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Original Article

Prevalence and Associated Factors of Protein-Losing Enteropathy After Fontan Surgery

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ABSTRACT

Background: Nowadays, the attention is more set on the complications of the Fontan surgery such as protein-losing enteropathy (PLE). Determining the frequency rate and the contributing factors of the Fontan surgery complications like PLE would confer optimized preventive approaches, reduced rates of adverse effects, and improved prognosis and survival. [17] This cross-sectional study aimed to determine the prevalence and associated factors of PLE in a referral heart center.

Methods: The present cross-sectional analysis was performed on 73 patients using history taking, careful clinical examinations, laboratory tests (eg, fecal alpha-1-antitrypsin, complete cell blood count, chemistry, and venous blood gas), and echocardiographic and angiographic evaluations.

Results: In our study, the prevalence of PLE was 4 (5.47%) cases. The associated factors were edema, diarrhea, abdominal pain, ascites, and hypoalbuminemia. The echocardiographic and angiographic findings revealed that the left ventricular ejection fraction was significantly reduced in our patients with PLE.

Conclusions: In light of our results, we conclude that in any post-Fontan surgery patient exhibiting clinical manifestations such as edema, diarrhea, abdominal pain, or ascites, screening for fecal alpha-1-antitrypsin can be helpful for the early detection of PLE. ***(Iranian Heart Journal 2020; 21(2): 13-20)***

KEYWORDS: Protein-losing enteropathy, Fontan surgery, Children, Iran

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Fontan and Baudet [1] described a pioneering surgical technique in 1971 and, thus, saved the lives of thousands of children afflicted with congenital heart diseases such as tricuspid atresia and single functional ventricle. Thereafter, Kreutzer et al [2] applied the modality to treat most forms of functional single ventricles. The subsequent years witnessed intermittent modifications in the technique and currently, the Fontan surgery is used for separating the systemic and pulmonary venous returns with the aim of palliating thromboembolic events and hypoxemia, preserving ventricular function, and prolonging survival. [3]

Sometimes, patients undergoing the Fontan surgery are at risk of developing the significant complication of protein-losing enteropathy (PLE), even several years after surgery. [4,5] PLE is an uncommon complication characterized by hypoproteinemia, hypoalbuminemia, pitting edema, increased fecal alpha-1-antitrypsin (A1AT), and ascites secondary to excessive gastrointestinal protein loss. [6] The detection of A1AT in a random stool sample has been widely used as the most sensitive screening tool in the diagnosis of PLE. [7]

The prevalence of PLE in patients after the Fontan and modified Fontan surgical techniques has been reported to be 13.4% and 5% to 15%, respectively. [8, 9] Nonetheless, it is associated with a high mortality rate and ominous prognosis. Indeed, the 5-year survival of patients with PLE after surgery has been reported to range between 46% and 59%, despite vigorous treatment. [5, 10] PLE is mainly manifested by symptoms of protein loss and waxing, including hypoproteinemia and edema, whereas other silent manifestations are ascites, diarrhea, pleural and pericardial effusion, and malnutrition. [11] Depending on the severity of PLE, steatorrhea, abdominal distension, lymphopenia, and hypogammaglobulinemia can also appear. [4, 11, 15]

Susceptibility to infections is related to hypogammaglobulinemia due to protein leakage and plastic bronchitis accompanied by the formation of exudative airway casts. [16] However, the risk factors for the occurrence of PLE are still ambiguous.

Nowadays, the attention is more set on the complications of the Fontan surgery such as PLE. Determining the frequency rate and contributing factors of the Fontan surgery complications like PLE would result in enhanced preventive approaches, reduced rates of adverse effects, and improved prognosis and survival. [17] In the current cross-sectional study, we aimed to determine the prevalence and associated factors of PLE in our referral heart center.

METHODS

Study Design and Setting

This cross-sectional study was conducted in order to determine the frequency and associated factors of PLE after the Fontan surgery in a referral heart center between September 2017 and December 2018. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.SMD.REC1396.9411169002), which granted sampling permit to Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran.

