21trisomy	PE, Ascitis, Edema	PDA ligation	Plan, Test
2	0M			PE, Edema		Operation, Plan
3	0M	CoA	Noonan	PE	CoA repair	Plan, Test
4	0M	HLHS		PE	PA banding	Operation
5	1M	HLHS		PE, Ascitis	Cardiac (detail unknown)	Operation, Plan
6	1M			PE, Edema		Operation
7	1M	Cardiac (detail unknown)	21trisomy	PE, Edema	PDA ligation	Operation, Plan
8	1M	Cardiac (detail unknown)		PE	PA banding	Plan, Test
9	1M		21trisomy	PE		Plan, Test
10	1M	Cardiac (detail unknown)		PE	Cardiac (detail unknown)	Plan, Test
11	1M			PE		Plan
12	1M			PE		Neutrition
13	1M			Ascitis		Operation, Plan
14	2M	Cardiac (detail unknown)		PE, Ascitis	Cardiac (detail unknown)	Plan
15	2M	esophageal atresia		PE	Esophageal atresia repair	Test
16	2M	HLHS		PE	Norwood	Operation
17	2M	TAPVR, esophageal atresia		PE	TAPVR repair	Operation
18	2M	CoA		PE	CoA repair	Operation
19	2M	Ebstein, Cardiac (detail unknown)		PE	Cardiac (detail unknown)	Operation
20	2M	TAPVR		PE	TAPVR repair	Operation
21	3M	HLHS		PE	Norwood	Operation, Plan
22	3M	Cardiac (detail unknown)		PE	Cardiac (detail unknown)	Operation
23	3M	Cardiac (detail unknown)		PE	PDA ligation	Operation, Plan
24	3M			PE		Operation
25	3M	esophageal atresia	18trisomy	Ascitis, Pericardial	PDA ligation, PA banding	Plan, Test
26	5M	HLHS		PE	Glenn	Plan
27	6M	HLHS		PE	Norwood, PA banding	Plan, Test
28	9M	Cardiac (detail unknown)		PE, Pericardial	Rastelli	Operation
29	1Y			Ascitis		Test
30	1Y	TAPVR		PE	TAPVR repair	Operation
31	2Y	polyductyle		PE	CoA repair	Operation, Plan
32	2Y	HLHS, TAPVR		PE	Fontan	Test
33	5Y	CoA		PE	CoA repair	Plan
34	7Y	HLHS		PE	Fontan	Plan, Test
35	9Y	HLHS		PE	Fontan	Plan, Test
36	13Y	HLHS		PE	Fontan	Operation, Plan
37	18Y	HLHS		PLE	Fontan	Plan

The consult purposes were classified into four categories; Operation was direct request of surgical operation, Plan indicates consult about treatment planning and/or strategy of cases, Test was question about concrete testing methods (how to do MR lymphography, etc), and Nutrition was about questions of dose/timing of restart in fasting case. Note the consultants aimed to discuss treatment plans, not simply request for surgical operations. M=months-old, Y=years-old. CoA, coarctation of aorta; HLHS, hypoplastic left heart syndrome; PA, pulmonary artery; PDA, patent ductus arteriosus; PE, pleural effusion; PLE, protein losing enteropathy; TAPVR, total anomalous pulmonary venous return.

phatic flow with microsurgical techniques.¹³⁾ However, the treatment strategy is not clearly indicated in the previous reports.

From the present study, the importance of common understanding is highlighted, as consults about treatment plans are more popular than actual surgical operation requests. Furthermore, the consultant specialists were mainly physicians, belonging to either cardiovascular, intensive care, or pediatrics specialties, but not surgeons or radiologists who actually perform surgeries. The types of hospitals from where consult request originated were not only specialty hospitals but also

general hospitals and university hospitals, where multiple specialists work together. Therefore, we consider it worthwhile to present our strategy for central lymphatic disease, even if it includes personal opinions.

