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Higher Incidence of Protein–Losing Enteropathy in Patients with Single Systemic Right Ventricle

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Abstract

Patients with single ventricle congenital heart disease are at risk of unpredictable protein-losing enteropathy (PLE) after surgical palliation. Based on prior reports of physiologic differences for patients with single morphologic right versus left ventricles, we hypothesized that those with right ventricular morphology would have a higher incidence of PLE. We performed a retrospective review of > 15 million pediatric hospitalizations from the Healthcare Cost and Utilization Project KID 2000–2012 databases for admissions 5–21 years old with ICD-9 codes for hypoplastic left heart syndrome (HLHS) and tricuspid atresia (TA) with and without PLE. Incidence of PLE was compared between those with HLHS and TA. In addition, outcomes and costs were compared between admissions with and without PLE and between HLHS and TA. Of 1623 HLHS admissions, 289 (17.8%) had PLE, and of 926 TA admissions, 58 (5.9%) had PLE ($p < 0.001$). Admissions with PLE were older compared to those without PLE (12 vs 10 years, $p < 0.001$) and PLE onset occurred at a younger age for HLHS than TA (11 vs 14 years, $p < 0.001$). There were no differences in hospital outcomes or costs. Review of this large administrative database suggests a higher incidence of PLE in patients with HLHS and a younger age of onset compared to those with TA. These data suggest that a single systemic right ventricle may be an independent risk factor for developing PLE.

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Conflict of interest Alyssa Bernardi declares that she has no conflict of interest. Sylvester Moses declares that he has no conflict of interest. Brent J. Barber declares that he has no conflict of interest. Marlys H Witte: declares that she has no conflict of interest. Michael D. Seckeler declares that he has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Keywords

Protein-losing enteropathy; Fontan; Single ventricle; Congenital heart defects

Introduction

Children born today with functionally single ventricle heart anatomy are more likely to live into adulthood than in previous decades thanks to the evolution of surgical and medical therapies. The Fontan procedure, first described almost 50 years ago, was indicated for children born with tricuspid atresia (TA) with systemic left ventricles [1]. Staged surgical palliation culminating in the Fontan procedure is now employed for a variety of single ventricle congenital heart disease (SV CHD) including hypoplastic left heart syndrome (HLHS) with systemic right ventricles [2]. Single ventricle palliation can result in a host of complications related to heart failure that can impact morbidity and mortality once these patients reach adulthood [3]. Fontan physiology, while both lifesaving and life prolonging, leads to complications most likely due to abnormally elevated systemic and portal venous pressure, which can lead to impairments in lymphatic physiology. Two severe lymphatic complications in patients with Fontan physiology are plastic bronchitis and protein-losing enteropathy (PLE). PLE is the loss of proteins into the intestinal lumen, which occurs in up to 12% of individuals after Fontan palliation [4]. The loss of serum proteins can lead to peripheral edema, pleural effusions and ascites, as well as derangements in coagulation, immunity and growth [5]. Previous studies at single centers have sought to describe the risk factors for developing PLE, as well as the healthcare costs associated with taking care of patients with PLE. However, there have been no large, multicenter studies to answer these questions. We hypothesized that previously reported abnormalities in systemic ventricular diastolic function in HLHS patients [6] lead to more lymphatic complications. The purpose of the current study was to utilize a large, national administrative database to compare the incidence of PLE in patients with SV CHD and Fontan physiology based on ventricular morphology. The secondary aim was to compare hospital outcomes and costs.

Methods

After approval from the Institutional Review Board at the University of Arizona, a retrospective review of > 15 million pediatric hospitalizations from the Healthcare Cost and Utilization Project KID 2000–2012 databases was performed. Inclusion criteria were an ICD-9 diagnosis code for HLHS (746.7), TA (746.1) or common ventricle (745.3) with and without an ICD-9 code for PLE (579.8, other specified intestinal malabsorption). Admission age 5–21 years old was used in order to capture patients after the Fontan procedure who had had Fontan physiology long enough to develop lymphatic complications. The databases were queried for demographics, length of stay (LOS), in-hospital mortality and direct hospital costs. The outcomes and costs were compared between all SV CHD admissions with and without PLE. Further analyses were made to compare the incidence of PLE in patients with HLHS and TA as well as outcomes and costs between the groups. Comparisons were made using independent *t*-test for normally distributed variables, Mann–Whitney *U* test

for non-normally distributed variable and χ^2 for categorical variables. Statistical analyses were performed using SPSS 25 (IBM Corporation, Armonk, New York, USA).

Results

There were 3751 admissions identified during the study period—1623 HLHS, 977 TA and 1151 common ventricle. There were 465 (12.4%) admissions with PLE. Demographics and comparisons between SV CHD admissions with and without PLE are shown in Table 1. Admissions with PLE were older and had longer LOS with no differences in in-hospital mortality or costs.

