

Clinical practice

Protein-losing enteropathy in children

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Abstract Protein-losing enteropathy (PLE) is a rare complication of a variety of intestinal disorders characterized by an excessive loss of proteins into the gastrointestinal tract due to impaired integrity of the mucosa. The clinical presentation of patients with PLE is highly variable, depending upon the underlying cause, but mainly consists of edema due to hypoproteinemia. While considering PLE, other causes of hypoproteinemia such as malnutrition, impaired synthesis, or protein loss through other organs like the kidney, liver, or skin, have to be excluded. The disorders causing PLE can be divided into those due to protein loss from intestinal lymphatics, like primary intestinal lymphangiectasia or congenital heart disease and those with protein loss due to an inflamed or abnormal mucosal surface. The diagnosis is confirmed by increased fecal concentrations of alpha-1-antitrypsin. After PLE is diagnosed, the underlying cause should be identified by stool cultures, serologic evaluation, cardiac screening, or radiographic imaging. Treatment of PLE consists of nutrition state maintenance by using a high protein diet with supplement of fat-soluble vitamins. In patients with lymphangiectasia, a low fat with medium chain triglycerides (MCT) diet should be prescribed. Besides dietary adjustments, appropriate treatment for the underlying etiology is necessary and supportive care to avoid complications of edema. PLE is a

rare complication of various diseases, mostly gastrointestinal or cardiac conditions that result into loss of proteins in the gastrointestinal tract. Prognosis depends upon the severity and treatment options of the underlying disease.

Keywords Protein-losing enteropathy · Hypoalbuminemia · Intestinal lymphangiectasia

Introduction

Protein-losing enteropathy (PLE) is a rare condition characterized by protein loss through the gastrointestinal tract, leading to reduced serum protein levels. Incidence and prevalence are unknown. Hypoproteinemia might be complicated by edema, ascites, pleural, and cardiac effusions. It can be caused by different disorders, with protein leakage through either mucosal injury, for example in inflammatory bowel diseases (IBD) and neoplasms, or through abnormalities of the lymphatic system, as in primary intestinal lymphangiectasia (PIL), congestive heart failure, or after Fontan procedure [11, 19, 22, 29]. Treatment of these underlying causes is the most desirable therapy. Therefore, every effort must be made to establish a diagnosis in a patient presenting with PLE.

Pathogenesis

PLE is not a single disease but a complication of a variety of intestinal disorders, in which the membranes lining the gastro-intestinal tract fail to hold back the proteins of tissue fluids. Although enteropathy is defined as an intestinal disease, the term PLE is more liberally used including loss from the esophagus and stomach as well. The serum protein level reflects the balance between synthesis, metabolism

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and loss. PLE is characterized by increased protein loss into the gastrointestinal tract compared to synthesis. The most affected protein is albumin, because of its slow turnover rate in steady state and therefore hypoproteinemia in PLE is usually detected as hypoalbuminemia. In order to diagnose PLE, other possible causes of hypoalbuminemia as stated in Table 1 have to be excluded.

Albumin is a water-soluble molecule that maintains plasma oncotic pressure and functions as a transport protein for hormones, fatty acids, ions, and bilirubin. In the steady state situation, the total amount of albumin broken down daily (6–10%) is equal to the amount synthesized [23, 31]. In healthy individuals, protein loss through the gut does not significantly contribute to the albumin catabolism. Enteric loss of albumin is only 10% of the normal turnover; but in patients with PLE, the enteric albumin loss can be increased up to 60% [27]. In these patients, the albumin synthesis is increased with 24%. The serum albumin levels remain low due to excessive losses. This suggests that although synthesis is expanded, the liver is not able to compensate completely for the extreme losses [31]. Not only albumin, but also other proteins with a slow turn-over rate such as immunoglobulins and ceruloplasmin are affected, this is contrary to levels of proteins with shorter half lives, such as, IgE, clotting factors, pre-albumin, and transferrin, which are almost preserved in the normal range [27].

When to consider PLE

PLE should be considered in patients with hypoalbuminemia and edema in whom other possible causes as stated above have been excluded. The clinical manifestations are determined by the underlying disorder. These will be discussed in the chapter “causes”.

Main laboratory findings are reduced serum concentration of albumin, gammaglobulins, and ceruloplasmin. Diminished oncotic pressure due to hypoalbuminemia may lead not only

to edema, but also to ascites and pleural or pericardial effusions. PLE can also be associated with fat malabsorption and deficiencies of fat-soluble vitamins due to small bowel involvement.

