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Treatment of Children with Protein – Losing Enteropathy After Fontan and Other Complex Congenital Heart Disease Procedures in Condition with Limited Human and Technical Resources

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ABSTRACT

Background Protein-losing enteropathy (PLE) is a disorder characterized by abnormal and often profound enteric protein loss. It's relatively uncommon complication of Fontan and other complex congenital heart disease (CCHD) procedures. Because of the complexity and rarity of this disease process, the pathogenesis and pathophysiology of protein-losing enteropathy remain poorly understood, and attempts at treatment seldom yield long-term success. **Aim of presentation** is to describe single centre experience in diagnosis, evaluation, management and treatment of children with protein-losing enteropathy after Fontan and other CCHD procedures in the current era and in centre with limited human and technical resources, follows with a comprehensive review of protein-losing enteropathy publications, and concludes with suggestions for prevention and treatment. **Material and methodology** Retrospectively we analyzed patients with CCHD and protein-losing enteropathy in our institution, starting from January 2000 to December 2012. The including criteria were age between two and 17 years, to have a complex congenital heart disease and available complete documentation of cardiac surgery under cardiopulmonary bypass. **Results** Of all patients we evaluated 18 cases with protein-losing enteropathy, aged 6 to 19 years (mean 14± 9); there were three children who had undergone screening procedure for D-transposition, one Tetralogy of Fallot, and remaining 14 patients had undergone Fontan procedures; (anatomic diagnosis are: six with tricuspid atresia, seven with d-transposition, double outlet right ventricle and pulmonary atresia and two with hypoplastic left heart syndrome). The diagnosis of protein-losing enteropathy was made at median age of 5.6 years, ranging from 13 months to 15 years. Diagnosis was made using alpha 1-anti-trypsin as a gold marker in stool. By physical examination in 14 patients edema was found, in three ascites, and six patients had pleural effusion. Laboratory findings at the time of diagnosis are: abnormal enteric protein loss was documented at the time of diagnosis in all 18 patients. At the time of diagnosis all patients receiving some form of anticoagulation, 17 patients receiving other medication: 17 – diuretics and ACE inhibitors, 12 digoxin, 9 antiarrhytmics. Cross-sectional echocardiography was performed for all patients and different abnormalities were registered. In 14 patients also magnetic resonance was performed. Therapeutic approach was based on the non-specific medication (diet, diuretics, digoxin, ACE inhibitors, and anticoagulants), heparin and corticosteroids therapy. Long-term response to this type of therapy was registered in three patients. Nine patients underwent treatment with heparin and corticosteroids and no one experienced long term benefit. Despite of needs for catheter therapy or surgical intervention in our study, in the absent of technical and human resources now any one had underwent those procedures. Six patients has been transferred abroad and in five of them surgical intervention was perform. **Conclusion** Protein-losing enteropathy remains a devastating complication of Fontan procedure and despite in advantages in surgical and medical therapy there is no evidence that protein-losing enteropathy is less common in the current area.

Key words tricuspid atresia, Fontan procedures, protein-losing enteropathy, complex congenital heart disease

1. BACKGROUND

The serum protein level reflects the balance between protein synthesis, metabolism, and protein loss. Protein-losing enteropathy is a disorder characterized by abnormal and often profound enteric protein loss from the digestive tract or the inability of the digestive tract to absorb proteins. (1) It is not a single disease, but an atypical manifestation of other diseases caused from bacterial or parasite infection, celiac sprue, Crohn's disease, lymphoma, HIV infection or after surgical correction of the complex congenital heart disease (CCHD). Symptoms depend on the underlying disease that is causing the

protein-losing enteropathy. (2) Its relatively uncommon complication of Fontan and other CCHD procedures. Because of the complexity and rarity of this disease process, the pathogenesis and pathophysiology of protein-losing enteropathy remain poorly understood, and attempts at treatment seldom yield long-term success. As such, the signs and symptoms of protein-losing enteropathy are diverse and may be protean. For practical purposes, the disease processes that cause protein-losing enteropathy can be grouped into the following 3 major categories: a) lymphatic obstruction; b) mucosal erosion or ulceration, and c) epithelial cell dysfunction in the absence of macroscopic compromise. Although observations of protein losing enteropathy in the Fontan syndrome have been made for ten years and the presence of this condition in these patients carries a high mortality rate, its pathophysiology in this setting has still not been elucidated. Numerous publications have provided data to support various hypotheses including early elevations of postoperative central venous pressure, low pulmonary vascular compliance, and elevated serum hepatocyte growth factor. (3, 4)

History In 1949, Albright et al demonstrated an increase in protein turnover in patients with protein-losing enteropathy. In 1958, Citrin et al were the first to use radio labeled tracers to demonstrate the actual loss of a protein-containing fluid into the GI tract. Several additional diagnostic techniques using radio labeled substrates were developed, but a major advance was made when Crossley and Elliot demonstrated that measurement of alpha1-antitrypsin (A1-AT) levels in the stool was a reliable and simple test for protein-losing enteropathy. This approach has identified various conditions that have subclinical protein-losing enteropathy as a component of the disease process.

