Effectiveness of High-dose Spiropranolactone Therapy in a Patient with Recurrent Protein-losing Enteropathy after the Fontan Procedure

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Abstract

Protein-losing enteropathy (PLE) is a rare and life-threatening complication that occurs after the Fontan procedure. We herein report the case of an 11-year-old Japanese boy who developed PLE six times after undergoing the Fontan procedure. High-dose spironolactone therapy has been effective for 2 years. His high level of serum aldosterone decreased to a nearly normal range and spironolactone may have a diuretic and anti-inflammatory potential.

Key words: protein-losing enteropathy, Fontan procedure, spironolactone

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Introduction

Protein-losing enteropathy (PLE) is a rare and life-threatening condition characterized by hypoalbuminemia due to intestinal protein loss. The prevalence of PLE after the Fontan procedure is 13.4%, and the 5-year mortality after its diagnosis is 46% (1). The diagnosis of PLE is based on serum hypoalbuminemia, a high level of fecal α1-antitrypsin, and radiotracer accumulation in the intestine when tested with technetium (Tc)-99m-labeled human serum albumin scintigraphy.

The pathogenesis of PLE is unclear, however, a high central venous pressure (CVP) of the Fontan circulation and infections are thought to be related to its onset. Symptoms include edema, abdominal bloating, diarrhea, and susceptibility to infections caused by protein leakage, such as albumin or immunoglobulin. Recent studies have demonstrated that anti-inflammatory agents, such as steroids (2) like spironolactone (3); intestinal cell membrane permeability stabilizers, such as heparin (4) or calcium (5); and sildenafil (6) or surgical fenestration (7) were effective in reducing the venous pressure against this complication. However, the effect of the aforementioned treatments is restrictive, and a standard treatment method has not yet been established.

Case Report

The patient was an 11-year-old Japanese boy with tricuspid atresia who underwent the Fontan procedure (total cavopulmonary connection) at 2.3 years of age. Although the follow-up catheterization data at 6 years of age revealed that his hemodynamics were well-maintained (superior vena cava mean 12 mmHg, inferior vena cava mean 12 mmHg, right pulmonary artery mean 12 mmHg, left pulmonary artery mean 12 mmHg, and left pulmonary venous wedge pressure mean 7 mmHg), he experienced PLE 4 years after surgery. One month after this catheterization, he developed mumps and subsequent facial and abdominal edema as well as a 1.5 kg weight gain. The result of laboratory investigations was remarkable for hypoalbuminemia, with a serum albumin level of 2.5 g/dL and fecal α1-antitrypsin level of 73.5 mg/dL (normal levels being <15 mg/dL). A computed tomography (CT) scan revealed ascites in the pelvis. Tc-99m-labeled human serum albumin scintigraphy showed tracer accumulation in the right ileum 3 and 6 hours after the injection (Fig. 1). Inflammatory bowel disease was not suspected on colonoscopy. According to these findings, he was diagnosed

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with PLE. After 3 weeks of intravenous heparin therapy (5,000 U/m²/day), the patient’s serum albumin rose to 4.0 g/dL, whereas edema and ascites were absent.

He developed PLE six times during a 3-year period and was treated without success using heparin, steroids, and calcium (Fig. 2). Besides PLE, this patient had idiopathic...
thrombocytopenic purpura at 8, 9, and 10 years of age and was treated with intravenous immunoglobulin (1 g/kg). He also developed epilepsy at 8 years of age, for which he has been taking sodium valproate and levetiracetam.

The patient’s fifth PLE episode occurred at 9 years of age without an apparent trigger. His condition improved by steroid therapy, and he was subsequently discharged; however, his symptoms worsened and he was readmitted 1 week after the initial discharge. His serum aldosterone level was 840 pg/mL at this time (normal levels being 35.4-240 pg/mL).

Although the patient took spironolactone and furosemide (0.5 mg/kg each) since undergoing the Fontan procedure, we tried high-dose spironolactone therapy orally administered at a dose of 4.6 mg/kg/day. The dosage was determined according to a previous report (3). The day after beginning spironolactone, the patient’s urine volume, which had been approximately 1,500 mL/day, reached 3,300 mL, and his edema significantly improved. His serum albumin level on day 11 increased to 3.1 g/dL, and he was discharged. He continues to take high-dose spironolactone, and PLE has not recurred for 2 years. He has not experienced adverse effects, such as gynecomastia or an electrolyte imbalance due to spironolactone. The patient’s serum aldosterone decreased to 286 pg/mL 1 year after his last hospital admission. Two years after starting high-dose spironolactone therapy, right heart catheterization revealed that the patient’s CVP was not elevated (superior vena cava mean 13 mmHg, inferior vena cava mean 13 mmHg, right pulmonary artery mean 13 mmHg, left pulmonary artery mean 13 mmHg, and left pulmonary venous wedge pressure mean 7 mmHg). His daily volume of urine is currently approximately 2,000 mL, and he urinates seven to eight times per day, getting up once at night without disturbance to his daily life. He visits our hospital for a follow-up every 2 months and leads a vigorous school life where he participates in normal athletic and social activities.

