CASE STUDY

Reversal of protein losing enteropathy with prednisone in adults with modified Fontan operations: long term palliation or bridge to cardiac transplantation?

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Abstract

Protein losing enteropathy (PLE), defined as severe loss of serum protein into the intestine, occurs in 4–13% of patients after the Fontan procedure and carries a dismal prognosis with a five year survival between 46% and 59%. Chronically raised systemic venous pressure is thought to be responsible for the development of PLE in these patients, with perhaps superimposed immunological or inflammatory factors. The success rate of contemporary medical, transcatheter, and surgical treatments attempting to reduce systemic venous pressure ranges from 19% to 40%. Prednisone treatment for PLE has been tried, with variable success rates reported in children. The effect of prednisone in adult patients with PLE after the Fontan procedure is largely unknown. Two cases of PLE in adults (a 39 year old woman and a 25 year old man) after modified Fontan procedure who responded dramatically to oral prednisone treatment are reported, suggesting that a trial of this "non-invasive" treatment should be considered as long term palliation or bridge to cardiac transplantation.

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Protein losing enteropathy (PLE), defined as severe loss of serum protein into the intestine, occurs in 4–13% of patients following the Fontan procedure.[1–3] Patients present with generalised oedema, ascites, pleural effusion or chronic diarrhoea,[1] and have a dismal prognosis with a five year survival between 46% and 59%.[1 2] PLE is thought to result principally from chronically raised systemic venous pressure causing intestinal lymphangiectasia with consequent loss of albumin, protein, lymphocytes, and immunoglobulin into the gastrointestinal tract. Treatment modalities include: low fat, high protein, medium chain triglyceride diet to reduce intestinal lymphatic production; albumin infusions to increase intravascular osmotic pressure; as well as institution of diuretics, afterload reducing agents, and positive inotropic agents to lower central venous pressure. Catheter based interventions such as balloon dilatation of a pathway obstruction or creation of an atrial fenestration,[4–6] as well as surgical interventions from conversion or take down of the Fontan circuit to cardiac transplantation[7] have also been advocated. Newer treatment modalities include subcutaneous heparin,[8 9] octreotide treatment,[10] and prednisone.[11–13] Mechanisms of action of these treatments are largely unknown but reports of their beneficial effects are accumulating in the literature. We report two cases of PLE in adult patients after modified Fontan procedure who responded dramatically to oral prednisone treatment.

Case 1

A 39 year old woman with tricuspid and pulmonary atresia had undergone a modified Fontan procedure (right atrium to pulmonary artery connection) at 28 years old. At the age of 38, she presented with generalised oedema and ascites. Laboratory tests revealed normal liver and kidney function, albumin 22 g/l (normal 38–50), total protein 41 g/l (normal 64–83), lymphocyte count 0.4 bil/l (normal 1.5–4.0), and α_1 antitrypsin clearance of 354 ml/day (normal < 22). Transthoracic echocardiography showed mild systemic ventricular dysfunction with moderate atrioventricular valve regurgitation and a widely patent Fontan connection. Contrast saline study injected from the right arm showed evidence of a venovenous fistula from rapid appearance of bubbles into the left atrium. Cardiac catheterisation revealed a mean right atrial pressure of 17 mm Hg without any Fontan pathway obstruction, and an oxygen saturation of 92% in air. A low fat, high protein, medium chain triglyceride diet along with albumin infusions and large doses of diuretics and angiotensin converting enzyme inhibitors had no clinical benefit. An atrial fenestration was considered but not done because of the presence of venovenous anastomoses allowing for some degree of right to left shunting. The patient was

started on a trial of subcutaneous octreotide treatment (120 μg twice a day for two weeks followed by 240 μg twice a day for two weeks and 480 μg twice a day for eight weeks). Because of the lack of clinical improvement and the patient's discomfort at the site of injection, octreotide was discontinued after 10 weeks.

Prednisone, 60 mg daily (1 mg/kg), was initiated. Response to treatment was dramatic. Within 11 days, the patient had lost 9 kg, with complete disappearance of generalised oedema and ascites. At that time, albumin concentration had risen to 30 g/l and total protein to 46 g/l. Intestinal biopsy was suggested but declined. The patient reportedly had not felt better for a long time. Unfortunately, one month after initiation of prednisone (while still taking 40 mg daily) she felt dizzy and had a cardiac arrest from which she could not be resuscitated. The presumed cause of death was arrhythmias. Symptomatic recurrent atrial tachyarrhythmia had previously been documented in this patient. Unfortunately, there was no postmortem examination.

Case 2

A 25 year old man with tricuspid and pulmonary atresia had undergone a modified Fontan procedure (right atrium to pulmonary artery connection) at the age of 14. In 1998, at the age of 25, the patient presented with generalised oedema and ascites. Laboratory tests showed normal liver and kidney function, albumin 22 g/l, total protein 45 g/l, lymphocyte count 0.7 bil/l, and α_1 antitrypsin stool clearance of 99 ml/day. He was diagnosed with PLE.

