Octreotide in Hennekam syndrome-associated intestinal lymphangiectasia

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Abstract
A number of disorders have been described to cause protein losing enteropathy (PLE) in children. Primary intestinal lymphangiectasia (PIL) is one mechanism leading to PLE. Few syndromes are associated with PIL; Hennekam syndrome (HS) is one of them. The principal treatment for PIL is a high protein, low fat diet with medium chain triglycerides supplementation. Supportive therapy includes albumin infusion. Few publications have supported the use of octreotide to diminish protein loss and minimize hypoalbuminemia seen in PIL. There are no publications on the treatment of PIL with octreotide in patients with HS. We report two children with HS and PLE in which we used octreotide to decrease intestinal protein loss. In one patient, octreotide increased serum albumin to an acceptable level without further need for albumin infusions. The other patient responded more dramatically with near normal serum albumin levels and cessation of albumin infusions. In achieving a good response to octreotide in both patients, we add to the publications supporting the use of octreotide in PIL and suggest that octreotide should be tried in patients with PIL secondary to HS. To the best of our knowledge, this is the first case report on the use of octreotide in HS-associated PIL.

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Key words: Hennekam syndrome; Lymphangiectasia; Octreotide; Protein losing enteropathy

INTRODUCTION
Protein losing enteropathy (PLE) occurs in a variety of intestinal disorders leading to excessive loss of proteins into the gastrointestinal (GI) tract[1]. There are two different mechanisms through which intestinal protein loss can occur: lymphatic system abnormalities and mucosal injury. Primary intestinal lymphangiectasia (PIL) is a congenital disorder of the lymphatic system resulting in impaired lymphatic drainage. In the intestines, impaired lymphatic drainage leads to excessive protein-rich chyle loss, hypoalbuminemia and peripheral edema. Mucosal edema leads to malabsorption and steatorrhea. The diagnosis of PIL is based on typical endoscopic and/or histological findings plus exclusion of a secondary cause of intestinal lymphangiectasia such as cardiac disease, malignancy or post-abdominal surgical complications[2,3]. A
number of disorders have been described to cause PLE in children. Few syndromes are associated with PIL; Hennekam syndrome (HS) is one of them[9]. HS (OMIM 235510) is an autosomal recessive disorder comprising intestinal lymphangiectasia, severe lymphedema of the limbs, genitalia and face, facial dysmorphism and mental retardation[4]. Several authors have reported additional symptoms of HS. The frequency of HS is uncertain with widespread occurrence of the gene. There is interfamilial variability in the phenotype. HS is characterized by generalized maldevelopment of the lymphatic system. PIL and PLE are reported in most patients[4-6]. Phenotypic abnormalities are due to impaired lymphatic flow resulting from insufficient CCBE1 gene function during lymphangiogenesis. The CCBE1 protein plays a direct role in the formation of lymphatic vessels and venous sprouting[7]. Mutations in the CCBE1 gene have been identified as a cause of HS[6-8]. The principal treatment for PIL is a high protein, low fat diet associated with medium chain triglycerides (MCT) supplementation. Supportive therapy includes albumin infusion and paracentesis, when required. In patients not responding to such therapy, other options, such as octreotide, antiplasmin, tranexamic acid and surgical resection of segmental or localized disease may be a therapeutic option[9,10]. Somatostatin and its synthetic analogue, octreotide, have been used to treat secretory diarrhea and other GI and pancreatic disorders[11]. The mechanism of action of octreotide in diminishing protein loss through the GI tract is still unclear. Both somatostatin and octreotide decrease splanchnic blood flow via splanchnic vasoconstriction. They also decrease intestinal motility, gastric emptying, gallbladder contraction and pancreatic secretion. Octreotide inhibits GI hormone secretion and results in decreased chloride secretion, increased chloride and sodium absorption and decreased water loss. Therefore, octreotide has been used in the treatment of secretory diarrhea associated with Zollinger-Ellison syndrome, acquired immunodeficiency syndrome, graft versus host disease, carcinoid syndrome, and multiple endocrine neoplasia-2A[11]. Octreotide inhibits triglycerides absorption[12]. Little is known about its action on chyle production and pressure regulation in the lymphatic system. Somatostatin inhibits thoracic lymph flow in dogs[13]. Reports of somatostatin and its analogues on reducing lymphatic fluid outflow in both pediatric and adult patients were described in surgically created thoracic duct injuries[14,15]. The most commonly reported adverse reactions in clinical trials following octreotide administration were diarrhea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycemia and constipation. Other commonly reported adverse reactions were pruritus, rash, alopecia, dizziness, localized pain, biliary sludge, thyroid dysfunction, loose stools, vomiting, asthenia, and hypoglycemia. In very rare instances, acute pancreatitis has been reported within the first hours or days of sandostatin treatment. Cardiac adverse effects include bradycardia and less commonly tachycardia[14].