Of the 1623 admissions with HLHS, 289 (17.8%) had PLE. Demographics and comparisons between HLHS admissions with and without PLE are shown in Table 2. Admissions with HLHS and PLE were older and had longer LOS with no differences in in-hospital mortality or costs.

Of the 977 admissions with TA, 58 (5.9%) had PLE. Demographics and comparisons between TA admissions with and without PLE are shown in Table 2. Admissions with TA and PLE were older with no differences in LOS, in-hospital mortality or costs.

Comparisons between admissions with HLHS and TA with PLE are shown in Table 3. PLE was present in 17.8% of HLHS admissions compared to 5.9% of TA admissions [$p < 0.001$, OR 3.44 (95% CI 2.56–4.61)]. Admissions with HLHS and PLE were younger than those with TA and PLE with no other differences in outcomes or costs.

Discussion

This analysis of a large, national administrative database has defined the incidence of protein-losing enteropathy in hospitalized patients with single ventricle congenital heart disease and identified a markedly higher incidence among patients with hypoplastic left heart syndrome compared to those with tricuspid atresia. Lymphatic complications, such as PLE and plastic bronchitis, can significantly impact morbidity and mortality of these patients as well as result in higher healthcare system costs.

The findings in the current study suggest that patients with a systemic right ventricle (HLHS) develop PLE more frequently and at a younger age than those with systemic left ventricles (TA). This is consistent with prior studies that suggest increased ventricular diastolic pressure in patients with systemic right ventricles [6] which would be expected to increase Fontan pressure and subsequently lymphatic pressure. In addition, SV CHD patients with systemic left ventricles (TA) have better early survival and HLHS is an independent risk of all-cause mortality and heart transplantation [7, 8]. While potentially inadequate coronary artery perfusion after the Norwood procedure for HLHS certainly contributes to these differences, perhaps there are additional risks related to the more frequent occurrence of PLE for these patients [9].

There are several limitations to this study. Administrative databases rely on accurate ICD-9 code entry and there is potential for errors in documentation; however, prior studies have

found that ICD-9 codes in administrative databases have an 80–85% specificity for congenital heart disease [10]. Given the large number of admissions identified, it is unlikely that there were enough coding errors to affect our findings. The ICD-9 codes for HLHS and TA were used as surrogates for single left and single right ventricles; however, there are other forms of CHD that lead to single right and left ventricle Fontan physiology, and there may be subtle, but important, physiologic differences in those patients leading to the development of PLE that are not accounted for in the current study. In addition, there is not a specific ICD-9 code for protein-losing enteropathy. Therefore, we used the ICD-9 code for protein malabsorption. It is most likely that the patients in this study would have PLE rather than other types of protein malabsorption based on their physiology. Regardless, it is unlikely that the code would be misused in only one type of SV CHD and lead to erroneous conclusions regarding the relative occurrence of PLE in patients with HLHS and TA.

The management of PLE is complex and there is no single treatment modality, other than heart transplantation, that seems to “cure” PLE. While future approaches in treatment may involve surgical lymphatic decompression at the time of the Fontan operation [11] or creation of a “lymphatic right to left shunt” later in life, these are still mostly theoretical and not universally applied [12]. Optimizing vigilant surveillance in those SV CHD patients most at risk for developing PLE may allow for earlier treatment with higher success rates leading to reduced morbidity and mortality.

References

1. Rychik J (2007) Protein-losing enteropathy after Fontan operation. *Congenit Heart Dis* 2:288–300 [PubMed: 18377444]
2. Fontan F, Baudet E (1971) Surgical repair of tricuspid atresia. *Thorax* 26:240–248 [PubMed: 5089489]
3. Puga FJ, Chiavarelli M, Hagler DJ (1987) Modifications of the Fontan operation applicable to patients with left atrioventricular valve atresia or single atrioventricular valve. *Circulation* 76(suppl 3):III53–III60 [PubMed: 2441897]
4. Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, Hsia T, Hsu DT, Kovacs AH, McCrindle BW, New-burger JW, Pike NA, Rodefeld M, Rosenthal DN, Schumacher KR, Marino BS, Stout K, Veldtman G, Younoszai AK, d’Udekem Y (2019) Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation* 140:234–284
5. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M (1998) Protein-losing enteropathy after the Fontan operation: an international multicenter study. *J Thorac Cardiovasc Surg* 115:1063–1073 [PubMed: 9605076]
6. Seckeler MD, O’Leary E, Jayakumar AK (2015) Ventricular morphology is a determinant of diastolic performance in patients with single ventricle physiology undergoing stage 3 palliative surgery. *Pediatr Cardiol* 36:732–736 [PubMed: 25487629]
7. Khairy P, Fernandes SM, Mayer JE, Friedman JK, Walsh EP, Lock JE, Landzberg MJ (2008) Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation* 117:85–92 [PubMed: 18071068]
8. Julsrud PR, Weigel TJ, Van Son JA, Edwards WD, Mair DD, Driscoll DJ, Danielson GK, Puga FJ, Offord KP (2000) Influence of ventricular morphology on outcome after the Fontan procedure. *Am J Cardiol* 86:319–323 [PubMed: 10922441]
9. Collins RT 2nd, Fram RY, Tang X, Robbins JM, Sutton MS (2013) Impact of anatomical subtype and medical comorbidities on hospitalizations in adults with single ventricle congenital heart disease. *Int J Cardiol* 168:4596–4601 [PubMed: 23938215]