Patients and Measurement

The present study recruited 73 patients, who were referred to our pediatric cardiology outpatient clinic between September 2017 and December 2018 (Fig. 1). A pediatric cardiologist performed history-taking and careful clinical examinations from all the children, who were aged between 1 and 18 years and scheduled for the Fontan surgery. The exclusion criteria consisted of age

below 1 year and age above 18 at the time of the Fontan surgery, in addition to having incomplete data and the diagnosis of PLE with other etiologies.

The objectives of the study were fully explained to the children's parents, and informed consent was obtained. For all the patients, echocardiography was carried out. The applied laboratory tests included complete blood count, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, calcium, albumin, total protein, the prothrombin time, the partial thromboplastin time, the international normalized ratio, and venous blood gas.

If the patients presented with peripheral edema, diarrhea, abdominal pain, or pleural/pericardial effusion accompanied by hypoalbuminemia, hypoproteinemia, hypocalcemia, or lymphopenia, they were assessed for fecal A1AT. A fecal A1AT level of higher than 54 mg/dL was regarded as PLE. [18]

All the study subjects were referred to a pediatric gastroenterologist to differentiate PLE from the other causes of hypoproteinemia and hypoalbuminemia.

The patients were divided into 2 groups of with and without PLE, and different factors were compared between the groups. The required data were extracted from existing data in the hospital records including age at surgery, preoperative heart anatomy, preoperative angiography indices (ie, pulmonary artery pressure and end-diastolic ventricular pressure), fenestration, postoperative hospitalization, postoperative anticoagulant use, and the time passed from surgery.

Outcome

The diagnosis of PLE was based on the Cromme–Dijkhuis definition. PLE was considered a hypoalbuminemia level of below 2.5 g/dL and a hypoproteinemia level of below 4.5 g/dL, along with an elevated fecal A1AT level (> 54 mg/dL in 24 hours) without overt protein loss via non-gastrointestinal routes.[18]

Statistical Analysis

The data were statistically analyzed using SPSS software, version 16. The Kolmogorov–Smirnov test was applied to check the normality. The quantitative and qualitative variables were reported as the mean (standard deviation [SD]) and frequencies (percentages). The Pearson χ^2 test and the Fisher exact test were used to compare the quantitative variables, and the χ^2 test was applied to compare the qualitative variables. The significance level was set at a *P* value of less than 0.05.

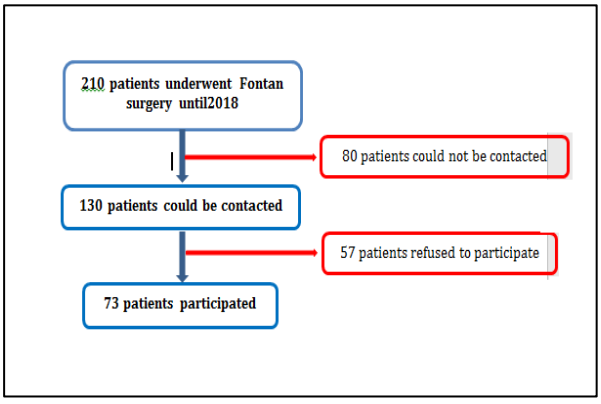

Figure 1: Flowchart for determining the patients

RESULTS

The current study was performed on 73 patients, of whom 43 (58%) were male. The mean age of the study population was 11 years. PLE was diagnosed in 4 (5.47%) patients. The mean ± SD of postoperative hospitalization in the patients with and without PLE was 45.3 ± 40.6 and 22.2 ± 12.7, respectively. The average time for the development of PLE after the Fontan surgery was 5.2 years. The mean ± SD of age at surgery in the patients with and without PLE was 8.1 ± 3.0 and 6.7 ± 3.0 years, correspondingly. The common clinical manifestations in the patients with and without PLE were cyanosis (100% vs 47.1%, respectively) and clubbing (100% vs 24.6%, respectively). The significant laboratory findings were hypoalbuminemia and hypoproteinemia. There was a significant relationship between edema and PLE inasmuch as edema increased the odds of PLE development ($P \leq 0.001$). Diarrhea, abdominal pain, ascites, and hypoalbuminemia had significant relationships with PLE ($P \leq 0.05$). There was no significant difference concerning anticoagulant usage in the patients with and without PLE (Table 1).

