Received: 13 January 2022 | Revised: 3 April 2022 | Accepted: 9 April 2022

DOI: 10.1111/petr.14295

BRIEF COMMUNICATION

WILEY

Protein-losing enteropathy recurrence after pediatric heart transplantation: Multicenter case series

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Abstract

Background: Protein-losing enteropathy (PLE) is a devastating complication of the Fontan circulation. Although orthotopic heart transplantation (HTx) typically results in resolution of PLE symptoms, isolated cases of PLE relapse have been described after HTx.

Methods: Patients with Fontan-related PLE who had undergone HTx at participating centers and experienced relapse of PLE during follow-up were retrospectively identified. Available data related to pre- and post-HTx characteristics and PLE events were collected.

Results: Eight patients from four different centers were identified. Median time from Fontan procedure to the development of PLE was 8 years, and median age at HTx was 17 years (range 7.7–21). In all patients, PLE resolved at a median time of 1 month after HTx (0.3–5). PLE recurrences occurred at a median time of 7.5 months after HTx (2–132). Each occurrence was associated with one or more significant clinical events; most commonly cellular- or antibody-mediated rejection; and less commonly graft dysfunction, infection, thrombosis, and posttransplant lymphoproliferative disease. PLE recurrences resolved after the successful treatment of the concomitant event, after a median time of 2 months in seven cases, while persisted and recurred in one patient in association with atypical mycobacterium infection and subsequent PTLD onset and relapses. Six patients were alive during follow-up at a median time of 4 years (1.3–22.5) after HTx.

Conclusions: This is the largest series of PLE recurrence after HTx. All cases were associated with one or more concomitant and significant clinical events. PLE typically resolved after resolution of the inciting clinical event.

KEYWORDS
Fontan circulation, pediatric heart transplant, protein-losing enteropathy

Abbreviations: ANP, atrial natriuretic peptide; AVVR, atrioventricular valve regurgitation; BNP, brain natriuretic peptide; CO, cardiac output; CVP, central venous pressure; HS, heparan sulfate; HSPGs, heparan sulfate proteoglycans; HTx, heart transplantation; IFN-γ, interferon-γ; IL-6, interleukin-6; PLE, protein-losing enteropathy; PTLD, posttransplant lymphoproliferative disease; TNF-α, tumor necrosis factor-α.

TABLE 1 Pre-HTx characteristics

Patient	CHD	Morphologic Ventricle	Age at Fontan (years)	Fontan type	Fenestration	Time from Fontan to PLE (years)	Time from Fontan to HTx (year)	Pre-HTx AVVR	Pre-HTx ventricular function	Pre-HTx Fontan pressure	Pre-HTx CI[a]	Pre-HTx EDP/PCWP	Age at HTx (years)
1	HLHS	Right	2.1	LT	No	0.9	13.4	Trace	Preserved	17	4	11	15.4
2	HLHS	Right	2	LT	Yes	11	19	Mild	Preserved	12	3.2	7	21
3	HLHS	Right	2	LT	Yes	13	4	Mod-Sev	Impaired	25	3.7	20	17
4	DORV	Right	2	EC	Yes	8	15	Mild	Preserved	12		11	17
5	HLHS	Right	3.5	EC	Yes	1.5	3.3	Mild	Impaired	15	3.1	9	7.7
6	TA/PS	Left	7	AP, then LT	No	10	10.6		Preserved				17.6
7	TA/TGA	Left	2	LT	Yes		16	Mild	Preserved	17	3.2	13	18.8
8	DORV	Right	3	EC	Yes	3	11	None	Preserved	20	3.2	16	14
Median			2.1			8.0	12.2			17	3.2	11.0	17.0

Note: Data left blank are unavailable.

Abbreviations: AP, aortopulmonary; AVVR, atrioventricular valve regurgitation; CI, cardiac index; DORV, double outlet right ventricle; EC, extracardiac; EDP/PCWP, end-diastolic pressure/pulmonary capillary wedge pressure; HLHS, hypoplastic left heart syndrome; HTx, heart transplantation; LT, lateral tunnel; TA/PS, tricuspid atresia/pulmonary stenosis; TA/TGA, tricuspid atresia/transposition of the great arteries.

