Acquired combined immunodeficiency associated with protein losing enteropathy complicating Fontan operation

S Chakrabarti, B R Keeton, A P Salmon, J J Vettukattil

Heart 2003;89:1130–1131

It is vitally important that the immunological aspect of protein losing enteropathy following Fontan procedures is highlighted, in order to decrease significant morbidity and mortality

Protein losing enteropathy (PLE), a condition characterised by severe loss of serum protein into the intestine, is a known complication of the Fontan circulations. PLE may occur in up to 13.4% of patients within 10 years of the procedure and has been reported to have a mortality rate of 56% within five years of diagnosis.¹ Along with the loss of proteins, significant loss of immunoglobulins and lymphocytes can also occur. This may lead to the development of immunological dysfunction, predisposing these individuals to infections and their associated complications. We report two children who developed immunodeficiency following Fontan procedures.

CASE 1

A total cavopulmonary connection (modified Fontan procedure) was performed on a 5 year old who had hypoplastic left heart syndrome. A previous bi-directional superior cavopulmonary anastomosis (Glenn procedure) had been performed two years earlier.

The child had remained well on follow up until 9 years of age, when she presented with history of loose stools, abdominal pain, vomiting, and generalised oedema. Urinalysis was unremarkable but her serum albumin was 15 g/l. Her electrolytes, and renal and liver functions were within normal limits. PLE was considered and she responded to high protein diet and diuretics. Her albumin slowly increased to 39 g/l by the next three weeks. She remained well for a few weeks but started to become hypoalbuminaemic intermittently. Subsequently she has improved on a prolonged course of subcutaneous heparin but has also needed a course of prednisolone. No significant pleural effusions or infective episodes

have been noted in the entire follow up period. The results of her blood tests are shown in table 1.

Acquired hypogammaglobulinaemia with T cell lymphopenia was diagnosed secondary to protein losing enteropathy, and cotrimoxazole prophylaxis was commenced. She continues on a high protein diet but still gets oedematous intermittently.

CASE 2

An 8 year old girl with pulmonary atresia with intact septum had undergone a total cavopulmonary connection seven years after an initial palliation which included a Glenn procedure. At the age of 10, she presented with diarrhoea, vomiting, swelling of extremities, and pyrexia. On examination, she was noted to have peripheral oedema and ascites. Blood tests revealed hypoalbuminaemia (16 g/l), but normal electrolytes and renal functions. Lymphopenia was also noted and a diagnosis of protein losing enteropathy was considered in view of her symptom evolution in the post-Fontan stage. Her albumin continued to be low and she responded partially to prolonged administration of subcutaneous heparin and prednisolone. It took about 12 months for the albumin to normalise (up to 34 g/l) but she developed glucose intolerance, secondary to the high dose steroid intake required to achieve remission. Results of her blood tests are shown in table 2.

DISCUSSION

PLE has been known to be associated with chronic cardiac conditions, including congestive cardiac failure, constrictive pericarditis, cardiomyopathy,² and post-Mustard operations.³ This complication is known to occur in 4–13% of patients following the Fontan procedure.^{1,4} The affected individuals usually present with effusions, ascites, oedema or chronic diarrhoea secondary to the gut protein loss and hypoalbuminaemia. The prognosis following PLE is guarded with a five year survival between 46–59%.^{1,4,5} Various risk factors have been hypothesised for the development of PLE, including presence of chronically elevated right atrial pressure,

See end of article for authors' affiliations

Correspondence to:
Dr Joseph J Vettukattil,
Wessex Cardiac Unit,
Tremona Road,
Southampton SO16 6YD,
UK; joseph.vettukattil@
suht.swest.nhs.uk

Table 1 Case 1: serial immunological profile

Date	IgG (g/l) (normal 5.4–16.1)	IgA (g/l) (normal 0.7–2.5)	IgM (g/l) (normal 0.5–1.8)	Albumin (g/l) (normal 32–47)	Lymphocyte (normal 1–5×10 ⁹ /cells/l)	CD3+ (normal 0.8–3.5×10 ⁹ /cells/l)
30 October 2000	3.5	0.7	0.7	29	1.2	–
2 November 2000	4.0	0.8	0.6	33	0.8	–
12 October 2001	3.2	1.0	0.8	28	0.6	0.22
10 June 2002	1.2	0.3	0.6	20	1.1	0.54

Table 2 Case 2: serial immunological profile

Date	IgG (g/l) (normal 5.4–16.1)	IgA (g/l) (normal 0.7–2.5)	IgM (g/l) (normal 0.5–1.8)	Albumin (g/l) (normal 32–47)	Lymphocyte (normal $1-5 \times 10^9$ cells/l)	CD3+ (normal $0.8-3.5 \times 10^9$ cells/l)
23 May 2001	2.0	0.7	0.5	18	0.4	0.08
11 July 2001	–	–	–	18	0.9	0.05
7 January 2002	1.2	0.2	0.5	34	0.6	0.10

longer cardiopulmonary bypass time, single right ventricle anatomy,⁶ coagulation factor anomalies,⁷ mucosal injury in the preoperative period, and activation of the renin-angiotensin system with increased concentrations of circulating angiotensin II.⁸

It is thought that PLE may be caused by high venous pressures with consequent loss of albumin, protein, lymphocytes, and immunoglobulin into the gastrointestinal tract. These patients may have had a deficit in the intestinal mucosa, causing continuous low grade loss of immunoglobulins. These losses may be limited in some IgG subclasses and more pronounced in others because of the different physical and chemical properties of these proteins. Testing IgG subclasses in PLE may result in different profiles of IgG subclasses with a prominent low level⁹ of IgG₂.