10. Frohnert BK, Lussky RC, Alms MA, Mendelsohn NJ, Symonik DM, Falken MC (2005) Validity of hospital discharge data for identifying infants with cardiac defects. *J Perinatol* 25:737–774 [PubMed: 16163368]
11. Kreutzer C, Klinger DA, Chiostrì B, Sendoya S, Lopez MD, Gutierrez A, Fraire RA, Torres SF (2019) Early experience of lymphatic decompression concomitant to Fontan–Kreutzer procedure Oral presentation at: American Association for Thoracic Surgery Annual Meeting; 5 5–7, 2019; Toronto, Canada
12. James H, Witte MH, Bernas M, Barber B (2016) Proposal for prevention or alleviation of protein/lymph-losing enteropathy (PLE/LLE) after Fontan circulation treatment of univentricular hearts: restoration of lymph balance with a “lymphatic right-to-left shunt”. *Lymphology* 49:114–127 [PubMed: 29906066]

Table 1

Comparisons of demographics, hospital outcomes, and costs between all single ventricle congenital heart disease admissions with and without protein-losing enteropathy (PLE)

	All single ventricle (<i>n</i> = 3751)		<i>P</i>
	PLE (<i>n</i> = 465)	No PLE (<i>n</i> = 3286)	
Age (year)	12 (7, 16)	10 (7, 15)	< 0.001
Female (<i>n</i> , %)	188 (40.4)	1332 (40.5)	0.960
LOS (day)	4 (2, 8)	3 (1, 8)	< 0.001
Death (<i>n</i> , %)	7 (1.5)	63 (1.9)	0.714
Costs (\$)	\$99,760 ± 214,589	\$84,394 ± 177,045	0.147

LOS length of stay

Comparisons of demographics, hospital outcomes and costs between hypoplastic left heart disease (HLHS) admissions with and without protein-losing enteropathy (PLE) and tricuspid atresia admissions with and without PLE

Table 2

	HLHS (n = 1623)		<i>P</i>
	PLE (n = 289)	No PLE (n = 1334)	
Age (year)	11 (7, 15)	8 (6, 13)	< 0.001
Female (<i>n</i> , %)	120 (41.5)	510 (38.2)	0.318
LOS (day)	4 (2, 8)	3 (1, 7)	< 0.001
Death (<i>n</i> , %)	6 (2.1)	25 (1.9)	0.813
Costs (\$)	\$100,851 ± 244,155	\$85,609 ± 196,616	0.258

	Tricuspid atresia (n = 977)		<i>P</i>
	PLE (n = 58)	No PLE (n = 919)	
Age (year)	14 (10.5, 17)	12 (7, 16)	0.033
Female (<i>n</i> , %)	30 (51.7)	398 (43.3)	0.222
LOS (day)	3.5 (2, 12)	3 (1, 8)	0.099
Death (<i>n</i> , %)	0 (0)	9 (1)	1.000
Costs (\$)	\$86,648 ± 120,204	\$75,384 ± 145,099	0.570

LOS length of stay

Table 3

Comparisons of demographics, hospital outcomes and costs between hypoplastic left heart disease (HLHS) and tricuspid atresia (TA) admissions with protein-losing enteropathy (PLE)

	HLHS PLE (<i>n</i> = 289)	TA PLE (<i>n</i> = 58)	<i>P</i>
Age (year)	11 (7, 15)	14 (10.5, 17)	< 0.001
Female (<i>n</i> , %)	120 (41.5)	30 (51.7)	0.191
LOS (day)	4 (2, 8)	3.5 (2, 12)	0.589
Death (<i>n</i> , %)	6 (2.1)	0 (0)	0.595
Costs (\$)	\$100,851 ± 244,155	\$86,648 ± 120,204	0.671

LOS length of stay