[a] L/min/m^2.

1 | INTRODUCTION

Protein-losing enteropathy (PLE) is characterized by enteric loss of protein including albumin, immunoglobulins, and clotting factors, leading to the clinical findings of peripheral edema, ascites, diarrhea, weight loss, and malabsorption.[1] Occurring in 5%–12% of cases,[2] it remains as a devastating complication of the Fontan circulation, with significant morbidity and 5-year survival rates of 50%–88%.[3,4]

Even though the mechanisms leading to PLE after Fontan are still not completely understood, hemodynamic conditions, systemic inflammation, lymphatic abnormalities, and injury to the intestinal epithelium have been implicated in the pathophysiology of PLE in these patients.[1,5–8]

Orthotopic heart transplantation (HTx) has shown to be curative therapy for Fontan-related PLE, with Schumacher et al.[9] reporting resolution of 98% of PLE cases after a median of 1 month after HTx. Interestingly, the authors described the persistence of PLE in one of the 43 HTx survivors at long-term follow-up, and recurrence of PLE after HTx in another four patients.[9] PLE occurrence and recurrence after HTx have been anecdotally reported elsewhere in the literature as well.[10–13] In light of these findings, we sought to examine the characteristics of a multi-institutional cohort patients with PLE recurrence after HTx from major referral centers for Fontan HTx.

2 | METHODS

Patients who developed Fontan-related PLE, had undergone HTx at participating centers, and experienced relapse of PLE during follow-up were evaluated. Patients were identified at individual participating centers through retrospective chart review of their respective heart transplant databases. Available clinical, echocardiographic, hemodynamic, and/or laboratory pre- and post-HTx data along with data related to PLE relapse were collected.

2.1 | Definitions

Active PLE was defined as symptomatic serum hypoalbuminemia, based on the assessment of the treating clinician, while the resolution of symptoms and the normalization of serum albumin levels were defined as *PLE resolution*. *PLE relapse* was defined, in accordance to prior definition used in multicenter study by Schumacher et al.,[9] as return of PLE symptoms, with serum hypoalbuminemia and need for treatment after at least 1 month after HTx in a patient who had previously had PLE resolution. *Rejection* was defined as a clinical event prompting augmentation of immunosuppressive therapy, with or without biopsy, in line with the currently accepted definition by the Pediatric Heart Transplant Society. *Infection* included clinical scenarios with the presence of signs and symptoms concerning for infection and/or positive microbiological testing requiring initiation of specific directed therapies.

3 | RESULTS

3.1 | Demographics

Eight patients from four different centers were identified (Table 1). Of note, four were previously included in the cohort by Schumacher et al.[9] as mentioned above, while the rest have not been reported before. The most common underlying congenital heart disease was hypoplastic left heart syndrome in four patients. Two had tricuspid atresia, one double outlet right ventricle and one double inlet left ventricle. In 75% of cases (6/8), the systemic ventricle was the morphologic right ventricle. Median age at the Fontan operation was 2.1 years (range 2–7); 50% (4/8) underwent a lateral tunnel Fontan, one had an initial atriopulmonary Fontan and was then converted to a lateral tunnel-type Fontan, and 3 (37.5%) had an extracardiac Fontan completion. Fontan fenestration was present in 75% (6/8) of patients.

3.2 | Pre-HTx PLE characteristics

Median time from Fontan procedure to the development of PLE was 8 years (range 0.9–13 years). All patients were treated with albumin infusions and three patients (37.5%) also received IV immunoglobulin as part of their PLE therapy pre-HTx. At time of HTx evaluation, two patients presented impaired ventricular function and the remaining six presented normal systemic ventricular function by echocardiogram. Data on atrioventricular valve regurgitation (AVVR) were available for seven patients, being mild or less in six patients and moderate to severe in one patient.