Causes of PLE

There are two different mechanisms through which an increase in intestinal plasma protein loss can occur: (1) abnormalities of the lymphatic system, resulting in leakage of protein-rich lymph and (2) mucosal injury, with increased mucosal permeability (Table 2).

Abnormality of the lymphatic system

Intestinal lymphangiectasia is an uncommon disorder and an important cause of protein-losing enteropathy. It was first reported in 1961 by Waldmann et al. [29]. The major symptoms were edema and hypoproteinemia, low serum albumin and gammaglobulin levels. Biopsies of the small intestine showed variable degrees of dilatation of lymph vessels in the mucosa and submucosa. The authors introduced the term “intestinal lymphangiectasia” for this condition.

Intestinal lymphangiectasia is characterized by diffuse or local dilatation of the enteric lymphatics, which can be located in the mucosa, submucosa, or subserosa. Because of stasis and eventually rupture of the lymph vessels, lymphatic fluid, rich in albumin and other proteins, leaks into the gastrointestinal tract [22]. Besides excessive protein loss, there is also malabsorption of both chylomicrons and fat-soluble vitamins. These structural lymphatic abnormalities can occur as congenital malformation, called PIL, or as acquired defects, secondary to other diseases.

PIL is generally diagnosed before 3 years of age, equally affecting boys and girls. The prevalence of PIL is unknown. Patients with PIL often present with pitting limb edema and gastrointestinal symptoms like intermittent diarrhea, nausea, or vomiting. Other major features are lymphopenia, hypoalbuminemia, and hypogammaglobulinaemia due to lymph leakage from the ruptured lymph vessels.

In secondary lymphangiectasia, the dilatation of the lymphatics is caused by obstruction of the vessels or an elevated lymph pressure, secondary to elevated venous pressure. Obstruction can be seen in patients with IBD, sarcoidosis, or lymphoma, whereas elevated lymph pressure is present in patients with congestive heart failure or constrictive pericarditis [9]. Syndromes that are also associated with intestinal lymphangiectasia include von Recklinghausen, Turner, Noonan, Klippel-Trenaunay, and Hennekam. Another group of patients, in which secondary lymphangiectasia is observed, are patients who have

Table 1 Causes of hypoalbuminemia

Causes of hypoalbuminemia	
1. Decreased production	
	Protein malnutrition
	Defective synthesis
2. Increased loss	
	Protein-losing enteropathy
	Nephrotic syndrome
	Excessive burns
3. Redistribution	
	Inflammation of vasculature (e.g., sepsis)
	Hemodilution

Table 2 Causes of protein-losing enteropathy

Mucosal injury
1. Inflammatory and ulcerative diseases
Inflammatory bowel disease: Crohn's disease/ulcerative colitis
Infections
Bacterial: <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Clostridium difficile</i>
Parasitic: <i>Giardia lamblia</i>
Viral: <i>Rotavirus</i>
Gastrointestinal malignancies:
Oesophageal, gastric, colonic adenocarcinomas
Lymphoma
Kaposi's sarcoma
NSAID enteropathy
Graft vs Host disease
Necrotizing enterocolitis
Ulcerative ileitis
2. Non-ulcerative diseases
Hypertrophic gastropathies (Ménétrier's disease)
Eosinophilic gastroenteritis
Food induced enteropathy
Coeliac disease
Tropical sprue
Small intestinal bacterial overgrowth
Vasculitic disorders: SLE, HSP
Lymphatic abnormalities
1. Primary intestinal lymphangiectasia (PIL)
2. Secondary intestinal lymphangiectasia
Obstructive: Crohn, sarcoidosis, lymphoma
Elevated lymph pressure: congestive heart failure, constrictive pericarditis
Syndromal: Turner, Noonan, Hennekam, Klippel-Trenaunay, v.Recklinghausen after Fontan procedure

SLE systemic lupus erythematosus, HSP Henoch Schönlein purpura

undergone a Fontan operation. This is a surgical procedure used in children with complex congenital heart diseases with a single effective ventricle either due to a defect of the heart valves (tricuspid atresia or pulmonary atresia) or underdevelopment of the left side of the heart (hypoplastic left heart syndrome). PLE is an uncommon but life-threatening complication of the Fontan operation that occurs in 4–13% of the patients and associated with a very high mortality and a 5-year survival rate of 46–50% [11, 19]. The pathophysiological mechanism of PLE after Fontan surgery is not completely well understood. Elevated systemic venous pressure and subsequent dilation of lymphatics and protein loss is thought to be an important factor [19]. Ostrow et al. [21] investigated other possible pathophysiological mechanisms of PLE after Fontan surgery and found abnormal abdominal vascular resistance and elevated levels of inflammatory markers. They suggested that diminished flow in the mesenteric artery in combination with elevated venous pressure could lead to impaired mesenteric perfusion, modulation of the intestinal cell membrane, and

protein leakage. The inflammation may additionally result in changes in the endothelial function.

