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**Case Report**

# Protein Loosing Enteropathy after Fontan Procedure - An Enigma

Dr. Lydia Jeris W*, Dr. Mohamed Thayub, Dr. Raghavan Subramanyan, Dr. Kotturathu Mammen Cherian

Frontier Lifeline Hospital, R 30 C, Ambattur Industrial Estate Rd, Mogappair, Chennai, Tamil Nadu 600101, India

***Corresponding Author**
Dr. Lydia Jeris W

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**Abstract:** Protein Loosing Enteropathy (PLE) is a disorder characterized by either increased loss of proteins from the digestive system or defect in the absorption of proteins. It is a rare complication seen in some cases of Fontan surgery, the reason for which remains an enigma. There are many causes elucidated like increased central venous pressure, decreased cardiac output, increased mesenteric resistance, lymphatic obstruction and so on. Though panoply of treatment options is available for the management of PLE post Fontan, there is still no consensus regarding the causes, consequences and treatment protocol. We present a case of 22 year old girl who underwent Fontan procedure for complex congenital heart disease at the age of 3. She developed diarrhea, hypoproteinemia, hypoalbuminemia, hypocalcemia 18 years after surgery and was diagnosed as protein loosing enteropathy post Fontan based on strong clinical findings after excluding other causes of hypoalbuminemia and was managed conservatively. PLE post Fontan has a grave prognosis and is essential to elucidate the exact pathophysiological abnormality thus paving way for better therapeutic management.

**Keywords:** Fontan procedure, Protein loosing enteropathy, alpha 1 antitrypsin.

## INTRODUCTION

Protein Loosing Enteropathy (PLE) is a disorder wherein there is abnormal and profuse loss of proteins from the enteric system. Fontan procedure is done in case of single functioning ventricle for channelizing the blood from venae cavae directly to pulmonary artery thus bypassing the ventricle. PLE after Fontan procedure is a rare disease with increased mortality and morbidity [1]. The pathogenesis and treatment of post Fontan PLE is still an enigma with various postulates being made. The cause of PLE post Fontan is attributed to various causes like increased systemic venous pressure, decreased cardiac output, chronically altered mesenteric blood flow, systemic inflammation, protein glycosylation defect and neurohumoral activation. Any patient who has undergone Fontan procedure and presents with diarrhea and hypoproteinemia should be suspected to have PLE. The diagnosis can be confirmed by doing a 24 hour stool alpha 1 antitrypsin level or serum alpha 1 antitrypsin level. Treatment strategies include measures to increase cardiac output, administration of steroids, unfractionated heparin, percutaneous intervention and surgery [2].

We present a case of a 21 year old female who was euglycemic, normotensive and in hypothyroid status. At the age of 3 years, she was diagnosed to have complex heart disease (tricuspid atresia, interrupted inferior venacava (IVC) and large atrial septal defect) for which she underwent left pulsatile bidirectional Glenn (BDG, Kawashima Fontan procedure). Completion of Kawashima Fontan (unfenestrated) extra cardiac hepatopulmonary connection using number 18 PTFE graft with main pulmonary artery interruption and atrial septectomy was performed after 9 years. She had been on regular follow up and was found to have mild facial puffiness, mild albuminuria and mild hypoproteinemia since then. Recently she was admitted for acute onset of diarrhea, extreme weakness and oral ulcer for two week duration. On examination, her vitals were stable. Facial puffiness and leg edema were seen. She was extremely weak, eyes sunken and hands in tetany position. Systemic examination was normal.

Investigations revealed very low albumin - 2g/dL (BCG method), total protein- 3.8g/dL (Biuret method), serum calcium (Arsenazo III method) - 4.5mg/dL. Urine had trace amount of protein. Serum TSH and T3 were elevated (7.98µIU/mL and 0.45pg/mL respectively). dsDNA, ANA and ENA were negative. Echo showed functioning Fontan circuit (well flowing Kawashima flow). No reversal of flow or thrombus was noted. Moderate AV regurgitation was seen. Branch pulmonary artery not well visualized? LPA measured 10mm with mild ventricular dysfunction. Fecal Calprotectin (ELISA) was within biological reference interval ruling out inflammatory bowel disease. $^{99m}$Tc nanocolloid bone marrow scintigraphy showed normal physiological pattern of tracer uptake in GI system. Other causes of hypoproteinemia like nephritic syndrome, liver disease and malnutrition were also ruled out. Though nuclear scan showed no tracer in GIT, still a diagnosis PLE was made based on strong clinical grounds.