**Discussion**

The mechanism of PLE after the Fontan procedure is still under debate. One of the probable causes of PLE is thought to be an elevated right atrial pressure, which may lead to lymphatic obstruction, intestinal congestion, and enteric protein loss (1). Using ultrasonography, Rychik et al. demonstrated that the systolic-to-diastolic wave velocity ratio and resistance index of the superior mesenteric artery were higher in a group with PLE after the Fontan procedure than in a group either without PLE or of normal cardiac function, regardless of the pressure (8). Although the pressure is not high, it is estimated that abnormal systemic hemodynamics cause secondary ischemia of the superior mesenteric artery. In addition, it is probable that infection also plays a role in the development of PLE (9).

Spironolactone is a non-selective aldosterone receptor antagonist. Its primary activity is the reduction of sodium reabsorption and diuretic action. Moreover, spironolactone is related to an anti-inflammatory action. The Randomized Aldactone Evaluation Study (RALES) demonstrated that spironolactone prevents fibrotic changes and reduces death in adult heart failure (10).

The first high-dose spironolactone therapy for PLE was reported by Ringel et al. (3). In our case, this therapy was effective in two ways. First, our patient’s urine volume doubled to 3,300 mL compared with that after the use of furosemide and spironolactone at a lower dosage. Due to this diuretic effect, extra fluid discharge was noted, and the patient developed edema. His daily urine volume was maintained at a sufficient level to obtain the antiedematous composition.

Mizuuchi et al. reported successful diuretic treatment with 2.5 mg/kg/day spironolactone and 2.0 mg/kg/day furosemide for PLE caused by the Fontan procedure in a patient with Noonan syndrome (11). It is thought that there is a dose-dependent effect of spironolactone therapy. Grattan et al. also described a patient with PLE after the Fontan procedure who experienced remission with high-dose spironolactone therapy. This patient was treated with growth hormone, an aldosterone antagonist, due to a short stature (12). The efficacy of selective, competitive vasopressin receptor 2 antagonist (tolvaptan) for PLE was also reported (13), although the authors concomitantly used not only tolvaptan, but also prednisolone.

Moreover, our patient’s elevated serum aldosterone decreased to a nearly normal range after the initiation of spironolactone therapy. We speculate that spironolactone inhibits the intestinal inflammatory cytokine release by aldosterone.

Shimizu et al. performed a jejunal biopsy on a 10-year-old patient with PLE post-Fontan procedure (14). They reported no pathological abnormalities, although the mucosal level of interferon-γ was markedly higher than that in the control. It is known that spironolactone inhibits the release of proinflammatory cytokines, including interferon-γ, in the treatment of rheumatic and juvenile idiopathic arthritis (15). Although we did not measure the serum or mucosal cytokines in our case, these facts suggest that inflammation is related to the onset of PLE and that spironolactone effectively reduces certain cytokines.

The serum aldosterone level of our patient decreased to a normal range as a result of 1-year high-dose spironolactone therapy. In general, aldosterone antagonists decrease the serum aldosterone levels because of a negative feedback mechanism. According to previous reports, spironolactone directly inhibits the synthesis of aldosterone, and this fact suggests that the effect of spironolactone is due to the combined antagonism of the action of mineralocorticoids and the direct inhibition of aldosterone synthesis. Erbler showed that the synthesis of aldosterone in rat’s adrenals was significantly inhibited in the presence of spironolactone in a dose-dependent manner (16). In a primary aldosteronism patient, aldosterone secretion was significantly reduced (though the plasma renin level increased) after 4 months of treatment with spironolactone (17).
Spironolactone is a safe and inexpensive medicine that has been in use for more than four decades. It is suitable for children because there are no severe side effects, such as the failure to thrive, osteoporosis, or diabetes mellitus, which is induced by steroid therapy. John et al. showed that spironolactone treatment was used more frequently (68%) in survivors with PLE among 42 patients at the Mayo Clinic (18). We described the successful management of PLE with spironolactone for this recurrent case and determined that other treatments were ineffective. Spironolactone is recommended not only for initial treatment, but also as a second-line therapy.

The authors state that they have no Conflict of Interest (COI).

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