**CASE REPORT**

**Case 1**

A male baby was born at term with a normal birth weight. There were no antenatal or postnatal complications. The infant was born with generalized anasarca and was found to have low serum total protein and serum albumin. There was a history of consanguinity and a family history of a 15-year-old maternal cousin with generalized edema diagnosed to have HS and managed at a different center. The infant was referred to our hospital at the age of 1 mo for evaluation of generalized edema. He had a history of diarrhea, occasional vomiting, abdominal distension and poor feeding. He was not thriving well. There were no symptoms of heart failure. He had normal urine output. Physical examination revealed generalized pitting edema of the lower limbs and non-pitting edema of the hands. There were dysmorphic features manifested as down slanting palpebral fissure, broad nasal bridge, flat stubby nose with midface hypoplasia, long philtrum and hypoplastic low set ears. Chest and cardiovascular examinations were unremarkable. The abdomen was distended and non-tender with ascites and no hepatosplenomegaly. He had scrotal edema. Investigations revealed normal full blood count (FBC), renal function, liver enzymes and liver function. He had low serum total protein (23 g/L), low serum albumin (16 g/L), and low serum immunoglobulin levels (immunoglobulin A of 0.09 g/L, IgG of 0.9 g/L and immunoglobulin M of 0.26 g/L). Urine analysis was negative for protein and 24-h urine protein was low (0.2 g/24 h). Human serum albumin scintigraphy revealed loss of protein into the intestinal tract. An upper GI endoscopy study revealed widespread whitish patches with snowflake appearance seen in the second and third parts of the duodenum. The stomach showed slight gastric wall edema. Histological examination of a biopsy specimen from the duodenum showed marked edema in the lamina propria. There were no dilated lymphatics observed on the examined specimens. Gastric biopsy revealed congestion and edema of the lamina propria. The lack of dilated lymphatics on histological examination of the intestinal biopsies was due to the patchy distribution of lymphangiectasia in the intestinal mucosa. The child was diagnosed with PLE due to PIL. Given the family history of HS, clinical features and dysmorphism, and a biochemical diagnosis of PLE, we suspected a diagnosis of HS. We performed a genetic test for mutation in the CCBE1 gene. He was found to have homozygous mutation c.305G>C (p.Cys102Ser) in the CCBE1 gene which confirmed the diagnosis of HS. He was started on MCT-based formula, a low fat, high protein diet, fat soluble vitamin supplements and intravenous infusion of albumin every few days due to the occurrence of severe pericardial effusion and recurrent ascites. However, his serum albumin continued to be on the low side. Given the severity of hypoalbuminemia and his requirement for frequent albumin infusions, he was started on octreotide subcutaneous (s/c) injections,
which gradually reached 100 μg twice daily. A few weeks later, the patient was discharged home on s/c octreotide injections. Albumin infusion requirement was reduced to once monthly 2 mo after starting octreotide therapy, and subsequently stopped. Total serum protein increased to 49 g/L and serum albumin to 28 g/L. He is now 3 years old, tolerating octreotide with no complications.

Case 2
A term male baby was born to a primi mother with a normal birth weight. There were no antenatal or postnatal complications. The infant was noted to have generalized edema from day 1 of life with low serum total protein and serum albumin. There was a history of consanguinity and 2 maternal cousins were diagnosed with HS (patient in case 1 and his older cousin). He was referred to our hospital at the age of 6 wk. There was no weight gain. There was no history of diarrhea, vomiting or jaundice. He was passing urine normally. There were no signs of heart failure or ascites. Physical examination revealed dysmorphic features in the form of hypertelorism, broad flat nasal bridge and a long hypoplastic philtrum. There was generalized edema, periorbital edema, bilateral non-pitting edema of the upper limbs and bilateral pitting edema of the lower limbs with scrotal edema. There was generalized edema, periorbital edema, bilateral non-pitting edema of the upper limbs and bilateral pitting edema of the lower limbs with scrotal edema. The remainder of the systemic examination was unremarkable.

Investigations revealed normal FBC, renal function, liver enzymes and liver function. He had low serum total protein (26 g/L) and low serum albumin (16 g/L). Urine analysis was negative for proteinuria. Twenty-four hour urine protein was normal. His bone profile revealed rickets with low 1, 25 hydroxyvitamin D and 25 hydroxyvitamin D. Stool alpha 1 antitrypsin was high at 2.34 g/L. Given the family history of HS, clinical features and dysmorphism, and a biochemical diagnosis of PLE, we suspected a diagnosis of HS and performed a genetic test for familial mutation in the CCBE1 gene. He was found to have homozygous mutation c.305G>C (p.Cys102Ser) in the CCBE1 gene using sequence analysis. This confirmed the clinical diagnosis of HS. The patient was managed conservatively with MCT-based formula, fat soluble vitamins, and rickets treatment with frequent albumin infusions and diuretics. Following albumin infusions, his generalized edema improved. The infant was left with genital, periorbital and lower limb non-pitting edema. Serum albumin decreased to very low levels of 12-16 g/L within a few days of albumin infusions. At the age of 8 wk, we started him on octreotide subcutaneous injections of 80 mg twice daily and increased this to 100 mg twice daily at the age of four months. His serum albumin levels increased to 36 g/L. Few months later with no further albumin infusions required. He is now 11 mo old with a good response to octreotide in terms of reducing hypalbuminemia and cessation of albumin infusions with no noted complications to octreotide.