Patient was managed conservatively with antibiotics, steroids, octreotide and rifaximine. As she had hypocalcemia she was treated with calcium infusion and injection calcium gluconate. She was also given Tablet Budesonide CR 3mg and antiplatelets. No tetany was seen since then. Counseling was given to the patient and family regarding the seriousness of the condition, guarded prognosis and chronic management. Diet counseling was also given to take a protein rich low fat diet and usage of Medium chain triglyceride (MCT) powder.

## DISCUSSION

Protein loosing enteropathy was first demonstrated by Albright in the year 1949 and Crupi was the first to describe PLE in a patient who underwent Fontan procedure [3]. PLE post Fontan is a rare complication with increased mortality and morbidity. The prevalence of the disease post Fontan surgery is not yet clearly known but is roughly estimated anywhere between 1 to 15% [4].

PLE occurs when there is excessive loss of serum protein due to break in the intestinal barrier. GI symptoms occur due to loss of large quantities of protein. They usually present with diarrhea, abdominal cramps, edema, pleural/ pericardial effusion, ascites, tetany and failure to thrive. The cause of diarrhea is attributed to bowel wall edema which occurs due to massive protein loss. Steatorrhea also occurs as a consequence of bowel wall edema. Protein loss leads to decreased oncotic pressure leading on to edema, ascites and effusion. Low protein level causes a decrease in the transport of calcium. Hence, hypocalcemia occurs in PLE leading on to tetany and poor growth. Other proteins like coagulation factors can be depleted leading on to abnormal clotting mechanism thus causing thromboembolism. There occurs dilatation of intestinal lymphatic leading on to lymphatic loss which results in lymphopenia.

Patient usually presents with weight gain, increased abdominal circumference or edema. Investigations would reveal hypoalbuminemia, hypocalcemia, hypogammaglobulinemia, lymphopenia, and hypercoagulability. Albumin is predominantly reduced. The confirmatory test for PLE is an abnormal stool α 1antitrypsin clearance. α 1antitrypsin is a protein which is produced in the liver. It is usually not metabolized and hence the α 1antitrypsin clearance should be low in normal individuals but in case of PLE, the clearance is very high, If this test is not possible to do, then a single spot analysis of α 1antitrypsin level in stool sample would give the clearance value and is a reliable test for confirming PLE [5].

There is another clinical entity called subclinical PLE wherein there is abnormality in the serum protein level or α 1antitrypsin level in stool but no signs and symptoms of PLE and these patients should be carefully monitored. Also in some patients the protein loss and edema are only transient and gets back to normal [7].

Fontan procedure is done to channelize the vena caval blood to flow directly in to the pulmonary artery bypassing the ventricular chamber leading to a normal circulation flow pattern. Fontan operation is a good surgical option for functional single ventricle but there are many increasing challenges being faced, one being PLE [8]. PLE can occur any time after surgery ranging from a few weeks to years. Why PLE occurs after Fontan surgery is a perplexing question and many explanations have been provided. Many conditions like lymphatic system abnormality, cardiovascular diseases, GI disorders, Crohns disease, autoimmune diseases and inflammation are found to play a key role in the development of PLE. Increased systemic venous pressure is an important factor in the pathogenesis of PLE as increased systemic venous pressure leads to dilation of the lymphatics which further leads on to loss of proteins. Survival rate of patients with PLE is only 50% after 5 years of Fontan procedure. PLE after Fontan is found to be more common in patients with abnormality in systemic venous drainage, poysplenia, heterotaxy, low lymphocyte count (predominantly CD4 and CD5) and increased left ventricular diastolic pressure.

Treatment of PLE includes medical, percutaneous intervention and surgical management. Medical measures include use of anti-congestive medication, albumin infusion, immunoglobulins, prophylactic use of antibiotics, steroids, heparin, diuretics, sildenafil and spironolactone [2, 9]. Diet should include high protein intake and medium chain triglycerides (MCT). Percutaneous intervention includes creation of fenestration in the interatrial septal region, AV pacing, azygous vein embolization and balloon dilatation with or without stent [10]. Various surgical measures tried

include usage of biological valve in the place where proximal anastomosis was done, valvuloplasty, conduit disobstruction, surgical atrial fenestration and heart transplantation [11].

In our case, a diagnosis of PLE post Fontan was based on strong clinical grounds like diarrhoea, hypoproteinemia, hypoalbuminemia, hypocalcemia with no liver involvement. Alpha 1 antitrypsin level in stool/ serum could not be done due to logistic issues, but fecal Calprotectin was done which was normal thus ruling out inflammatory causes. She was managed medically and her symptoms improved.

## CONCLUSION

PLE after Fontan procedure is a rare complication with increased mortality and morbidity. Though many postulates have come up on the pathophysiological basis of the disease, there is a long way to go to know the exact causes and consequences of PLE after Fontan. More research is required in this field to know exact pathophysiology which would aid in effective therapeutic intervention.

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