Coupled with this, loss of lymphocytes leading to cellular immunity dysfunction may also occur.^{10–11} Immune compromise itself may lead to further mucosal changes¹² and more protein loss furthering the damage. The intestinal tract is also one of the most metabolically active tissues in the body, with mucosal renewal taking place every 3–5 days. Associated hypoproteinemia impedes villi regeneration and mucosal repair, compounding the problems. The overall picture may resemble that of combined immunodeficiency resulting from the involvement of both the humoral and the cellular immunity. The gastrointestinal tract is a portal of entry for numerous pathogens, and infections are a major cause of morbidity and mortality in immunocompromised patients. Apart from various viruses and bacteria, fungal infections are extremely common, ranging from superficial candidiasis to severe systemic infections with candida or aspergillosis.¹³ Severe and atypical infections are known to occur during PLE in a post-Fontan state.¹⁴

It is logical to postulate that there is an increased risk for immune dysfunction following the Fontan procedure. More conclusive data are needed to substantiate the hypothesis. It appears that such a situation may exist not only in patients with PLE, but also in those with prolonged chylothorax, secondary to the protein and cellular loss from chyle. Hypoalbuminaemia is quite promptly corrected in the immediate postoperative period by albumin infusions, thereby potentially masking the other “losses”, which need to be monitored vigorously. In both our patients the albumin concentrations have been low for prolonged periods of time. The immunoglobulin and lymphocyte counts have also been low, but appear to be unrelated to the albumin values. In the second patient, in spite of a normal albumin concentration, the globulin and lymphocyte counts are significantly low. It is therefore likely that various factors are involved, rather than simple loss of proteins and lymphocytes from the gut. Selective loss of any or more of these factors may also be possible.

PLE has been reported to occur anywhere from weeks to years after the Fontan operation.⁸ With no definite risk factors yet conclusively proved, it is very difficult to predict its occurrence. This necessitates a screening programme and we suggest that yearly immunoglobulins and T cell functions need to be assessed in all post-Fontan patients in follow up. Some of these patients, who have immune dysfunction as a

facet of their main diagnosis (for example, asplenia syndromes) would need to be in their own immunological follow up programmes.

Administration of immunoglobulins as replacement following PLE has been used with very good results.¹⁵ Immune dysfunction post-Fontan state would risk it lingering on until the PLE is well controlled. Risk of recurrence is high, coupled with the recurrence of the PLE. Use of corticosteroids in the treatment of PLE increases the risk of immune suppression as well. In cases where the immune dysfunction is thought to be transient (for example, secondary to constrictive pericarditis), return of full functional status (total lymphocytes and CD3+ and CD4+ counts) may take a prolonged period of time. It is of vital importance that the immunological aspect of PLE is highlighted to decrease significant morbidity and mortality. Serum immunoglobulin assays must be undertaken routinely along with serum electrophoresis and T cell function studies. Prophylactic antibiotics and vaccination against potentially severe viral infections, immunoglobulin replacement therapy, and prompt detection and treatment of infections are the mainstay of the management strategies of this difficult condition.

Authors' affiliations

S Chakrabarti, B R Keeton, A P Salmon, J J Vettukattil, Wessex Cardiac Unit, Tremona Road, Southampton, UK

REFERENCES

- Feldt RH, Driscoll DJ, Offord KP, *et al.* Protein losing enteropathy after the Fontan operation. *J Thorac Cardiovasc Surg* 1996;**112**:672–80.
- Valberg LS, Corbett WEN, McCorriston JR. Excessive loss of plasma protein into the gastrointestinal tract associated with primary myocardial disease. *Am J Med* 1965;**39**:668–73.
- Krueger SK, Burney DW, Ferlic RM. Protein-losing enteropathy complicating the Mustard procedure. *Surgery* 1977;**81**:305–6.
- Feldt RH, Driscoll DJ, Offord KP, *et al.* Five- to fifteen-year follow-up after Fontan operation. *Circulation* 1992;**85**:469–96.
- 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.
- Powell AJ, Gauvreau K, Jenkins KJ, *et al.* Perioperative risk factors for development of protein-losing enteropathy following a Fontan procedure. *Am J Cardiol* 2001;**88**:1206–9.
- 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 Clinic Proc* 1998;**73**:777–9.
- Rychik J, Spray TL. Strategies to treat protein-losing enteropathy. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2002;**5**:3–11.
- Garty BZ. Enteropathy and IgG subclass deficiency. *J Pediatrics* 1996;**128**:722–23.
- Koch A, Hofbeck M, Feistel H. Circumscribed intestinal protein loss with deficiency in CD4+ lymphocytes after the Fontan procedure. *Eur J Pediatrics* 1999;**158**:847–50.
- Muller C, Wolf H, Gottlicher J, *et al.* Cellular immunodeficiency in protein-losing enteropathy. Predominant reduction of CD3+ and CD4+ lymphocytes. *Dig Dis Sci* 1991;**36**:116–22.
- Doe WF. Immunodeficiency and the gastrointestinal tract. *Clin Gastroenterol* 1983;**12**:839–53.
- Aggarwal V, Williams MD, Beath SV. Gastrointestinal problems in the immunosuppressed patient. *Arch Dis Child* 1998;**78**:5–8.
- Cheung YF, Leung MP, Yuen KY. Legionella pneumonia and bacteraemia in association with protein-losing enteropathy after Fontan operation. *J Infection* 2001;**42**:206–7.
- De Giocoso C, Maggiore G, Scotta MS. Administration of intravenous immunoglobulin in two children with hypogammaglobulinaemia due to protein losing enteropathy. *Clin Exp Immunol* 1985;**60**:447–8.