The echocardiographic and angiographic findings revealed that the mean of the left ventricular ejection fraction was significantly reduced in the PLE group. In the PLE and non-PLE groups, respectively, tricuspid atresia was seen in 50% and 53.6%, double-inlet left ventricle in 25% and 20.2%, complete atrioventricular canal defects in 25% and 5.8%, levo-transposition of the great arteries–large ventricular septal defects (VSDs) in 0% and 7.2%, dextro-transposition of the great arteries–large VSDs in 0% and 4.3%, tetralogy of Fallot–large VSDs in 0% and 1.45%, large VSDs in 0% and 2.9%, double-outlet right ventricle–large VSDs in 0% and 1.45%, and mitral valve atresia in 0% and 2.9%—without statistically significant differences between the 2 groups (Table 2).

Table 1: Demographic and clinical manifestation findings across the groups

Factor		With PLE (n=4)	Without PLE (n=69)	*P* value
Gender	male female	3(75%) 1(25%)	40(57%) 29(42%)	≤0.001
Mean of age	(y)	11.75	11.42	
Clinical Manifestation				
Edema		3(75%)	1(1.4%)	≤0.001
Diarrhea		1(25%)	0(0%)	≤0.05
Abdominal pain		3(75%)	2(2.8%)	≤0.001
Cyanosis		4(100%)	33(47.8%)	
Ascites		4(100%)	1(1.4%)	≤0.001
Clubbing		1(25%)	17(24.6%)	
Hypoalbuminemia		3(75%)	65(94.2%)	≤0.005
Hypoproteinemia		1(25%)	13(18.8%)	
Laboratory Finding				
PT	Sec	18.5 ± 2.08	16.25 ± 3.09	
PTT	Sec	36.00 ± 1.63	34.45 ± 8.89	
INR		1.65 ± 0.16	2.12 ± 5.02	
WBC	C/mm^3	7350.00 ± 2747.73	6618 ± 2073.60	
Lymphocyte	C/mm^3	23.65 ± 13.54	31.83 ± 9.73	
Neutrophil	C/mm^3	72.00 ± 11.34	63.34 ± 10.64	

Hemoglobin	mg/dl	15.10 ± 2.47	14.82 ± 1.87	
Hematocrit	%	45.28 ± 7.64	44.05 ± 5.30	
Platelet count	C/mm^3	329.50 ± 120.51	217.85 ± 63.63	0.002
BUN	mg/dl	13.25 ± 2.22	12.02 ± 4.04	
Creatinine	mg/dl	0.65 ± 0.17	0.60 ± 0.15	
AST	u/l	37.25 ± 16.68	32.82 ± 8.12	
ALT	u/l	35.50 ± 11.90	23.66 ± 9.08	0.015
ALP	u/l	381.25 ± 212.03	466.43 ± 210.03	
calcium	mg/dl	8.85 ± 0.70	9.49 ± 1.20	
Venous Blood Gas				
PH		7.41 ± 0.08	7.38 ± 0.04	
PO_2	mm Hg	40.33 ± 7.51	35.69 ± 24.27	
PCO_2	mm Hg	33.00 ± 16.37	38.00 ± 7.16	
HCO_3	mEq/l	20.33 ± 6.81	22.40 ± 3.92	

PLE, Protein-losing enteropathy; PT, Prothrombin time; PTT, Partial thromboplastin time; INR, International normalized ratio; WBC, White blood cell; BUN, Blood urea nitrogen; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase

Table 2: Echocardiographic and angiographic findings across the groups

Factor		With PLE (n=4)	Without PLE (n=69)	*P* value
LVEF	%	15.81 ±3500	5.48 ± 49.04	0.001
AV valve regurgitation		mild to moderate	mild to moderate	0.648
PAP (mm Hg)		2.3 ±13.5	3 ±13.75	0.916
SVEDP (mm Hg)		5 ± 11.5	2 ±11.6	0.842