Our Treatment Strategy for Central Lymphatic Disease

We do not insist on the previous classification of central lymph disease, such as congenital, traumatic, or venous congestions. The reasons for this are that diagnosis and treatments are not based on one-to-one correspondence; furthermore, we have also experienced

several clinical cases with a combined pathophysiology, as previously reported.¹⁴⁻¹⁶⁾ For example, lymphography on postoperative chylothorax after Fontan surgery showed no specific leaking point, instead lymphatic fluid congestion and recurrence in the abdomen or lower, more than just in the thoracic duct. In such cases, the diagnosis should be combined with congenital thoracic obstruction with venous congestion, not a traumatic type of congestion. In short, combined pathophysiology of congenital and venous congestion does exist.

We consider lymphatic flow assessments based on treatment plans as necessary. The current flow-oriented treatments are classified either as “drain”, by bypass creation, or as “plug” by IVR; therefore, we use “drains” for cases with congested lymph, and “plugs” for cases with leakage of lymph. To classify the types of cases, central lymphatic dynamics must be assessed. In other words, when lymphatic congestion or recurrence was confirmed, LVA was used to create a bypass to drain the lymphatic fluid. When orthodromic leakage was visualized, embolization was performed using IVR. Therefore, evaluation of lymph flow recurrence, leakage quantity, and various other points were used as primers to decide the treatment plans.

On the other hand, lymphatic scintigraphy was applied as the first-line technique to visualize the entire flow image. Scintigraphy is advantageous because of its high reproducibility, small differences in results depending on the procedures, and its wide applicability in almost all cases. In addition, fluorescent indocyanine green (ICG) lymphography has been frequently used to evaluate peripheral lymph flow recurrence on the body surface in either the extremities or in the trunk. ICG lymphography follows a very simple procedure: injecting a small amount of agent subcutaneously; therefore, it is highly reproducible. We used ICG lymphography not only for peripheral but also for central lymphatic disease to assess the pathophysiology because it is a less invasive method as compared to other methods; also, there is no risk of radiation exposure, and it can thus be safely used even in neonates. However, observational timing, points to observe, and result evaluation requires experience. Thus, we considered ICG lymphography as a supplemental examination. Although MRL is a valuable method to visualize central lymph flow dynamically and in detail, it is not yet available in many hospitals. For MRL, direct perfusion of the agent into the ingui-

nal lymph node is necessary; therefore, experienced surgeons and radiologic engineers are required. In our experience, owing to the difficulty in puncturing procedures patients younger than 5 years, this technique is not suitable in this population so far. In addition to this, this technique can be quite invasive in small infants. Therefore, we try it whenever possible, but do not consider it as minimal requirement. Savla et al. proposed the classification of central lymph flow with MRL results as traumatic, pulmonary lymphatic perfusion syndrome (PLPS), and central lymphatic flow disorder (CLFD).¹⁵⁾ Our proposed combined congestion and recurrence theory was similar to CLFD.

Lymphatic venous anastomosis indicate for obstructive situation at the venous angle (by clot formation), in which all cases showed general lymphatic recurrence. In such cases, cervical lymphatic venous anastomosis is effective at the venous angle, at the exit of the central lymphatic system.¹³⁾ Peripheral LVA is considered when lymphatic recurrence occurs even without obstruction at the venous angle. In cases with recurrence extending to the extremities, LVA is a good indication because it can be completed less invasively. However, we consider IVR instead, in cases with high peripheral venous pressure, because lymphatic fluid is not easily collected through the bypass created. We suggest LVA for patients older than one week and with body weight greater than 2,500 g.

IVR therapy for central lymphatic disease is represented by thoracic ductal embolization and lipiodol lymphography. Thoracic ductal embolization is highly effective, and an immediate effect is expected; however, special techniques are required, especially in small infants.¹⁷⁾ Complications are reported to be limited due to speedy spontaneous collateral formation postoperatively. However, some cases reported intractable iatrogenic lymphedema following lymphatic congestion and recurrence. On the other hand, lipiodol lymphography is a classical evaluation method of lymph flow, and it is expected to be a less invasive therapy. The mechanism of action was considered to be either the agent itself directly obstructing the leakage point due to high viscosity or the local selective adhesion of the pleura following agent leakage.^{18,19)} However, it is contraindicated in cases with right-to-left shunting because a previous report indicated that lipiodol could cause cerebral infarction through the systemic circulation.²⁰⁾ Therefore, we suggest lipiodol lymphography in cases with