Mucosal injury

Inflammatory and ulcerative diseases

A variety of conditions can cause mucosal erosions, the most common being IBD like Crohn's disease and ulcerative colitis. The mechanism of protein loss is probably related to enhanced leakage of protein-rich fluids across the eroded mucosa. In addition to mucosal cell injury, IBD can also lead to secondary lymphangiectasia, with subsequently leakage of protein-rich lymph through the gut [3]. Although not extensively studied, certain enteric infections can also damage the intestinal mucosal leading to excessive protein loss. These losses can be severe during infections with bacteria-like *Salmonella* and *Shigella* [4], but has also been reported in infections with *Giardia lamblia* [26]. Recently, the rare case of *Rotavirus*

gastroenteritis complicated by protein-losing enteropathy has been reported [15]. In children with hemolytic and uremic syndrome and prodromal diarrhea, significant hypoalbuminemia can also be found [13].

Non-ulcerative diseases

A number of conditions can alter the integrity of the mucosal cell, followed by enhanced permeability and subsequent protein leakage into the lumen. One of the non-ulcerative gastrointestinal disorders in childhood PLE is Ménétrier's disease, also known as giant hypertrophic gastropathy. This rare disorder is characterized by giant rugal folds in the stomach and an increase in intracellular permeability and wider tight junctions between cells that result into protein loss. Patients usually present with non-specific gastrointestinal complaints, such as nausea, vomiting, anorexia, weight loss, and generalized edema. One of the major causes of Ménétrier's disease is the cytomegalovirus; however, an association with *Helicobacter pylori* has also been described [5, 8, 18]. In children, the disease is usually self-limited without recurrence or sequelae, unlike adults in whom the disease is chronic.

In children with milk and soy sensitivity or allergic eosinophilic gastroenteritis (AEG), hypoalbuminemia can be detected. Biopsies taken from the mucosa from these patients shows marked eosinophilic infiltration of the gastrointestinal tissues with increased mast cells. It is suggested that mast cell infiltration is related to increased intestinal permeability and protein loss in patients with AEG [6, 17, 20].

In celiac disease, protein loss is a consequence of loss of villi and surface epithelium, which facilitates the leakage of plasma proteins between the cells.

Excessive protein loss is also associated with vascular disorders like systemic lupus erythematosus (SLE) or Henoch Schönlein Purpura, either at diagnosis or during the course of these diseases. In these disorders, hypoalbuminemia is caused by increased capillary permeability.

How to diagnose PLE

In most patients, the diagnosis will be derived from history, physical examination, and clinical manifestations. However, if necessary, protein-losing enteropathy can be established by the detection of alpha-1-antitrypsin in a stool sample, or with the use of functional imaging.

Alpha-1-antitrypsin

PLE can be detected by increased alpha-1-antitrypsin concentration in a collected stool sample [25]. It is a sensitive marker because alpha-1-antitrypsin is of similar size to albumin (50 kDa), not actively secreted, not absorbed and, with

the exception of the stomach, not degraded. The measurement of alpha-1-antitrypsin clearance requires both a blood sample to determine alpha-1-antitrypsin plasma level and a 24-h stool collection to determine stool volume and stool alpha-1-antitrypsin level. Normal alpha-1-antitrypsin clearance is <24 ml/24 h, this increases to >56 in patients with diarrhea [22]. When alpha-1-antitrypsin clearance is above normal levels, the diagnose PLE can be made. However, the detection of alpha-1 antitrypsin does not show the site of protein loss in the intestine. Furthermore, it will not show a positive result when the stomach is the place of leakage [28].

Functional imaging

An important advantage of functional imaging is the possibility to localize the site of the protein loss. Several radiopharmaceuticals have been used for the detection of protein leakage. In-111-transferin, Tc-99m human immunoglobulin, Tc-99m dextran, Tc-99m human serum albumin (Tc-99m HSA), and Tc-99m methylene diphosphonate (Tc-99m MDP) are some of the more prominent tracers investigated, the latter two being frequently used.

