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Primary intestinal lymphangiectasia is an uncommon condition that usually presents early in childhood. This incurable condition is consequent to underlying lymphatic abnormalities that lead to loss of lymphatic contents into the intestinal lumen. This article outlines an approach to the assessment of children presenting with characteristic features and consideration of other conditions that could lead to enteric protein loss. An overview of the management of primary intestinal lymphangiectasia is outlined.

Key words: gastroenterology; lymphatic system; nutrition.

Protein-losing enteropathy (PLE) reflects increased enteric protein loss secondary to luminal, hepatic or other systemic diseases. Clinical signs of the condition predominantly reflect the consequences of reduced serum albumin levels, and include peripheral oedema, ascites, pleural or pericardial effusions. PLE can be due to lymphatic dysfunction or loss of protein from the intestinal mucosa and is confirmed by elevated faecal α-1-antitrypsin levels.

Primary intestinal lymphangiectasia (PIL) is the most well characterised cause of lymphatic dysfunction leading to enteric protein loss in children. Patients with PIL typically present with oedema, hypoproteinaemia, hypoalbuminaemia and hypogammaglobulinaemia. PIL generally presents early in childhood: most diagnoses being made before the age of 3 years. However, some individuals can present later in childhood or even as adults.

A number of other conditions can cause secondary intestinal lymphangiectasia (IL): these can be focal or generalised. These include intestinal volvulus, following repair of congenital heart disease, connective tissue disorders, sarcoidosis, inflammatory bowel disease, cancer and chromosomal abnormalities such as Turner Syndrome. Investigations are required to exclude secondary causes of intestinal lymphangiectasia, particularly in those who present later.

This review aims to highlight key aspects of the pathophysiology and management of PIL in children.

Structure and Function of the Human Lymphatic System

The lymphatic system comprises a network of vessels that connect the interstitium, the vascular system, and lymphoid organs such as lymph nodes. Lymphatic channels coalesce to form a one-way systemic network that collects lymph from the extremities and propels it via a succession of individual lymphatic chambers that subsequently empty into the venous circulation. The gastrointestinal (GI) tract has a particularly rich lymphatic supply, with its extensive network paralleling that of the adjacent vascular system. Initial lymphatics are the entry conduit by which interstitial fluid, various cellular components and protein enter the lymphatic system. These non-fenestrated, single-layer endothelial-lined structures allow unidirectional flow of luminal contents towards collecting lymphatics. Collecting lymphatic vessels are distinguished from initial lymphatics by the presence of smooth muscle cells and they comprise functional units known as lymphatic chambers or lymphangiomas.

Lymph nodes, within which adaptive immune responses are initiated, are located along the lymphatic network and are plentiful within the GI tract. The GI mucosa also has additional lymphoid structures that augment host immune responses. Gut-associated lymphoid tissues (GALT) are present in the wall of the GI tract and are comprised of Peyer’s patches and solitary lymphoid follicles. These local systems protect the host by inducing adaptive immune responses and lymphocyte proliferation and differentiation following exposure to luminal antigens.

The lymphatic system has three main functions: the maintenance of fluid homeostasis within tissues, immunological protection against foreign antigens, and the transport and distribution of digested lipids. Lymph consists of a tenth of the fluid that
leaks out of capillary beds and enters initial lymphatics; the remaining 90% is absorbed into the venous circulation. Additionally, intestinal lymphatics also transport macromolecules synthesised within the GI tract as well as nutrients absorbed via the luminal mucosa, particularly chylomicrons. More than half of lymph is formed within the abdominal viscera, which then flows through mesenteric lymphatics before entering the thoracic duct and venous circulation. Lymphatic ‘loading’ of fluid and protein is directly proportional to interstitial fluid volume and solute content. Any disruption to this homeostasis can result in oedema.