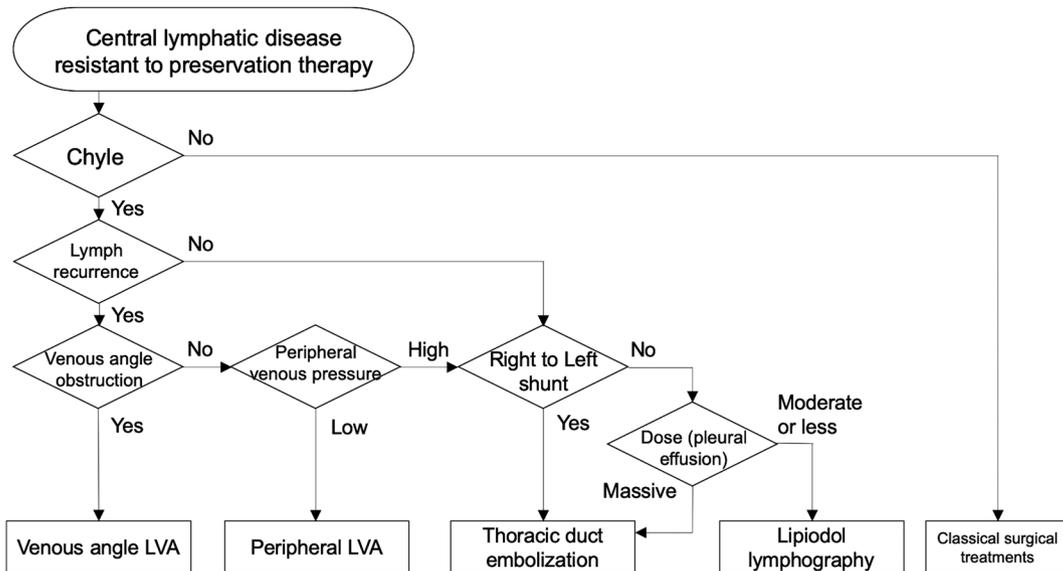


Fig. 4 Flowchart of treatment strategy for central lymphatic disorder resistant to preservation therapies

Flow oriented treatments were plannable with the present flowchart. Briefly, lymphatic venous anastomosis (LVA) is suitable for lymph recurrent cases, to create bypass from lymph to vein, at venous angle or peripherally. On the other hand, interventional radiological approach, such as thoracic duct embolization, and lipiodol lymphography were effective for antegrade lymphatic leakage. LVA, lymphatic venous anastomosis.

relatively small leakage to the thoracic cavity without right to left shunting. It is suitable for patients weighing $>1,000$ g because microscopic magnification assists in inguinal node injection even in small neonates.

For decision-making, we apply these novel therapies to intractable situations resistant to preservation therapy for at least one month so as to avoid unnecessary surgical interventions, according to previously reported suggestions for surgical interventions.³⁾ Even for intractable chylothorax, we note that pleural effusion assessments are necessary, with property, cell counts, and lymphocyte fraction of effusion. This is because other approaches using a normal lymphatic system could be effective,²¹⁾ if not chyle (Fig. 4).

The limitations of this study include bias because all the consults were answered by a single team. Consulters were easily contacted if they were acquainted with our team members. Furthermore, consults were mainly from the Kanto region, where our hospital is located. However, we received many similar consults from all over the country, but even these numbers were limited. Furthermore, consults from other specialties were much more popular than ours. Also, concrete treatment strategy is considered to be an important and general concern, as it was the major reason for the consult, especially by pediatric cardiovascular specialists.

Conclusion

Multiple evaluation methods and treatment options are available for central lymphatic diseases, with improved physiological understanding. Establishing a standardized treatment strategy is considered necessary since similar questions were raised during the consults by different physicians belonging to different hospitals, specialties, and regions.

Conflicts of Interest

All authors have no conflict of interest.

Authors' Contributions

Motoi Kato: Protocol creation, Data collection, Data interpretation, Manuscript, preparation, Research submit decision

Reiko Kato: Data interpretation (assist), Manuscript preparation (assist)

Azusa Watanabe: Research supervise

Shoji Watanabe: Research supervise

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