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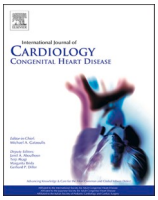

Protein losing enteropathy in adults with congenital heart disease and biventricular circulation

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Protein-losing enteropathy (PLE) is a rare condition characterized by excessive loss of protein from the gastrointestinal tract, and it is postulated to result from a combination of factors such as increased lymphatic pressure due to elevated central venous pressure, impaired lymphatic drainage, and increased permeability of the intestinal mucosa [1,2]. The description of PLE in the congenital heart disease (CHD) literature focused mostly on patients with Fontan palliation [1,2]. However, the physiologic abnormalities associated with PLE are not unique to the Fontan physiology, but can also occur in other patients with CHD and biventricular circulation (CHD-BiV), especially those presenting with right heart failure [3]. The purpose of this study was to describe the clinical characteristics of patients with CHD-BiV presenting with PLE, and to identify the echocardiographic indices associated with PLE. The Mayo Clinic Institutional Review Board approved this study, and there were no conflicts of interest.

We identified adults with CHD-BiV and a diagnosis of PLE, defined as spot stool α-1 antitrypsin >100 mg/dl and at least one of the typical clinical features of PLE (diarrhea, pedal edema, ascites, pleural effusion, or malnutrition [body mass index <18.5 kg/m2]). Resolution of PLE was defined as a subsequent stool α-1 antitrypsin ≤100 mg/dl and resolution of PLE-related symptoms. For each patient with PLE, we identified 10 patients (controls) with the same CHD diagnosis but without a diagnosis of PLE [4]. Multivariable logistic regression analysis was used to identify the correlates of PLE, and the covariates included in the model were age, sex, and echocardiographic indices (systemic ventricular dysfunction, ≥moderate systemic atrioventricular valve regurgitation (AVVR), non-systemic ventricular dysfunction, ≥moderate non-systemic AVVR, and estimated right atrial pressure). Cox regression was used to assess the relationship between PLE and all-cause mortality.

In this study, we identified 19 patients with PLE and 190 controls. Compared to controls, the patients with PLE were older, more likely to have atrial arrhythmias, and also had worse hepatic and renal function (Table 1). The PLE group also had worse echocardiographic indices of subpulmonary ventricular function (non-systemic ventricular systolic dysfunction defined as ejection fraction <50% or fractional area change<35%, AVVR, and higher right atrial pressure), Table 1. On multivariable analysis, the echocardiographic correlates of PLE were right atrial pressure (odds ratio [OR] 1.84, 95% confidence interval [CI] 1.39–3.72), ≥moderate non-systemic AVVR (OR 2.16, 95% CI 1.18–4.96), and non-systemic ventricular dysfunction (OR 4.24, 95% CI 1.93–11.45) after adjustment for age and sex.

Within the PLE group, the most common clinical presentations were pedal edema (n = 17; 90%), diarrhea (n = 15; 79%), ascites (n = 6; 42%), and pleural effusion (n = 4; 21%). None of the patients presented with malnutrition. The medical therapies used include budesonide (n =

Abbreviations: AVVR, Atrioventricular valve regurgitation; CHD-BiV, Congenital heart disease with biventricular circulation; CI, Confidence interval; HR, Hazard ratio; OR, Odds ratio; PLE, Protein-losing enteropathy.

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Table 1
Baseline characteristics.

