Protein-Losing Enteropathy

Navroop Nagra

Continuing Education Activity

Protein-losing enteropathy (PLE) is a syndrome where there is an excess loss of proteins in the gastrointestinal tract. It can occur in many clinical conditions. Management of PLE is complex and challenging and requires a team approach. This activity illustrates the etiology, pathogenesis, signs, and symptoms, work up, and also highlights the role of the interprofessional team in the diagnosis and management of protein-losing enteropathy.

Objectives:

Identify the etiology of protein-losing enteropathy.

Explain the expected history, physical, and evaluation of protein-losing enteropathy.

Outline the treatment and management options available for protein-losing enteropathy.

Review the importance of improving care coordination among interprofessional team members to improve outcomes in a patient having protein-losing enteropathy.

Access free multiple choice questions on this topic.

Introduction

Protein-losing enteropathy (PLE) is a condition in which excess loss of proteins occurs through the gastrointestinal tract due to different etiologies. It should be suspected in patients with low serum proteins and in whom other causes of hypoproteinemia have been ruled out.[1]

Etiology

The three main groups of disorders that cause excess protein loss in stools are:

Primary Erosive/Ulcerative gastrointestinal Disorders

This group of conditions includes inflammatory bowel diseases (both ulcerative colitis and Crohn disease), gastrointestinal malignancies, any erosions or ulcers of stomach or duodenum, *Clostridium difficile* colitis, carcinoid syndrome, graft vs. host disease.

2. Non-Erosive/Non-Ulcerative Gastrointestinal Disorders

This group includes topical Sprue, celiac disease, Menetrier disease, amyloidosis, cutaneous burns, eosinophilic gastroenteritis, bacterial overgrowth, Intestinal parasitic infections, Whipple disease, collagenous colitis, AIDS, mixed connective tissue diseases, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA).[2][3]

3. Disorders Causing Increased Interstitial Pressure or Lymphatic Obstruction

This grouping can be due to primary intestinal lymphangiectasia, right-sided heart failure, constrictive pericarditis, congenital heart disease, Fontan procedure for single ventricle, cirrhosis with portal hypertension gastropathy, hepatic venous outflow obstruction, mesenteric tuberculosis or sarcoidosis, retroperitoneal fibrosis, lymphoenteric fistula, lymphoma, and thoracic duct obstruction.[4][5][6]

Epidemiology

The incidence and prevalence of protein-losing enteropathy are not known. It can affect people of any age, race, or sex without any specific predilection.

Pathophysiology

This condition occurs when the loss of proteins through the gastrointestinal tract exceeds the synthesis of proteins by the body, leading to hypoproteinemia. Normally most of the proteins entering the gut are degraded into amino acids and are reabsorbed. In conditions causing inflammation and erosions of the gastrointestinal tract, the mucosal permeability increases, leading to excessive leakage of serum proteins into the gut, and poor reabsorption. This state leads to hypoproteinemia. In diseases causing increased lymphatic pressure and lymphatic obstruction, there is an increased leak of lymph into the gastrointestinal tract and decreased absorption of chylomicrons, resulting in a deficiency of fat-soluble vitamins and protein loss.[1]

Histopathology

Histopathology depends on the underlying cause. For example, In protein-losing enteropathy caused by Crohn disease, we can see granulomas and acute and chronic inflammation of the colonic wall. Crypt abscesses, crypt branching, increased lamina propria cellularity, basal plasmacytosis, basal lymphoid aggregates are present in ulcerative colitis. Various other mucosal abnormalities can be seen depending upon the etiology.[7]

History and Physical

The clinical features of protein-losing enteropathy depend on the underlying etiology. Loss of serum proteins leads to decreased oncotic pressure in capillaries, which, in turn, leads to peripheral edema (most common presenting symptom) due to transudation of fluids from capillaries to the subcutaneous tissue. Patients can also present with abdominal distension due to ascites and pleural effusions. In primarily gastrointestinal causes of protein loss, they can have diarrhea, bloating, abdominal pain, etc. This condition can cause loss of immunoglobulins and lymphocytes, which cause immunocompromised state leading to frequent infections, and also patients can get opportunistic infections. Patients with protein loss due to cardiac diseases can present with symptoms of heart failure like pitting edema, pleural effusion, shortness of breath, elevated jugular venous pressure.

Evaluation

Diagnosis of protein-losing enteropathy should be suspected in patients with hypoproteinemia once the other common causes like severe malnutrition, nephrotic syndrome, or chronic liver diseases have been ruled out. Since the protein loss in PLE occurs independent of their molecular weight, these patients have low albumin and low globulins in their serum. If there are isolated low serum albumin and normal serum globulins, then alternative causes should be considered.