**DISCUSSION**
To date, no publications have supported the use of octreotide to diminish protein loss and minimize hypoalbuminemia seen in PIL. These publications are summarized in Table 1. Most clinical research on the use of octreotide in humans has been limited to adults. One of the first experiences of using octreotide in PIL was by Bac et al[17] in 1995. They reported a patient with PLE due to intestinal lymphangiectasia. The patient was treated with and responded to octreotide with normalization of serum albumin and a decrease in fecal protein loss. Few subsequent case reports have supported this experience[18-20]. The suggested dose of octreotide ranges from 100 μg two or three times a day to 200 μg two times a day or the slow release formulation which can lead to clinical, biochemical and histological improvement[10,18,20]. The first use of somatostatin in pediatric patients was for non-GI conditions such as excessive growth hormone release, hypoglycemia and others[21,22]. Almost all the experience in pediatric patients with PIL is in the form of case reports[13]. In 1998, Ballinger et al[23] reported the use of octreotide in an adolescent with PIL. Enteric protein loss was decreased and serum albumin levels were stabilized with resolution of peripheral edema and cessation of recur-accumulation of recurrent pleural effusions. A recent study of a series of 6 pediatric patients[24] suggested that octreotide might be useful in controlling findings and maintaining serum albumin

Table 1 Cases of intestinal lymphangiectasia treated with octreotide in the literature

| Number of patients | Age of patients | Etiology of PLE | Dose of octreotide | Pre octreotide serum albumin | Post octreotide serum albumin | Ref. |
|-------------------|----------------|----------------|--------------------|-----------------------------|------------------------------|-----|
| 6                 | 0-24 mo        | PIL            | 15-20 μg/kg twice daily | 14-25 g/L                   | Normal in 3/6                | [2] |
| 1                 | 38 yr          | IL             | 100 μg twice daily | 12 g/L                      | Above 40 g/L                 | [17]|
| 1                 | 21 yr          | PIL            | 150 μg twice daily | 22 g/L                      | 39 g/L                       | [18]|
| 1                 | 25 yr          | IL             | Slow release octreotide 20 mg every 4 wk | 20 g/L | 35 g/L | [19]|
| 1                 | 27 yr          | Type 1 IL      | 200 μg twice daily then SR octreotide 30 mg | 19 g/L | NA (graph indicates every 4 wk) | [20]|
| 1                 | 47 yr          | Cirrhosis induced IL | 0.1 mg three times daily | 22 g/L | 28 g/L | [21]|
| 1                 | 17 yr          | PIL            | 200 μg twice daily | 15 g/L | 22-26 g/L | [24]|
| 2                 | 2-12 mo        | HS associated IL | 100 μg twice daily | 16 g/L | 28-36 g/L | Current report |

IL: Intestinal lymphangiectasia; PLE: Protein losing enteropathy; PIL: Primary intestinal lymphangiectasia; SR: Slow release; NA: Not available; HS: Hennekam syndrome.
at normal levels. Serum albumin level was maintained at normal levels in 3 patients. The requirement for albumin infusions decreased in all 6 patients. This study concluded that octreotide should be considered in the long-term treatment of PIL when other options are ineffective. They also suggested weighing the benefits of octreotide against the risk of adverse effects.

Pediatric case reports have shown that octreotide decreases stool output in a variety of cases.[25-27] In these case reports, there was no standardization of dose or duration of octreotide use to achieve the required effect. The specific use of octreotide in diarrhea secondary to chemotherapy,[28-30] GVHD[31,32] and immunodeficiency[33] has been reported in adults. Despite this, there are reports on the failure of octreotide to diminish stool output in a variety of cases.[34,35] In one case report, octreotide failed to induce a clinical response and a study performed on an established guinea pig showed that octreotide did not alter lymphatic function.[36]

We report 2 children who were genetically diagnosed as having HS and associated PIL with PLE, who suffered from generalized mixed edema secondary to hypoalbuminemia and lymphangiectasia. By using octreotide in both patients, we eliminated the need for albumin infusions with resolution of pericardial effusion and ascites in one patient. The other younger patient's serum albumin increased dramatically to a normal level with reduced effect on the lymphatics in HS compared to PLE. This was attributed to lymphangiectasia and a probable reduced effect on the lymphatics in HS compared to PLE. To the best of our knowledge, this is the first case report on the use of octreotide to diminish stool in HS-associated PIL. The lack of clinical data based on randomized trials in the pediatric population makes it difficult to confirm a positive effect of octreotide on PIL and PLE from the literature. There is a need for multicenter pediatric trials in this regard.

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