The lymphatic system also provides a molecular communication system, and transportation of antigens and their presenting cells. Antigens transported via afferent lymphatics and sequestered in lymphoid structures elicit immunological responses via activation of naïve T and B lymphocytes. Upon leaving the lymph nodes these activated cells re-enter the systemic circulation and defend against foreign antigens.

The lymphatic system within the GI tract plays a crucial role in the absorption of lipids, especially long-chain triglycerides (LCT). Intraluminal digestion of LCT involves emulsification by bile salts, enzymatic hydrolysis by lipase, and reconfiguration into chylomicrons. Chylomicrons then enter the lymphatic system via lacteals. The concentration of lipids within lymph, and its flow through intestinal lymphatics, correlates with dietary lipid intake.

A recent study delineated the importance of calcitonin receptor-like receptor (Calcrl) in lymphatic function. Deletion of this receptor in lymphatic tissues resulted in intestinal lymphangiectasia, characterised by PLE and dilated lacteals with consequent inability to absorb lipids. In addition, Calcrl/adrenomedullin signalling was identified as an upstream regulator of the Notch pathway, previously identified to be important in intestinal lacteal maintenance and junctional integrity. Further, integrity of lacteals is essential for the structural and functional maintenance of intestinal villi, underlining the pathophysiological relevance of these processes.

**Clinical Presentation of PIL**

PIL most frequently develops early in childhood. However, presentation has been described in adolescence, and rarely, in adulthood. PIL can present with peripheral oedema, ascites, GI symptoms and impaired growth. Investigations typically show immunological deficiencies, lymphopenia and hypoalbuminaemia. The condition is characterised by the presence of abnormally dilated, distorted and obstructed lymphatic vasculature. Increased hydrostatic pressure within the GI lymphatic system leads to reversal of lymph flow, resulting in the rupture of intestinal lacteals with consequent leakage of their contents into the lumen of the GI tract.

**Diagnosis of PIL**

In a child with suggestive symptoms, initial testing would typically reveal hypoalbuminemia, lymphopenia and hypogammaglobulinemia. Serum levels of fat-soluble vitamins may also be low and should therefore be checked. Severe vitamin D deficiency leading to rickets or hypocalcaemia has been described as a presenting feature of PIL. Elevated faecal levels of α-1-antitrypsin are reflective of increased protein loss from the small or large intestine. Secondary causes of intestinal lymphangiectasia should be excluded, depending on the clinical scenario.

Definitive diagnosis can be obtained by histological assessment of mucosal biopsies obtained endoscopically from the duodenum. Capsule endoscopy and double-balloon enteroscopy (enabling more extensive inspection of the small bowel) have also been employed for diagnosis. The typical endoscopic appearance of lymphangiectasia is of multiple white-tipped villi in the duodenum resembling snowflakes. The administration of a fat-rich meal, for instance a meal containing full cream, prior to fasting, can enhance the appearance of the villi. Dilated lacteals would typically be seen on histological examination of small bowel biopsies.

The enteroscopic appearance in individuals with PIL may have prognostic relevance. One group has shown that six patients with non-white tipped villi had lower serum albumin, higher stool α-1-antitrypsin levels, higher immunoglobulin A and M, but better response to corticosteroids compared to eight individuals with white tipped villi.

Other than endoscopic and histologic findings, imaging may also have a role. For instance, intestinal technetium-dextran lymphoscintigraphy to specify the location of intestinal protein loss was described many years ago.

**Management of Primary Intestinal Lymphangiectasia**

Currently, PIL is incurable. In secondary IL, however, the lymphatic dysfunction may be resolved by appropriate management of the underlying cause. Surgical management may be curative in mechanical causes, such as volvulus. Optimal management of other conditions, such as sarcoidosis, may improve or resolve the concurrent lymphatic dysfunction. In addition, the management options considered for PIL, especially nutritional interventions, can also be considered for secondary causes.