Alpha 1 antitrypsin (A1AT) intestinal clearance is the primary and most common test performed to diagnose PLE. This protein has high molecular weight, is minimally degraded in the gut and is excreted intact. Its clearance is calculated by 24 hr stool collection and measuring A1AT in serum and stool.

Alpha 1-antitrypsin clearance = (stool volume) x (stool alpha 1-antitrypsin)/ (serum alpha-1 antitrypsin).

The normal clearance of A1AT is under 13ml/24 hours. Clearance greater than 27 ml/ day indicates increased gastrointestinal protein loss and points towards the diagnosis of PLE. Clearance is affected by diarrhea. Any condition causing diarrhea leads to increased clearance of A1AT, so the higher threshold of more than 56ml/24 hr should be used in these conditions. Increased stomach acidity and decreased ph lead to increased degradation of A1AT, so the performance of this test should be while the patient is on antacids especially if there is suspicion of hypersecretory state causing increased protein loss. Gastrointestinal bleeding can also cause increased clearance of A1AT.

Other tests like 51Cr-labeled albumin clearance(considered gold standard), technetium 99 labeled serum albumin scintigraphy can also be performed if there is high clinical suspicion of PLE with negative A1AT clearance test. These tests have high sensitivity, but they are very cumbersome, expensive and not readily available so not routinely performed.[8]

Once the diagnosis of PLE is established with increased A1AT clearance, further workup is needed to find the underlying etiology and to guide treatment. Important consideration should be given to the history and physical examination of the patient. Detailed history helps in narrowing down the list of conditions causing hypoproteinemia and PLE and guides the approach towards further work up. Basic labs like complete blood count with differential, liver function tests, renal function tests should be performed in all patients. In cases where symptoms suggest gastrointestinal causes of protein loss, tests for celiac disease, infectious work for chronic intestinal infections, appropriate imaging of abdomen and pelvis, upper and lower gastrointestinal endoscopies with biopsies, capsule endoscopies (if upper and lower endoscopies are unremarkable) should be performed. Autoimmune workup should be ordered if SLE or RA is suspected. Echocardiogram and workup on the lines of heart failure should be done if cardiac causes of PLE is suspected. Fontan procedure in patients with congenital heart disease is a well-known cause of PLE and has been extensively studied

Treatment / Management

Treating the underlying pathology is the mainstay of treatment. Besides this, dietary modifications also play a critical role in the management of protein-losing enteropathy. Diet rich in protein and medium chain triglycerides and low in fat is considered the best diet in this condition. Patients may require 2 to 3g/kg/day of protein. Replacement of micronutrients, electrolytes, and vitamin deficiencies should occur as appropriate.

If heart failure is the cause of PLE, then optimization of heart failure medications needs to be done. Diuretics are an option for symptoms of anasarca and fluid overload. Pericardiectomy can help in constrictive pericarditis. Treatment with immunosuppressive medications should be the approach in inflammatory bowel disease, SLE, RA, and other inflammatory conditions. Treat parasitic infections if they are the cause of PLE. Surgical resection can be a consideration in Menetrier disease[9] and refractory inflammatory bowel disease. Octreotide has been considered beneficial in primary intestinal lymphangiectasia and Menetrier disease by decreasing lymphatic pressure and reducing intestinal protein loss. Budesonide and corticosteroids may be helpful in eosinophilic gastroenteritis and some cases of PLE due to Fontan procedure.[10]

Routine monitoring is advisable after initiation of treatment in the form of checking micronutrients and vitamin deficiencies, serum protein levels, and A1AT clearance.

Differential Diagnosis

Any condition that leads to low serum proteins should be in the differential diagnosis of PLE. Differential diagnosis also varies depending on the primary underlying etiology causing PLE. Some common conditions are chronic liver diseases which lead to low serum albumin due to decreased synthesis, renal conditions causing significant proteinuria (like nephrotic syndrome), severe protein-calorie malnutrition, malabsorption syndromes, heart failure, cutaneous burns.[11]

Prognosis

Prognosis is variable and dependant on the underlying cause of protein-losing enteropathy. If there is a successful treatment of the underlying cause, then it can lead to complete resolution of PLE.

Complications

Complications depend mostly on the underlying disease causing protein-losing enteropathy. Patients with Inflammatory bowel disease can develop colon cancer, anemia, primary sclerosing cholangitis, and many other complications. PLE due to ulcerative diseases can have a perforation of ulcer and peritonitis. Patients with *Clostridium difficile* colitis can develop toxic megacolon. Patients can develop a deficiency of micronutrients and vitamins (particularly fat-soluble vitamins). Due to the loss of immunoglobulins and lymphocytes, patients get prone to recurrent and opportunistic infections.