PLE, Protein-losing enteropathy; LVEF, Left ventricular ejection fraction; AV, Aortic valve; PAP, Pulmonary artery pressure; SVEDP, Systemic ventricular end-diastolic pressure

Additionally, the anatomic findings showed that the rate of PLE was significant in the patients with situs inversus ($P = 0.02$) and fenestrated palliative surgery ($P \leq 0.05$). As is depicted in Table 3, the frequency of PA-banding ($P = 0.019$), the bridge-to-transplant shunt ($P = 0.036$), and the atriopulmonary Fontan surgery ($P = 0.006$) differed between the groups; nevertheless, there was no significant difference between the PLE and non-PLE groups vis-à-vis the other variables. Other differences between the groups were the need for a palliative approach ($P = 0.024$) and the type of the Fontan surgery ($P = 0.006$). ECG abnormalities were seen in 25% and 8.8% of the patients with and without PLE, respectively, with the difference not constituting statistical significance ($P > 0.05$). The mean postoperative hospitalization was 45.3 ± 40.6 and 22.2 ± 12.7 in the patients with and without PLE, correspondingly, which constituted a statistically significant difference ($P = 0.001$) (Table 3).

DISCUSSION

The frequency rate of PLE was 5.47% in our study, as opposed to 12% reported by Lin et al, [19] 14.3% by Park et al, [20] 8.3% by Pundi et al, [21] and 7.3% by Ohuchi et al. [22] The reason for the different rates of PLE in various studies might be different criteria for the diagnosis of PLE or different sample sizes.

The odds of the occurrence of PLE were higher in our patients with edema, abdominal pain, diarrhea, or ascites. This was in agreement with the findings of studies by Mertens et al and Jonathan et al. [17, 23-25]

PLE is characterized by decreased levels of albumin. We hypothesized that a low albumin level is a predictive factor for the future development of PLE in patients after the Fontan surgery. This was in concordance with the results of a study by Tarek et al. [26] Elsewhere, Kwok et al [27] reported that hypoalbuminemia, ventricular dysfunction, and artificial valve insufficiency had a meaningful relationship with PLE development. Pundi et al [28] posited that increased mean pulmonary artery pressure and increased left atrial pressure before and after the Fontan surgery were 2 critical factors related to postoperative PLE.

In our study, heterotaxy syndrome, the need for a palliative surgical operation other than the Glenn or Fontan surgery, and the type of the Fontan surgery comprised the risk factors for PLE. Lin et al [19] reported various associated factors such as hypoalbuminemia and increased levels of fecal A1AT and right atrial and pulmonary artery pressures.

Ohuchi et al [22] reported that an elevated central venous pressure, higher left ventricular end-diastolic pressure, higher pulmonary artery resistance, lower O_2 saturation, lower systemic blood pressure, and lower left ventricular ejection fraction were all seen more frequently in their patients with PLE. In addition, elongated pump duration, heterotaxy syndrome, increased ventricular end-diastolic pressure, raised pulmonary vascular resistance, and ventricular morphology were reported as risk factors in other studies. [5, 23, 29]

The type and duration of medical treatment after the Fontan surgery may also affect the occurrence of PLE. [30, 31]

CONCLUSIONS

In patients who undergo the Fontan surgery and develop such clinical manifestations as ascites, edema, abdominal pain, and diarrhea, screening for fecal A1AT can be helpful for the early detection of PLE. New therapeutic approaches and preventive strategies are necessary to treat this group of patients, to prevent late complications, and to improve the surveillance of the Fontan procedure. Indeed, we recommend future multicenter studies on this topic, with larger sample sizes and extended follow-up periods in our country, Iran.

Conflict of Interest

The authors hereby declare no conflict of interest.

Ethical Approval

All the procedures performed in the current study were in accordance with the standards of the Ethics Committee of Iran University of Medical Sciences and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This limited cross-sectional study meets the criteria for waiver by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.SMD.REC1396.9411169002).

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