There are three main components to the management of PIL: nutritional, medical and surgical. Nutritional treatments are based on our understanding of the underlying pathophysiology. The other interventions are supported by data from case reports and series, with no published randomised controlled data. Successful management of intestinal lymphangiectasia does require a multidisciplinary approach, including a paediatric gastroenterologist, an experienced paediatric diettitian, a coordinating nurse and psychological support.

**Nutritional intervention in PIL**

As noted, LCT absorption is an important aspect of lymphatic function (reviewed in references 25–28). Consequently, the first line of management of PIL comprises the restriction of dietary LCT and the concomitant use of medium chain triglyceride (MCT)-predominant formulae or supplements. Together these changes reduce intestinal lymph flow and result in less intestinal losses. The absorption of MCT via the portal venous system (bypassing the intestinal lymphatics) provides adequate dietary fat and calories. As the complete exclusion of LCT also reduces intake of essential fatty acids, these may need to be supplemented (e.g. by the use of walnut oil).
Complete restriction of LCT is very difficult to achieve as small amounts of LCT are present in many foods. In addition, maintenance of rigorous restrictions is hard to maintain, requiring first acceptance on the part of the patient and parent, and then ongoing diligent adherence. Consequently, comprehensive education, training and ongoing support from an experienced dietitian is essential.

MCT can be provided within particular enteral formula products that have high proportions of this fat. Liquid MCT products can be added to supplement dietary intake and can also be used instead of fat in cooking. Fat-soluble vitamin measurement and supplementation is required in almost all instances.

Monitoring of outcomes of nutritional interventions

The outcome of these dietary interventions should be delineated and monitored with regular and ongoing review of symptoms, physical examination (e.g. extent of oedema), anthropometry and serial measurement of albumin, immunoglobulin (Ig) G and fat-soluble vitamins. Successful management of PIL should lead to normal levels of serum albumin and IgG, resolution of peripheral oedema (or other clinical findings), resolution of diarrhoea (or other symptoms) and resumption of expected growth.

Measurement of faecal α₁-antitrypsin provides an additional assessment of the response to dietary interventions. Treatment should lead to reduced losses, but commonly does not lead to complete normalisation.

Short- and medium-term improvements with nutritional management alone have been documented in a number of cases series. One such report outlined the impact of nutritional intervention in six children with PIL over treatment periods of up to 8 years. Dietary intervention in these children led to improved gut symptoms and normal growth patterns. However, symptoms recurred upon reduced adherence to strict dietary changes. Interestingly, although clinical and growth parameters improved satisfactorily, the children continued to have elevated faecal α₁-antitrypsin levels, further indicating that the intervention was not curative.

More recently, the impact of diet was assessed in a combined group of 38 children with PIL. Overall, benefits were noted in 24 (63%) of the 38 cases reviewed, with reduced benefit noted in the adult patients.

In the setting of incomplete or unsatisfactory response to initial dietary changes, a further option is to institute complete gut rest with delivery of all nutrition parenterally. While this enables further reduction in lymphatic losses, the provision of parenteral nutrition requires ongoing intravenous access (with associated potential complications), prolonged hospitalisation to facilitate training of the patient and family and large cost implications. Furthermore, this approach requires total adherence and significant social implications.

Intravenous administration of albumin and immunoglobulin

Hypoalbuminaemia can be corrected by the administration of intravenous albumin (in conjunction with frusemide). This should be based on clinical indications (such as significantly increased ascites) rather than just upon correction above a certain threshold. A single infusion of albumin would be expected to lead to transient improvement of the albumin level and will likely need to repeated periodically.

Whilst hypogammaglobulinaemia can also be partially corrected by the administration of intravenous immunoglobulin, this should only be considered in the setting of recurrent infections, as outlined in several case reports. One such report described the benefits of subcutaneous intravenous immunoglobulin in one individual with PIL with ongoing severe hypogammaglobulinaemia.