Transthoracic echocardiography showed mild to moderate systemic ventricular impairment, no atrioventricular valve regurgitation, and a widely patent Fontan anastomosis. Previous cardiac catheterisation had excluded an obstructed Fontan circuit. Contrast saline study showed evidence of a venovenous fistula as well as pulmonary arteriovenous fistulae. Systemic oxygen saturation was 87% in air. A low fat, high protein, medium chain triglyceride diet was instituted along with albumin infusions and increased doses of diuretics, digoxin, and angiotensin converting enzyme inhibitor without any satisfactory improvement. In view of the patient's reluctance to undergo any further invasive procedures and because of the existing venovenous collaterals acting as a "spontaneously occurring atrial fenestration", we decided on medical management.

In light of our previous experience with prednisone a trial of 60 mg daily (1.2 mg/kg) was initiated. After one week of treatment the patient's condition improved remarkably with a 6 kg weight loss and complete disappearance of oedema. Despite the dramatic clinical response to treatment, laboratory tests at that time showed a persisting low albumin (25 g/l) and a total protein of 52 g/l. With slow tapering doses of prednisone (by 10 mg every two weeks), the patient remained oedema free, and two months after the initiation of prednisone, his albumin concentration (40 g/l), total protein (59 g/l), and α_1 antitrypsin stool clearance (2 ml/day) were all normal. The patient is currently on a tapering dose of prednisone without any clinical or laboratory evidence of recurrence.

Discussion

High central venous pressure has been suggested as the principal cause of PLE, impeding thoracic lymphatic drainage with consequent intestinal lymphangiectasia and protein leak. However, autoimmune and inflammatory processes have also been postulated as possible pathogenic factors.[11 14] Indeed, PLE has been described in association with autoimmune diseases such as lupus erythematosus,[15–18] sarcoidosis,[19 20] and allergic gastroenteropathy.[21] Furthermore, immune deposits have been found in the intestinal capillary walls of patients with PLE with a dramatic response to corticosteroid treatment.[14] Cases of PLE after the Fontan procedure in the presence of low central venous pressure have also been described.[9 12] Some authors have shown high mean right atrial pressure to be a predisposing risk factor in the development of PLE.[3] However, this has been refuted by others.[2 22] All this would suggest a perhaps more complex and multifactorial cause of PLE than was first anticipated.

Mertens *et al* report on a contemporary series of patients with PLE in which the overall medical success rate in treating PLE was 25%, the transcatheter success rate 40%, and the surgical success rate 19% with an associated mortality of 50%.[1] Because of the grave prognosis and low success rate of present treatments, alternatives focusing not only on an increased hydrostatic pressure as the cause of PLE but on other potential contributing factors such as immunological or inflammatory mechanisms seem justified.

Corticosteroid treatment for PLE after Fontan procedure has been reported so far in 30 patients, most of them children with no case reports of adults. Long term remission with prednisone has been achieved in 10 of 30 patients, partial benefit has been seen in 11 with no benefit in nine.[1 2 4 5 7 10–13 23] Dosages range from 2 mg/kg/day of oral prednisone or the equivalent dosage administered as methylprednisolone intravenously in children, to 25–60 mg of oral prednisone twice a day in adolescent patients, with a slow tapering regimen over five to six months. Of the 21 patients responding to prednisone, nine patients had relapses on stopping the medication, necessitating a return to higher doses and a slower tapering regimen, and five patients could not be completely weaned off treatment.

The mechanism of action of corticosteroids in the treatment of PLE is unclear. Prednisone has been shown to produce resolution of intestinal lymphangiectasia in patients with biopsy proven PLE after Fontan procedures[13 24] leading some to postulate that corticosteroids may have a stabilising effect on intestinal capillary and lymphatic membranes or lead to a reduction in lymphatic tissue volume.[12]

Whether it does so through its anti-inflammatory properties[11 12] or its cellular anabolic effect[11] is unknown.

The close temporal relation of initiation of prednisone treatment and the clinical resolution of PLE in our two adult patients strongly suggest that prednisone was responsible for the improvements. The delay between dramatic clinical response and laboratory normalisation in our patients, and described by others,[11] supports a membrane stabilising effect of prednisone leading to a rapid stop of protein leakage from the gut and the peripheral vasculature, with quick disappearance of oedema followed by a slower normalisation of albumin and protein concentrations as they are being gradually replenished through normal protein synthesis. Whether prednisone is more likely to work in cases of PLE without central venous hypertension remains to be determined.

Our limited experience suggests that prednisone is effective in adult patients with PLE, even in those with raised central venous pressure. Given the potential morbidity of cyanosis and the risk of paradoxical emboli associated with transcatheter or surgical atrial fenestration, and the high reported surgical mortality of Fontan conversion or take down,[1] a trial of prednisone should be considered in adult patients with PLE, either as a long term palliation or a bridge to cardiac transplantation.