Pre-HTx hemodynamic data were available in seven patients. Median cardiac index was 3.2 L/min/m^2 (range 3.1–4), while median Fontan pressure was 17.0 mmHg (range 12–25). The patient with significantly elevated Fontan pressures of 25 mmHg also presented with impaired ventricular function and moderate to severe AVVR on echocardiography. Systemic ventricular end-diastolic pressure and/or pulmonary capillary wedge pressure widely varied from 7 to 20 mmHg, with a median of 11.0 mmHg.

3.3 | Post-HTx PLE characteristics

Median age at HTx was 17 years (range 7.7–21), occurring at a median time of 12.2 years (range 3.3–19) after Fontan completion. Half of patients required extracorporeal membrane oxygenation after transplant and one developed acute renal failure requiring dialysis.

In all eight cases, PLE initially resolved at a median time of 1 month after HTx (range 0.3–5 months [data unavailable in one case]) after which PLE treatment was discontinued.

3.4 | PLE relapse

Clinical characteristics of PLE recurrence are depicted in Table 2. PLE recurrence occurred at a median time of 7.5 months after HTx (range 2–132 months). All cases presented with clinical signs of fluid overload, such as peripheral edema and/or ascites, and hypoalbuminemia (albumin level median 2.2 g/dl, range 1.6–2.6, in all six patients with data).

In all cases, PLE recurrence was associated with a significant clinical event. The most common was cellular- or antibody-mediated rejection in five cases, followed by infection in three, thrombosis in two (superior mesenteric artery and innominate vein), and posttransplant lymphoproliferative disease (PTLD) in one. There was also clinical, echocardiographic, hemodynamic, and/or laboratory evidence of graft dysfunction in four cases. In two cases, there was combination of these events occurring concomitantly with PLE relapse; venous thrombosis and rejection in one case; and rejection, influenza A infection, and arterial thrombosis in another patient.

In seven patients, there was only one episode of PLE recurrence, which resolved after 0.75, 1, 2, 9, and 10 months after onset (median time of 2 months) (exact time to resolution of PLE relapse was unavailable for three patients). One patient (patient #7 in Table 2) presented with several relapses of PLE; first relapse occurred after HTx in association with an atypical mycobacterium infection, which resolved, and subsequent PLE recurrences developed with PTLD onset and relapses.

Six patients (75%) were alive after a median time of follow-up of 4 years (1.3–22.5) after HTx. Among the two deaths, one died in a motor vehicle accident and one suffered a sudden cardiac arrest at home, assumed to be secondary to rejection.

4 | DISCUSSION

To our knowledge, this is the largest case series on PLE recurrence after HTx. In our cohort, we have identified several factors that might have played a role in this phenomenon.

4.1 | Alterations in cardiac hemodynamics

Low cardiac output (CO) and elevated central venous pressure (CVP) have been previously associated with the development of PLE.[1,3,14] Although all patients with Fontan physiology have inherently altered CO, relatively higher CO has been reported in PLE Fontan patients compared to non-PLE Fontan patients.[4,15] In fact, 75% of patients in our cohort were showing normal pre-HTx cardiac index. Unfortunately, data regarding heart failure regimen or use of inotropes at the time of evaluation of CO were limited in detail.

An interesting finding in our cohort was an almost uniform elevation of the pre-HTx CVP, with a median Fontan pressure of 17 mmHg. High Fontan pressure is not always present in PLE patients but appeared to be more consistently present within our cohort of patients who experienced relapse. Even though PLE recurrence occurred after restitution of biventricular circulation, effects of long-standing single ventricle physiology with elevated CVP could

have predisposed these patients to PLE recurrence after HTx. Over this background, an acute or subacute hemodynamic insult leading to transiently elevated right heart pressures may trigger the recurrence of PLE after HTx.