2. AIM OF PRESENTATION

The aim of presentation is to describe single centre experience in diagnosis, evaluation, management and treatment children with protein-losing enteropathy after Fontan and other CCHD procedures in the current era, follows with a comprehensive review of protein-losing enteropathy publications, and concludes with suggestions for prevention and treatment. In order to confirm the site of protein loss as originating from the intestinal tract, a test called "alpha-1-antitrypsin stool clearance" was performed. This involves the collection of stool over a 24 hour period of time and the drawing of a single blood specimen.

3. MATERIAL AND METHODOLOGY

Retrospectively we analyzed patients with CCHD and protein-losing enteropathy in our institution, starting from January 2000 to December 2012. The including criteria were age between two and 17 years, to have congenital heart disease and available complete documentation of cardiac surgery under cardiopulmonary bypass. Protein-losing enteropathy was defined as hypoalbuminemia and hypoproteinemia with no identifiable mode of protein loss other than the gastrointestinal tract. The diagnosis of protein losing enteropathy is typically made by excluding other causes of protein loss, such as nephrotic syndrome. Endoscopy and barium imaging can be used to localize the cause of the protein loss in the bowel. Faecal excretion of Alpha 1-antitrypsin was used as a marker of protein losing enteropathy.

4. RESULTS

Of all patients we evaluated 18 cases with protein-losing enteropathy, aged 6 to 19 years (mean 14± 9); there were three children who had undergone screening procedure for D-transposition, one Tetralogy of Fallot, and remaining 14 patients had undergone Fontan procedures; (anatomic diagnosis are: six with tricuspid atresia, seven with d-transposition, double outlet right ventricle and pulmonary atresia and two with hypoplastic left heart syndrome). The diagnosis of protein-losing enteropathy was made at median age of 5.6 years, ranging from 13 months to 15 years. Diagnosis was made using alpha 1-antitrypsin as a gold marker in stool. By physical examination in 14 patients edema was found, in three ascites, and six patients had pleural effusion. Laboratory findings at the time of diagnosis are: abnormal enteric protein loss was documented at the time of diagnosis in all 18 patients. At the time of diagnosis all patients receiving some form of anticoagulation, 17 patients receiving other medication: 17 – diuretics and ACE inhibitors, 12 digoxin, 9 antiarrhytmics. Cross-sectional echocardiography was performed for all patients and different abnormalities were registered. In 14 patients also magnetic resonance was performed. Therapeutic approaches for protein-losing enteropathy depend on the underlying etiology. In our study therapeutic approach was based on the non-specific medication (diet, diuretics, digoxin, ACE inhibitors, and anticoagulants) and specific treatment: heparin and corticosteroids therapy. Non-specific medical therapy, using diuretic therapy, digoxin and angiotensin-converting enzyme aimed to decrease central venous pressure and to improve cardiac function. Long-term response to this type of therapy was registered in three patients. Despite of needs for catheter therapy or surgical intervention in our study, in the absent of technical and human resources now any one had underwent those procedures. Six patients has been transferred abroad and in five of them surgical intervention was perform. One patient died during the surgery, where previously surgical correction of tetralgy has been done.

Signs and symptoms A complete dietary history should be obtained to evaluate for possible protein malnutrition, which results in diminished albumin synthesis. Despite strictly defined protein –losing enteropathy being the excessive loss of serum proteins into the gastrointestinal lumen, the simplicity of this definition belies the complexity of the disease process, the manifestations of which are not limited to hypoalbuminemia and secondary clinical phenomena, including hematologic and immunologic abnormalities. (5.6) Non-specific symptoms of dyspnoea or fatigue are common. Some degree of peripheral oedema, ascites, pleural or pericardial effusions are less common. Gastrointestinal findings such are diarrhea, steatorrhoea or melena are relatively uncommon. Uncontrolled protein-losing enteropathy may present

rarely with additional secondary signs of celiacia or malabsorption syndromes. Most commonly, protein-losing enteropathy presents with edema. When analyzing the cause of edema, certain aspects of the history and physical examination should be emphasized. Low serum protein levels can result in the accumulation of fluid outside of the normal vascular spaces and in the abdomen, ankles and shins. (7, 8)

5. DISCUSSION

The diagnosis of PLE is made on the basis of history and data for surgical correction of CCHD, clinical symptoms and laboratory confirmation. Alpha-1-antitrypsin is a protein normally found in the blood and in the stool. If PLE is present, the quantity in the stool increases in relation to the blood sample, indicating that protein loss is originating from the gut. Alpha-1 Antitrypsin or α_1-antitrypsin (A1AT) is a protease inhibitor belonging to the serpin superfamily. It is generally known as serum trypsin inhibitor. It protects tissues from enzymes of inflammatory cells, especially neutrophil elastase, and has a reference range in blood of 1.5 - 3.5 gram/liter.