1 Mertens L, Donald JH, Sauer U, *et al.* Protein-losing enteropathy after the Fontan operation: an international multicenter study. *J Thorac Cardiovasc Surg* 1998; **115**:1063–73.

2 Feldt RH, Driscoll DJ, Offord KP, *et al.* Protein losing enteropathy after the Fontan operation. *J Thorac Cardiovasc Surg* 1996;**112**:672–80.

3 Feldt RH, Driscoll DJ, Offord KP, *et al.* Five- to fifteen-year follow-up after Fontan operation. *Circulation* 1992;**85**:469–96.

4 Lemes V, Murphy AM, Osterman FA, *et al.* Fenestration of extracardiac Fontan and reversal of protein-losing enteropathy: case report. *Pediatr Cardiol* 1998;**19**:355–7.

5 Rychik J, Rome JJ, Jacobs ML. Late surgical fenestration for complications after the Fontan operation. *Circulation* 1997; **96**:33–6.

6 Warnes CA, Feldt RH, Hagler DJ. Protein-losing enteropathy after the Fontan operation: successful treatment by percutaneous fenestration of the atrial septum. *Mayo Clin Proc* 1996;**71**:378–9.

7 Sierra C, Calleja F, Picazo B, *et al.* Protein-losing enteropathy secondary to Fontan procedure resolved after cardiac transplantation. *J Pediatr Gastroenterol Nutr* 1997;**24**:229–30.

8 Kelly AM, Feldt RH, Driscoll DJ, *et al.* Use of heparin in the treatment of protein-losing enteropathy after Fontan operation for complex congenital heart disease. *Mayo Clin Proc* 1998;**73**:777–9.

9 Donnelly JP, Rosenthal A, Castle VP, *et al.* Reversal of protein-losing enteropathy with heparin therapy in three patients with univentricular hearts and Fontan palliation. *J Pediatr* 1997;**130**:474–8.

10 Bac DJ, Van Hagen PM, Postema PTE, *et al.* Octreotide for protein-losing enteropathy with intestinal lymphangiectasia [letter]. *Lancet* 1995;**345**:1639.

11 Rychik J, Piccoli DA, Barber G. Usefulness of corticosteroid therapy for protein-losing enteropathy after the Fontan procedure. *Am J Cardiol* 1991;**68**:819–21.

12 Rothman A, Snyder J. Protein-losing enteropathy following the Fontan operation: resolution with prednisone therapy. *Am Heart J* 1991;**121**:618–19.

13 Zellers TM, Brown K. Protein-losing enteropathy after the modified Fontan operation: oral prednisone treatment with biopsy and laboratory proved improvement. *Pediatr Cardiol* 1996;**17**:115–17.

14 Itoi K, Sasaki T, Sawai T, *et al.* Protein-losing gastroenteropathy in association with immune deposits in gastrointestinal mucosal capillaries. *Am J Gastroenterol* 1989;**84**: 187–91.

15 Pelletier S, Ekert P, Landi B, *et al.* Exudative enteropathy in disseminated lupus erythematosus. *Ann Gastroenterol Hepatol* 1992;**28**:259–62.

16 Tanaka T, Damiao AO, Gabriel A, *et al.* Protein-losing enteropathy in systemic lupus erythematosus. *Rev Hosp Clin Fac Med Sao Paulo* 1991;**46**:34–7.

17 Pereira AS, Pereira Filho RA, Trevisan MA, *et al.* Intestinal lymphangiectasia in systemic lupus erythematosus. *Arq Gastroenterol* 1980;**17**:210–12.

18 Trentham DE, Masi AT. Systemic lupus erythematosus with a protein-losing enteropathy. *JAMA* 1976;**236**:287–8.

19 Godeau B, Farcet JP, Delchier JC, *et al.* Protein-losing enteropathy in gastrointestinal sarcoidosis associated with malignant lymphoma. *J Clin Gastroenterol* 1992;**14**:78–80.

20 Popovic OS, Brkic S, Bojic P, *et al.* Carcoidosis and protein-losing enteropathy. *Gastroenterology* 1980;**78**:119–25.

21 Scudamore HH, Phillips SF, Swedlund HA, *et al.* Food allergy manifested by eosinophilia, elevated imunoglobulin E level, and protein-losing enteropathy: the syndrome of allergic gastroenteropathy. *J Allergy Clin Immunol* 1982;**70**: 129–38.

22 Hess J, Kruizinga K, Bijleveld CMA, *et al.* Protein-losing enteropathy after Fontan operation. *J Thorac Cardiovasc Surg* 1984;**88**:606–9.

23 Ventriglia F, Mundo L, Bosco G, *et al.* Regression of post-Fontan protein-losing enteropathy after surgical correction of hemodynamic faults other than high right atrial pressure. *Tex Heart Inst J* 1996;**23**:233–5.

24 Silverman A, Roy CC. Protein-losing enteropathy. In: Silverman A, Roy CC, eds. *Pediatric clinical gastroenterology.* 3rd ed. St Louis: The CV Mosby Co, 1983:304–23.