These observations are further supported by: (1) the fact that half of our cohort displayed concomitant signs of cardiac allograft dysfunction, and (2) reports of post-HTx PLE recurrence in prior Fontan patients in the setting of severe post-HTx tricuspid valve regurgitation.[10,11]

4.2 | Abnormalities of lymphatic system

Both structural and functional abnormalities of the lymphatic system have been described in Fontan patients and could further contribute to the development of post-HTx PLE recurrence. Structural derangements include dilation of the thoracic duct, lymphangiectasia, lymphatic collateralization, and the presence of hepatoduodenal lymphatic channels.[7,8,16] These hepatoduodenal lymphatic connections may be an anatomical variant with otherwise no clinical significance in patients without elevated CVP, but they could become clinically evident in Fontan patients with persistently elevated venous pressure, and subsequent lymphatic congestion.[8] Conversely, prolonged single physiology may be a nidus for the development of lymphatic system abnormalities over time, which could also persist after HTx.

Functional lymphatic abnormalities have been described in response to neurohumoral stimulation and may further contribute to the development of PLE after HTx. Both atrial (ANP) and brain (BNP) natriuretic peptides experimentally alter the mesenteric lymphatic collection, by affecting the lymphatics' spontaneous contractions and increasing the permeability to albumin and fluid.[17] ANP and BNP are secreted in response to myocardial stress, in the context of volume and/or pressure overload.[18] BNP also increases in response to cardiac allograft rejection, mediated by inflammatory cytokines.[19] These findings might explain how elevation of biomarkers could not only contribute to PLE relapse during an episode of rejection and/or hemodynamic derangement but also how adequate treatment of the hemodynamic insult or rejection-mediated inflammatory response could lead to resolution of the PLE relapse.

4.3 | Inflammation

Recent studies suggest that PLE development in Fontan patients is likely related to both intestinal and systemic pro-inflammatory states.[20,21] At the intestinal level, the loss of heparan sulfate (HS) and HS proteoglycans (HSPGs) from the basolateral membrane of the enterocytes, which could occur in pro-inflammatory states due to higher epithelial barrier turnover,[22] has been described during PLE episodes,[23] with reappearance of HS after resolution of PLE.[24] In relation to this, based on previous experimental models of PLE,

TABLE 2 Post-HTx and PLE relapse characteristics

Patient	Age at HTx (years)	Months to PLE resolution	HTx to first PLE recurrence (months)	Concurrent clinical issue w/PLE	PLE symptoms
1	15.4	1	4.4	Allograft dysfunction, AMR	Low albumin
2	21	0.5	8	Necrotizing fasciitis, sepsis	Edema, ascites, low albumin
3	17	0.3	10	CMR	Low albumin, edema
4	17	4	6	Elevated RVEDp (early after AMR that was improving on biopsy)	Low albumin, ascites
5	7.7	2	26	Venous thrombus, elevated EDP and BNP levels; treated for rejection	Low albumin, edema, ascites
6	17.6		132	Allograft dysfunction and severe TR	Low albumin, edema
7	18.8	5	7	Atypical mycobacterium infection, then PTLD continues with symptoms as PTLD recurs	low albumin, diarrhea, ascites
8	14	1	2	Influenza A infection Rejection SMA thrombosis	Low albumin, ascites

Note: Data left blank are unavailable.

Abbreviations: AMR, antibody-mediated rejection; ARF, acute renal failure; BNP, brain natriuretic peptide; CMR, cellular-mediated rejection; ECMO, extracorporeal membrane oxygenation; EDP, end-diastolic pressure; MVA, motor vehicle accident; PTLD, posttransplant lymphoproliferative disease; SMA, superior mesenteric artery; SVC, superior vena cava; TR, tricuspid regurgitation.

