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Are children with protein-losing enteropathy after the Fontan operation at increased risk of cytomegalovirus enteropathy? A report of two cases

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Brief Report

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Abstract

Introduction: Aetiology of protein-losing enteropathy in single-ventricle type CHD is multifactorial. *Report:* We describe two Fontan patients with protein-losing enteropathy who presented with cytomegalovirus-associated colitis. *Discussion:* Fontan patients display risk factors for cytomegalovirus-induced gastroenteropathy that may affect lymph angiogenesis, disease development, and progression. *Conclusion:* Cytomegalovirus enteropathy may be common among Fontan patients who suffer from protein-losing enteropathy. Polymerase chain reaction is important for detection.

Introduction

Protein-losing enteropathy in single-ventricle type CHD is a devastating complication after surgical palliation. Pathophysiologic processes are still poorly understood. It most likely has a multi-factorial aetiology and develops on the basis of an increased central venous pressure, genetic predisposing factors, alterations in haemodynamics, and inflammatory processes.[1,2]

Several studies report on infections as potential trigger, but no association to cytomegalovirus has previously been described.[1]

Report

Case 1

A boy with hypoplastic left heart syndrome who underwent an extracardiac fenestrated Fontan operation presented at the age of 6 years with six episodes of haematuria without significant proteinuria and concurrent hypoproteinaemia (3.6 g/dl). Renal disease was ruled out and haematuria resolved without treatment, but hypoproteinaemia and oedemas of the hands and eyelids remained. Random α1-Antitrypsin in stool turned out to be elevated and protein-losing enteropathy was diagnosed.

Workup included endoscopy of the gut, duodenum, and colon, and biopsies were taken of each segment. Besides a mild chronic inflammatory process of the colon and swelling of the mucous membrane, no macroscopic and histologic alteration could be found. Cytomegalovirus DNA was isolated in one specimen of the ascending colon, and cytomegalovirus colitis was diagnosed. The patient was treated with ganciclovir for 6 weeks and hypoproteinaemia resolved.

However, 1 year later, the patient presented again with hypoproteinaemia. Cytomegalovirus reactivation was excluded via serologic and urinary analysis and colonoscopy. Furthermore, the patient developed signs of plastic bronchitis 6 months later. Lymphatic imaging via the inguinal lymph nodes at that time demonstrated extensive lymphatic malformations that could not be treated with lymphatic intervention. Creation of a surgical anastomosis between the innominate vein and the right atrial appendage led to resolution of hypoproteinaemia.

Case 2

A boy with a history of single-ventricle type CHD and malposition of the great arteries who previously underwent a Norwood and Glenn operations at our facility was admitted for an extracardiac fenestrated Fontan completion at the age of 4 years. The post-operative course was complicated by profound cardiac insufficiency, acute renal impairment, and prolonged pleural effusions. In addition, the patient developed severe persistent diarrhoea with profound hypoproteinaemia (as low as 3.5 g/dl) that did not resolve during a 2-month course of budesonide. Finally, endoscopy of the gastrointestinal tract was performed and demonstrated

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mild inflammatory processes in the colon. A specimen of the ascending colon was positive for cytomegalovirus DNA (polymerase chain reaction).

Diarrhoea improved during a 4-week course of ganciclovir, but protein levels remained low. Three weeks after cessation of antiviral therapy, cytomegalovirus recurred (positive serum cytomegalovirus polymerase chain reaction) and another course of ganciclovir was initiated for 8 weeks. Again, protein levels did not improve and despite three consecutive negative serum and urinary samples for virus DNA, cytomegalovirus reactivated (positive urine cytomegalovirus polymerase chain reaction) just after discontinuing therapy. The following 10 months the patient received continuously antiviral therapy, and total protein levels increased temporary up to 6.2 g/dl. During follow-up, all subsequent serum, urine, and colonoscopy specimens remained negative for cytomegalovirus DNA. However, profound hypoproteinaemia recurred during treatment and the patient developed severe failing Fontan circulation. The patient was finally scheduled for heart transplantation but was rejected due to multiple end organ damage.

Discussion

We describe two patients with protein-losing enteropathy after the Fontan operation where during workup cytomegalovirus colitis was diagnosed. No such association has been reported before.

Cytomegalovirus infection in German children and adolescents is common (IgG seroprevalence: 21.4–33.5%).[3] Involvement of the gastrointestinal tract is rare but even occurs in immunocompetent children and adults.[4,5]

Fontan patients may be at increased risk for cytomegalovirus Enteropathy. In the majority of patients, cytomegalovirus colitis most likely results from viral reactivation rather than primarily infection.[5,6] Steroid use and RBC transfusion within 1 month – treatments that are commonly seen in Fontan patients – were identified to be independent risk factors for the development of cytomegalovirus colitis in a limited case control study of 51 immunocompetent adult patients.[5] Furthermore, cytokines like tumour necrosis factor-α and interferon-γ that have been suggested to play a central role in viral reactivation from latency have been reported to be elevated in Fontan patients.[7,8]

Cytomegalovirus may play a pathophysiologic role in the development of protein-losing enteropathy in certain Fontan patients. The association of cytomegalovirus and protein-losing enteropathy has been well documented in immunocompromised children and adults as well as in several other specific diseases.[9,10] Pathophysiologic mechanisms and implication on disease development are not clear. However, human cytomegalovirus can infect lymphatic endothelial cells and promote angiogenesis and lymph angiogenesis through interleukin-6 and granulocyte-macrophage colony-stimulating factor.[11] It hence may have the potential to affect lymphatics and promote protein-losing enteropathy. As both of our patients showed an unfavourable progression of disease despite treatment, there is concern that cytomegalovirus infection might be a risk factor for poor prognosis.

Cytomegalovirus-induced end organ disease in previously immunocompetent patients has been reported mostly in critically ill patients. A transient depression in immunity may predispose these patients to cytomegalovirus reactivation.[12] It is not clear weather our observation reflects a causative relation between protein-losing enteropathy and cytomegalovirus infection or just an incidental finding in severely affected patients. Interestingly, we could not demonstrate a sustained improvement from protein-losing enteropathy after eradication in both patients. A possible explanation could be that promotion of inflammation is not the only pathophysiologic mechanism but changes in lymphatics occur too.

Conclusion

Cytomegalovirus enteropathy may be common among patients after the Fontan operation who suffer from protein-losing enteropathy. Routine endoscopic workup including polymerase chain reaction of specimens is important to identify affected patients. Further investigations are warranted to investigate extend and impact of cytomegalovirus infection on disease development, progression, and prognosis in this special population.

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Conflict of interest. None.

Ethical standards. For this case report, no ethical clearance or informed consent was obtained because it summarises retrospective data that were exclusively collected for treatment and not for research.

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