Consultations

If the clinician suspects protein-losing enteropathy in any patient consultation with a gastroenterologist should be done as the first step to start the work up. Once the diagnosis is confirmed, then further consultations can be done depending on the underlying cause. If a heart condition is the primary cause of PLE, then the patient should be referred to a cardiologist for optimization of heart failure and other cardiac causes. If the workup reveals malignancy, then referral to oncologist should be made.

Deterrence and Patient Education

Protein-losing enteropathy is a pathological condition in which there is an increased loss of proteins through the gastrointestinal tract, which leads to low serum proteins. Most patients present with peripheral edema. Many diseases can lead to PLE. Appropriate consultants should be seen depending on the primary cause. The prognosis depends on the underlying condition causing PLE.

Pearls and Other Issues

Treatment of underlying cause is the best treatment for protein-losing enteropathy. There is an equal loss of albumin and globulin in this condition. It can leads to immunodeficiency due to the loss of immunoglobulins and lymphocytes and make the patients prone to opportunistic infections. A1AT clearance if the primary test used for diagnosis of PLE.

Enhancing Healthcare Team Outcomes

The management of this condition requires an interprofessional approach team approach, including physicians, specialists, specialty-trained nurses, dieticians, and pharmacists, all collaborating across disciplines to achieve optimal patient results. [Level V] Consultation to gastroenterology, cardiology, hematology/oncology, nurse practitioner, and nephrology needs to be done depending on the primary disease-causing PLE. Diet modification also plays a vital role in management, so a consultation with a nutritionist should be a consideration. Management requires individualization to each patient. PLE carries a favorable prognosis with successful resolution of the underlying condition.

Review Questions

References

1. Craven MD, Washabau RJ. Comparative pathophysiology and management of protein-losing enteropathy. J Vet Intern Med. 2019 Mar;33(2):383-402. [PMC free article: PMC6430879] [PubMed: 30762910]

2. Zubiaga Toro L, Ruiz-Tovar J, Castro MJ, Ortiz de Solórzano FJ, Luque de León E,

Jiménez JM, Carbajo MÁ. Whipple disease after bariatric surgery: from malabsorption to malnutrition status. Nutr Hosp. 2019 Mar 07;36(1):238-241. [PubMed: 30834767]

3. Akkelle BS, Tutar E, Sengul OK, Celikel CA, Ertem D. A Rare Complication of Giardiasis in Children: Protein-losing Enteropathy. Pediatr Infect Dis J. 2018 Dec;37(12):e345-e347. [PubMed: 30408010]

4. Miranda WR, Borlaug BA, Hagler DJ, Connolly HM, Egbe AC. Haemodynamic profiles in adult Fontan patients: associated haemodynamics and prognosis. Eur J Heart Fail. 2019 Jun;21(6):803-809. [PubMed: 30672076]

5. Schumacher KR, Yu S, Butts R, Castleberry C, Chen S, Edens E, Godown J, Johnson J, Kemna M, Lin K, Lowery R, Simpson K, West S, Wilmot I, Gossett JG. Fontan-associated protein-losing enteropathy and post–heart transplant outcomes: A multicenter study. J Heart Lung Transplant. 2019 Jan;38(1):17-25. [PubMed: 30391195]

6. Melenovsky V, Kubanek M, Kacer P. Protein-losing enteropathy in an adult with non-ischaemic cardiomyopathy: complete reversal by heart transplantation. ESC Heart Fail. 2018 Oct;5(5):842-845. [PMC free article: PMC6165937] [PubMed: 30051970]

7. Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, Ziade N, Hashash JG. A comprehensive review and update on ulcerative colitis. Dis Mon. 2019 Dec;65(12):100851. [PubMed: 30837080]

8. Chau TN, Mok MY, Chan EY, Luk WH, Lai KB, Li FT, Leung VK, Wong R. Evaluation of performance of measurement of faecal α(1)-antitrypsin clearance and technetium-99m human serum albumin scintigraphy in protein-losing enteropathy. Digestion. 2011;84(3):199-206. [PubMed: 21757911]

9. Gompertz M, Montenegro C, Bufadel ME, Defilippi C, Castillo J, Morales C. [Ménétrier disease. Report of one case]. Rev Med Chil. 2012 Sep;140(9):1174-8. [PubMed: 23354640]

10.

John AS, Driscoll DJ, Warnes CA, Phillips SD, Cetta F. The use of oral budesonide in adolescents and adults with protein-losing enteropathy after the Fontan operation. Ann Thorac Surg. 2011 Oct;92(4):1451-6. [PubMed: 21784410]

11. Rieder SC, Huber LC, Trachsler J, Herberger E. [CME: Nephrotic Syndrome in Adults: Presentation, Diagnosis, Therapy]. Praxis (Bern 1994). 2019;108(5):347-355. [PubMed: 30940036]

Disclosure: Navroop Nagra declares no relevant financial relationships with ineligible companies.

Disclosure: Shyam Dang declares no relevant financial relationships with ineligible companies.