Bode et al. suggested that certain genetic mutations, affecting the expression of genes involved in the biosynthesis, expression, or metabolism of HSPGs, could predispose Fontan patients to develop PLE.[25] Furthermore, this altered gene expression could be provoked by venous hypertension.[25]

At a systemic level, chronic congestive heart failure and low cardiac output result in the activation of a systemic inflammatory response,[15,26] in which pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), C-reactive protein, and interleukin-6 (IL-6) can be increased.[26,27] Using a tissue culture model, Bode et al.[6] demonstrated that the disruption of the intestinal epithelial barrier and protein leakage were induced synergistically by an elevated venous pressure, TNF-α (potentiated by IFN-γ), and loss of HS. In our cohort, PLE recurrence mostly occurred in association with infection, cardiac allograft rejection, and/or PTLD. In this manner, rejection and PTLD have been in fact associated with a pro-inflammatory state with cytokine release, mostly IL-6.[28–30] We speculate that an inflammatory stimulus could have triggered the PLE recurrence in our cohort, most likely on the background of structural and/or functional lymphatic abnormalities and chronic, acute, or acute-on-chronic altered hemodynamics. These observations are further supported by the fact that episodes of PLE recurrence in our cohort resolved in all patients after resolution of the inciting clinical event, and even continued to recur in one patient with subsequent PTLD relapses. This could indicate important prognostic features in the case of PLE recurrence after HTx.

4.4 | Limitations

The authors acknowledge that a limitation of the study is the presence of missing data, both pre- and post-HTx, more importantly regarding time to resolution of PLE relapse and levels of albumin during PLE relapses. These cases involved patients who underwent HTx and developed recurrence of PLE at least more than 10–15 years before the conduction of the present study. As available data were collected by authors at each participating institution's database, missing data were related mostly to transfer of care of patient and/or provider moving to a different institution. In this manner, the authors clarify that these patients were included due to medical records specifically documented a clear clinical scenario of PLE symptoms and hypoalbuminemia, even though serum albumin levels could not be recovered.

5 | CONCLUSIONS

Although the pre- and post-HTx histories and presentations were diverse within our study cohort, we hypothesize that PLE recurrence could have occurred as a result of several interrelated factors, many of which likely contributed to PLE pathogenesis prior to transplant. Long-standing Fontan circulation, with primarily elevated CVP, was present pre-HTx, and secondary lymphatic structural abnormalities could have developed and even persisted after HTx. An index

Albumin level	PLE recurrence resolution	Time to resolution (months)	Alive at follow-up?	Last follow-up (years since HT)	Notes
2.6	Y		N	4.8	• Recurrent episodes of rejection. • Died from sudden cardiac arrest at home (presumed rejection)
2.1	Y	2	N	3	• Died in MVA
2.2	Y	0.8	Y	4	• HTx complicated by graft dysfunction requiring ECMO, and dialysis
2.6	Y	10	Y	1.3	• HTx complicated by coagulopathy and bleeding, ARF and dialysis, SVC syndrome
1.6	Y	9	Y	3	
	Y		Y	22.5	• HTx complicated by graft dysfunction requiring ECMO • PTLD
1.7	N		Y	4	• HTx complicated by graft dysfunction requiring ECMO
	Y	1	Y	8	• HTx complicated by graft dysfunction requiring ECMO

clinical event occurred in all cases concomitantly with PLE recurrence which most likely enhanced a systemic pro-inflammatory state with release of cytokines, directly or indirectly leading to lymphatic functional abnormalities, disruption of the intestinal epithelial barrier, and protein leakage. The fact that PLE resolved after resolution of the inciting clinical events not only supports our hypothesis but also provides prognostic implications to providers encountering PLE recurrence after HTx.

CONFLICT OF INTEREST

Authors have no interests to disclose.

AUTHOR CONTRIBUTIONS

All authors have substantially contributed by acquiring data for the work, drafting and/or revising the manuscript for intellectual content, and approving final version to be published.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article.

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How to cite this article: Sagray E, Johnson JN, Schumacher KR, West S, Lowery RE, Simpson K. Protein-losing enteropathy recurrence after pediatric heart transplantation: Multicenter case series. *Pediatr Transplant*. 2022;26:e14295. doi:10.1111/petr.14295