	PLE group (n = 19)	Control group (n = 190)	p
Age, years	54 ± 11	38 ± 9	<0.001
Female	12 (63%)	92 (48%)	0.2
Systemic left ventricle	16 (84%)	160 (84%)	0.9
Body mass index, kg/m^2	24.4 ± 2.1	29.7 ± 2.6	<0.001
CHD Diagnosis			
Tetralogy of Fallot	7 (37%)	70 (37%)	0.9
Ebstein anomaly	1 (5%)	10 (5%)	0.9
Congenitally corrected TGA	1 (5%)	10 (5%)	0.9
d-TGA s/p atrial switch operation	2 (11%)	20 (11%)	0.9
Pulmonic stenosis	2 (11%)	20 (11%)	0.9
Atrioventricular canal defect	3 (16%)	30 (16%)	0.9
Atrial septal defect	1 (5%)	10 (5%)	0.9
Palliated/unrepaired cyanotic heart disease	2 (11%)	20 (11%)	0.9
Comorbidities			
Hypertension	6 (32%)	58 (31%)	0.8
Coronary artery disease	2 (11%)	11 (6%)	0.7
Atrial fibrillation/flutter	9 (47%)	15 (8%)	<0.001
Laboratory data			
Stool α-1 antitrypsin	446 (291–502)	–	
eGFR, ml/min/1.73 m [2]	63 (48–94)	92 (72–121)	<0.001
NT-proBNP, pg/ml	2611 (988-5942)	214 (88–615)	<0.001
MELD-XI score	12.4 (10.9–16.3)	9.8 (9.4–10.9)	<0.001
Total protein, mg/dl	4.9 ± 2.4	6.8 ± 1.7	<0.001
Albumin, mg/dl	2.8 ± 1.9	4.5 ± 0.8	0.007
Echocardiogram			
Systemic LV ejection fraction, %	56 ± 8	62 ± 11	0.6
Systemic RV fractional area change, %	33 ± 4	38 ± 7	0.7
Systemic AVVR	2 (11%)	8 (4%)	0.5
Non-systemic RV fractional area change, %	31 ± 9	44 ± 8	0.02
Non-systemic LV ejection fraction, %	43 ± 5	49 ± 11	0.4
Non-systemic AVVR	9 (47%)	11 (6%)	<0.001
RA volume index, ml/m^2	38 ± 11	22 ± 18	<0.001
Estimated RA pressure, mmHg	15 (10–20)	5 (5–10)	<0.001
Non-systemic ventricular systolic pressure, mmHg	59 ± 14	33 ± 7	<0.001

Abbreviations: AVVR: Atrioventricular valve regurgitation; CHD: Congenital heart disease; eGFR: Estimated glomerular filtration rate; LV: Left ventricle; MELD-XI: Model for end-stage liver disease excluding international normalized ratio; NYHA: New York Heart Association; PLE: Protein-losing enteropathy; RA: Right atrium; RV: Right ventricle; TGA: Transposition of great arteries.

11; 58%), heparin (n = 13, 68%), octreotide (n = 9; 47%), mineralocorticoid antagonist (n = 11; 58%), and loop diuretics (n = 19; 100%).

Overall, 5 (26%) and 17 (9%) patients died in the PLE and control groups, respectively, and the 5-year survival was lower in the PLE group (72% versus 91%, p = 0.006). PLE was associated with all-cause mortality after adjustment for age and sex (hazard ratio [HR] 2.56, 95% CI 1.88–3.47). The PLE group was followed for 76 ± 22 months with 5 (26%) patients having resolution of PLE. Four of these 5 patients had surgical interventions between the diagnosis and resolution of PLE. These interventions were atrial baffle revision in a patient with Mustard operation, heart transplant in a patient with tetralogy of Fallot, non-systemic AVV replacement in a patient with Ebstein anomaly, and pulmonary valve replacement in the patient with tetralogy of Fallot and restrictive right ventricular physiology. The resolution of PLE was associated with a lower risk of mortality (unadjusted HR 0.62, 95% 0.45–0.79).

In conclusion, the echocardiographic correlates of PLE in patients with CHD-BiV circulation were right atrial pressure, ≥moderate non-systemic AVVR, and non-systemic ventricular dysfunction, and PLE was associated with significant mortality at 5 years. Among patients with PLE, 26% had resolution of PLE, mostly after surgical interventions. These findings suggest that non-systemic ventricular and valvular dysfunction may play an important role in the pathogenesis of PLE, and that targeting these hemodynamic lesions may modify the disease process and improve outcomes in the CHD population. The study was limited by small sample size and non-standardized medical therapies, which prohibited rigorous analysis of the relative benefits of different therapies for PLE.

CRediT authorship contribution statement

Marwan H. Ahmed: Writing – review & editing, Writing – original draft. **William R. Miranda:** Writing – review & editing, Writing – original draft. **Heidi M. Connolly:** Writing – review & editing, Writing – original draft. **Snigdha Karnakoti:** Writing – review & editing, Writing – original draft. **Patrick S. Kamath:** Writing – review & editing, Writing – original draft. **C. Charles Jain:** Writing – review & editing, Writing – original draft. **Maan Jokhadar:** Writing – review & editing, Writing – original draft. **Luke J. Burchill:** Writing – review & editing, Writing – original draft. **Alexander C. Egbe:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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