Pharmacological options for the management of PIL

Octreotide

Octreotide, a long-acting analogue of somatostatin, has been shown to be helpful in some cases of PIL. The short- and longer-term response rates to octreotide have not been described. Furthermore, the precise mode of action of octreotide in the setting of PIL has not been defined: indeed, one group demonstrated that octreotide had no effect on lymphatic function in an animal model.

Corticosteroids

Some individuals with PIL have had positive benefit with oral corticosteroids (prednisone or budesonide). The main rationale for corticosteroids is due to their putative role in enteric protein losses in inflammatory conditions.

Anti-plasmin

Anti-plasmin therapy has been shown to be helpful in two individuals with PIL. The administration of tranexamic acid in an adolescent girl with PIL resistant to dietary changes and octreotide resulted in increased albumin levels and fewer episodes of GI bleeding. Tranexamic acid also lead to significant improvements in a young adult with PIL. In this case, tranexamic acid was used after diet, octreotide and selective embolization had been tried unsuccessfully. The long-term benefits of tranexamic acid in these two cases was not clear. In addition, there are no other reports of this therapy.

Heparin

Various reports have shown reduced expression of heparin on the basolateral aspects of epithelial cells in the setting of secondary lymphangiectasia and demonstrated that supplementary heparin abrogated protein leak in vitro models. A small number of reports suggest that low dose heparin may be efficacious, particularly in secondary IL.

Rapamycin and Everolimus

These two inhibitors of the kinase mammalian target of rapamycin have been demonstrated to be beneficial in PIL in two discrete cases. The introduction of everolimus in a 12-year child with refractory PIL resulted in resolution of diarrhoea and reduced enteric protein losses. These improvements persisted over a 12-month period of treatment. Another case report outlined significant and prompt improvements in gut symptoms and enteric protein losses following the use of rapamycin in a child with concurrent tuberous sclerosis.
A recent animal study provides some rationale for the use of these drugs. Rapamycin led to a reduction in lymphangiectasia in a neonatal mouse model of widespread airway lymphangiectasia, mediated by inhibition of mammalian target of rapamycin.60

**Other medical interventions**

In two separate cases, chemotherapy has been shown to result in long-term resolution of PIL. Both cases involved individuals with non-Hodgkin’s lymphoma.61,62 Chemotherapy for the non-Hodgkin’s lymphoma in both cases resulted in ongoing resolution of enteric protein losses. The mechanism of these outcomes has not been elucidated.

**Surgery**

Intestinal resection has been described in some individuals with medically-tractable PIL.63–66 As this appears to have been most useful in cases with restricted intestinal involvement rather than those with extensive or generalised changes, the role of surgical intervention is unclear. Further, the long-term outcomes of a limited resection are unclear.

**Intestinal Lymphatic Hypoplasia**

Intestinal lymphatic hypoplasia, characterised by the absence or marked reduction in intestinal lymphatics, can resemble PIL, but lymphopenia is not typically present.67,68 The advent of D2-40 antibody, which binds a sialoglycoprotein present on human lymphatic endothelium, has enabled the characterisation of this condition.67,68 Among the patients included in an Australian cohort, the extent and severity of lymphatic hypoplasia varied, with some correlation to the severity of the clinical features.67 The approach and management concepts for this entity are generally similar to those described for PIL.

**Conclusion**

PIL is a rare condition that mainly presents in early childhood. Multiple investigations are required to confirm the diagnosis and to characterise the impact of the condition. Although there is no high-level evidence to support specific therapies, the management involves nutritional interventions with consideration of other supportive and therapeutic interventions.

**References**


7 Casley-Smith JR. The role of the endothelial intercellular junctions in the functioning of the initial lymphatics. Angiologica 1972; 9: 106–31.


10 Davis RB, Kechele DO, Blakeney ES, Pawlak JB, Caron KM. Lymphatic deletion of calcitonin receptor-like receptor exacerbates intestinal inflammation. JCI Insight 2017; 2: e92465.