Protein-losing enteropathy is a poorly understood and enigmatic disease process affecting patients with single ventricle after Fontan operation. In those afflicted, PLE after Fontan operation results in significant morbidity and mortality. The pathophysiology of the disease is unknown; however, a proposed mechanism incorporates a combination of phenomena including: a) altered hemodynamics, specifically low cardiac output; b) increased mesenteric vascular resistance; c) systemic inflammation; and d) altered enterocyte basal membrane glycosaminoglycan make-up.

A paradigm for the clinical management of PLE after Fontan operation is proposed. In the early 1970's, Dr. Francois Fontan developed and formalized an intriguing concept where he felt that if conditions were appropriate, venous blood returning from the body could be channeled to the lungs in a passive fashion without the use of a ventricular pumping chamber. By effectively connecting the veins carrying blood returning from the body (vena cavae) directly to the vessels carrying blood to the lungs (pulmonary arteries), blood circulatory patterns similar to that found in the normal heart could be achieved. The use of a staged surgical approach resulting in the Fontan operation has allowed for the survival of many children with a variety of complex defects, including tricuspid atresia, single left ventricle, and hypoplastic left heart syndrome (HLHS). Protein-losing enteropathy occurs in up to 10% of patients following the modified Fontan procedure and it is a serious complication of a Fontan operation with a very high mortality rate. Further investigation is needed to determine the exact mechanism of the disease and to develop new therapeutic approaches. As the number of survivors after the Fontan operation has increased, protein-losing enteropathy has been noted to occur in some children within a few weeks after the Fontan operation, or years later, in children who are otherwise doing well from a cardiovascular standpoint.

Heparin is thought to possibly have a stabilizing effect on the capillary endothelium, reducing protein leakage into the extra vascular space and gut lumen, although the precise mechanism of action is unknown. Although heparin has been successfully used to treat some patients with protein-losing enteropathy that develops after the Fontan procedure, it is by no means the treatment of choice for all the etiologies of protein-losing enteropathy. (7) Nine patients underwent treatment with heparin and corticosteroids and no one experienced long term benefit. Despite of needs for catheter therapy or surgical intervention in our study, in the absent of technical and human resources now any one had underwent those procedures. Six patients has been transferred abroad and in five of them surgical intervention was perform.

Corticosteroids including budesonide, have been used in patients with protein-losing enteropathy associated with collagen vascular diseases, inflammatory bowel disease, or after Fontan procedure to complex congenital heart disease. In our cohort group 14 children have been treated with Methyl-prednisolon, (2mg/kg) and in 12 children level of Alpha-1-antitrypsin at stool has decreased. Treatment with oral prednisone attenuated the protein loss with subsequent normalization of her serum total protein and albumin levels. Discontinuation of prednisone therapy was associated with relapse, which was again treated successfully with low-dose oral prednisone.

Sporadic case reports have documented the successful use of other agents such as cyclosporine for protein-losing enteropathy. Immunosuppressive drugs should not be used in cases of protein-losing enteropathy secondary to infections. In our study we didn't use any type of immunosuppressive therapy.

Diet

In patients whose protein-losing enteropathy is related to lymphatic pathology, decreasing the lymphatic circulation provides some benefit. This requires dietary limitation of long-chain triglycerides because their absorption from the gut stimulates lymphatic flow. In order to provide adequate energy, medium-chain triglycerides must be added as an alternative source of lipid calories. As described below, fat soluble vitamins must also be supplemented because their absorption is compromised in these patients. (4) All patients from our cohort have undergone dietary limitation of long-chain triglycerides with fat soluble vitamins supplements. Long-term response to this type of therapy was registered in 11 patients.

Treatment with oral prednisone attenuated the protein loss with subsequent normalization of her serum total protein and albumin levels. Discontinuation of prednisone therapy was associated with relapse, which was again treated successfully with low-dose oral prednisone.

6. CONCLUSION

Protein-losing enteropathy remains a devastating complication of Fontan procedure and despite in advantages in surgical and medical therapy there is no evidence that protein-losing enteropathy is less common in the current area. Despite the pathogenesis and pathophysiology of protein-losing enteropathy remaining poorly understood, there is small evidence to implicate lymphatic in-

sufficiency as central to the disease process. All patients diagnosed with or at risk for protein-losing enteropathy require regular evaluation for adequate growth and evidence of fat-soluble vitamin (ADEK) deficiencies.

Recommendation all patients diagnosed with or at risk for protein-losing enteropathy requires regular evaluation for adequate growth and evidence of fat-soluble vitamin (ADEK) deficiencies. Patients who develop protein-losing enteropathy after Fontan procedures represent a particularly vulnerable cohort with a high rate of significant morbidity and mortality. Close follow-up coupled with an aggressive approach to reverse this problem is warranted.

Familiarize the patient and his or parents with the signs of edema and the earliest signs and symptoms of fat-soluble vitamin deficiency, and inform them that increased infections could be secondary to loss of immunoglobulins and/or lymphocytes. An ongoing relationship with the physician and frequent monitoring is essential to minimize morbidity (9).

CONFLICT OF INTEREST: NONE DECLARED

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