Several studies have reported that Tc-99m HSA is able to diagnose PLE. Halaby et al. [14] showed a positive scan in 12 out of 18 patients with PLE. Chiu et al. [7] reported an increased sensitivity of Tc-99m HSA of 96%, and a specificity of 100% in 26 patients. No adverse reactions to the tracer were described. Functional imaging with Tc-99m serum albumin has been able to identify the region of protein leakage [24, 30].

After PLE has been diagnosed, a search for the underlying cause should be performed. Bacterial, viral, and parasitic stool cultures can be used to search for infectious diseases. Serologic evaluation will reveal immune disorders and ECG or echocardiography might be necessary to determine the cardiac condition. To localize the intestinal area of involvement, radiographic studies like CT or MRI can be used. Endoscopy can detect characteristic mucosal alterations like giant gastric folds in Ménétrier's disease. In patients with suspected lymphangiectasia, a high-fat meal before endoscopy is recommended because this increases enteric lymph flow and elevates lymphatic pressures leading to more prominent lymphatics with increased leakage of lymph into the bowel lumen, seen as white spots on the mucosa (Fig. 1). During endoscopy, biopsies are obtained to confirm histological features. Wireless capsule endoscopy identifies abnormalities of the small intestinal intestine in a non-invasive way without using ionizing radiation. It can safely be performed in children >1.5 years old [12]. The approach to the patient with suspected protein-losing gastroenteropathy is outlined in Figure 2.

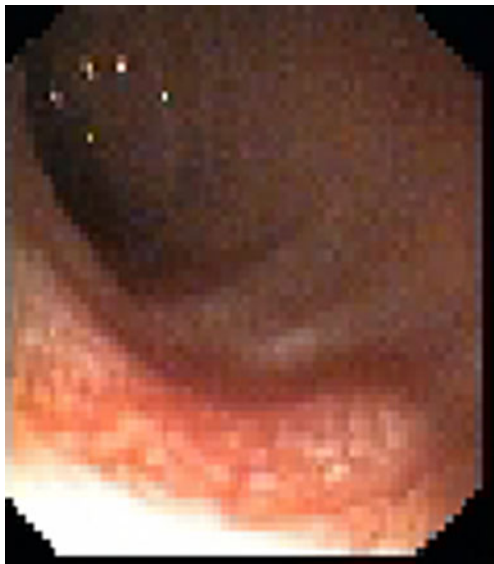


Fig. 1 Endoscopic image of a child with intestinal lymphangiectasia after a high-fat meal showed scattered white spots on the mucosa of the duodenum

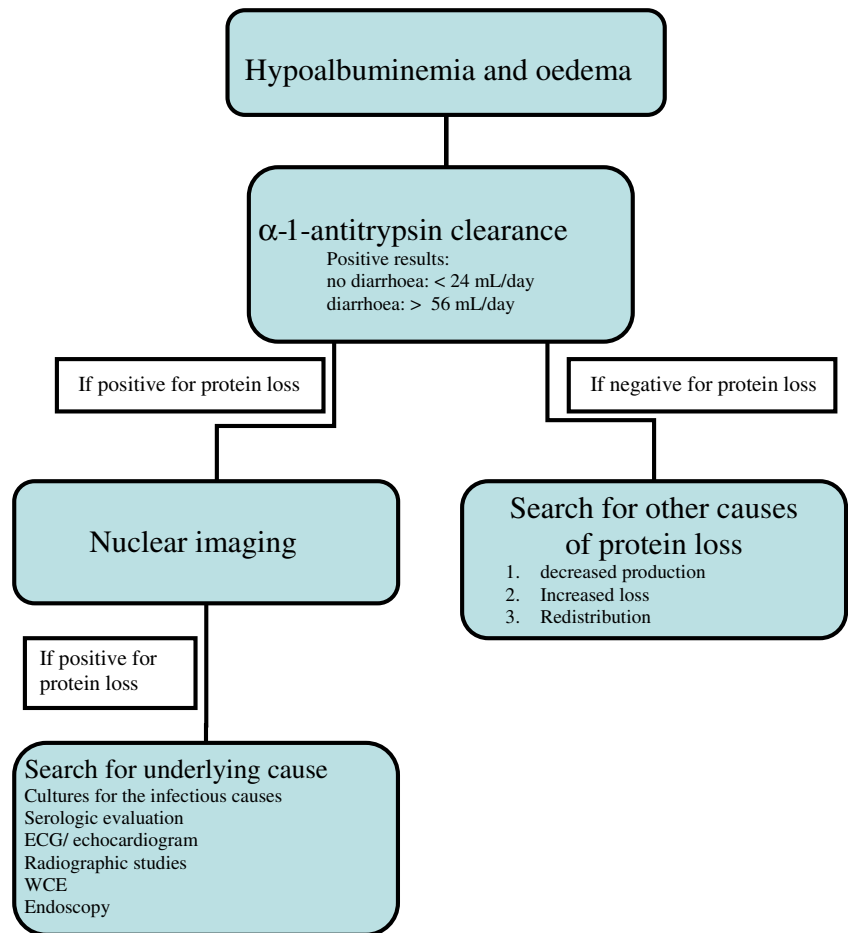
Treatment recommendations

The actual treatment of PLE should consist of maintenance of nutritional status and treatment of the underlying disease.

Maintenance of nutritional status

In all patients with PLE, a high-protein diet is recommended. Normal protein requirements are age dependent, varying between 1.5 g/kg/day for a newborn and 0.66 g/kg/day at the age of 18 years, in PLE this amount may increase to 1.5–3.0 g/kg/day to achieve a positive protein balance [1]. This increased protein intake can be accomplished through dietary changes, but sometimes protein supplements are necessary. Along with the dietary treatment, water-soluble forms of fat-soluble vitamins should be supplemented. In a number of diseases, a specific diet is indicated such as gluten-free diet in celiac disease or hypoallergenic diets in patients with allergic gastroenteropathy.

Fig. 2 Work up in children with hypoalbuminemia and edema



Treatment of PIL consists of lifelong dietary modification with high protein and low fat substituted with MCT. Exclusion of long chain fatty acids (LCT) reduces lymphatic flow and pressure, and thus prevents rupture of malformed lymphatics, while MCT are directly absorbed into the portal venous circulation and bypass the enteric lymphatics. MCT oil should not completely replace all dietary fats, as this would result in a deficiency of essential fatty acids. If a MCT diet is necessary, the essential fatty acids should be included in the regimen [2, 10]. In case of poor response to this treatment, partial or total parenteral nutrition can be considered. To date, few publications have suggested that octreotide treatment in patients with PIL was associated with a decrease in enteral protein loss in clinical improvement. The mechanisms of action of these somatostatin analog remains unclear [10].

Treatment of the underlying disease

In patients with PLE associated with acquired lymphangiectasia, underlying causes should be treated in order to decrease intestinal protein loss. When cardiac diseases cause PLE, protein loss can be improved after surgery or medical treatment. In patients who underwent a Fontan procedure, PLE is sometimes reversible after surgical intervention (Baffle fenestration), or after the use of corticosteroids or heparin [11]. In patients with Ménétrier's disease usually only supportive care is required, but treatment with gangciclovir or, in case of gastric inflammation, H₂ receptor blockers or proton pump inhibitors can be necessary in complicated cases [18]. In Whipple's disease, infections with *H. pylori* or other bacteria, the pathogens should be treated with appropriate antibiotics. When symptoms of inflammatory diseases are present as in IBD, graft-versus-host disease, or SLE, corticosteroids have been demonstrated to improve the course of PLE [16].

When medical treatment of PLE has failed, surgical resection remains an option, especially when protein loss is due to hypertrophic gastritis, inflammatory bowel diseases or neoplasms limited to isolated segments of the bowel. Most other PLEs are too widely distributed for resection [16].

In acute situations infusions of albumin can be used to increase plasma oncotic pressure. Albumin infusions are effective only in the short-term and can be used only as bridging intervention. Supportive care with stockings and limb elevation is very useful to avoid complications from peripheral edema. The skin should be protected and skin infections treated early.

Prognosis

Very little is known about morbidity and mortality of PLE. It depends on the underlying diseases and the availability of

proper treatment. Only in the Fontan studies, as mentioned above, mortality rates are as high as 46% [19].

Conclusion

Protein-losing enteropathy is characterized by loss of proteins into the gastrointestinal tract and develops as a rare complication of various diseases, mostly gastrointestinal or cardiac conditions. The resulting hypoproteinemia can lead to edema, sometimes ascites, and pleural or cardiac effusions. Alpha-1 antitrypsin clearance and scintigraphic techniques are useful tools to measure protein loss and localize the site of protein leakage. Disorders that cause PLE can be identified by clinical history, laboratory tests, and radiographic studies. The prognosis of PLE is unknown and mainly depends upon the underlying disease. Treatment of PLE mainly consists of appropriate treatment of the underlying cause and maintenance of the nutritional state with dietary modification.

Conflict of interest The authors have no financial conflict of interest to report.

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