Review

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# Hypocalcaemic tetany linked to vitamin D deficiency and hypomagnesemia in primary intestinal lymphangiectasia: a literature review

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**Abstract**

Primary intestinal lymphangiectasia (PIL) is a rare disorder in children causing protein-losing enteropathy. Vitamin D deficiency and hypomagnesemia contributed to the tetany. The literature review reflects the importance of screening for these deficiencies and regular serum magnesium monitoring in PIL cases with neuromuscular or ionic abnormalities.

**Keywords:** hypomagnesemia, primary intestinal lymphangiectasia, tetany, vitamin D deficiency

## Introduction

Intestinal lymphangiectasia (IL) also known as Waldmann's disease[1] is a rare disorder responsible for protein-losing enteropathy[2]. It is characterized by focal or diffuse dilatation of bowel lymphatics[2–4] in the lamina propria region of the villi, often extending into the submucosa[5]. The global prevalence and incidence of primary intestinal lymphangiectasia (PIL) are still unknown[3,6,7]. It was first reported by Waldmann et al. in 1961[6]. Since then, fewer than 200 cases of PIL have been documented in children worldwide[6,7]. Intestinal lymphangiectasia can be either primary or secondary depending upon underlying aetiology. PIL is a congenital disorder of the mesenteric lymphatics that leads to lymph obstruction and leakage in the intestine[2,8]. Leakage of lymph into the intestinal lumen leads to hypoproteinemia, lymphocytopenia, and hypogammaglobulinemia affecting the body's immune response[9]. In contrast, secondary intestinal lymphangiectasia (SIL) usually occurs in adults[10] because of increased pressure within the enteric lymphatics due to the diseases like constrictive pericarditis, lymphoma, sarcoidosis, systemic lupus erythematosus, scleroderma, inflammatory bowel disease, malignancies, or cardiac surgery[2,8]. So, it is important to rule out secondary disorders before diagnosing intestinal lymphangiectasia as primary, through tests for proteinuria, rheumatic conditions, neoplastic diseases, or parasitic infections[8,10]. Diagnostic tests mainly involve intestinal endoscopy and biopsy, while the treatment option varies from nutritional supplement to more advanced surgical procedure[2].

This literature review highlights hypocalcaemic tetany as a rarely recognized PIL complication and emphasizes diagnostic challenges often encountered by physicians throughout the treatment process.

### HIGHLIGHTS

- Hypocalcaemic tetany is an uncommon presentation in primary intestinal lymphangiectasia (PIL).
- PIL in some cases may manifest with hypocalcaemic tetany and vitamin D deficiency.
- Atypical presentation in PIL highlights diagnostic challenges and the need for thorough investigations.

## Discussion

PIL, also known as Waldmann's disease, is a rare disorder and significant cause of protein-losing enteropathy where lymphatic malformation leads to blockage, rupture, and leakage of the lymph fluid into the intestinal lumen resulting in hypalbuminemia, lymphopenia, and hypogammaglobulinemia[9,11]. Furthermore, the condition can also result in the depletion of fat, electrolytes, and fat-soluble vitamins[3].

### *Epidemiology of PIL*

The prevalence of symptomatic PIL is not well established[3]; however, it predominately affects children of age, younger than 3 years but may be diagnosed later in adulthood[12]. Therefore, the mean age of onset of the disease is 12 years[3]. The disease is equally prevalent in both sexes and has no racial preferences[2,9,10]. Most of the cases are of sporadic origin and familial forms of the disease are rarely reported[3,12].

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### *Etiopathogenesis of PIL*

The exact causes of IL have not been determined, and the genetic basis of the disease is still not well-understood[3]. It may be associated with certain genes mutation (likely VEGFR3, PROX1, FOXC2, and SOX18) that are involved in lymphatic development[8]. Mutations in these genes often result in lymphatic malformations, defective valve formation, and altered cell-cell adhesion, leading to lymphedema through vessel occlusion, dilation, loss of functional lymphatics, or fibrosis[13]. The Table 1 illustrates the consequences of mutations of these genes and their respective roles in the development of PIL. Hokari et al. found variable changes in the expressions of regulatory molecules involved in lymphangiogenesis in the duodenal mucosa of patients with PIL[2]. PIL is known to be associated with conditions, such as Yellow Nail Syndrome, Klippel-Trenaunay-Weber syndrome, Von Recklinghausen, Noonan, Turner, and Hennekam syndrome[2].

### *Clinical presentation of PIL*

The diagnosis of PIL primarily relies on a combination of clinical, biological, radiological, endoscopic, and histopathological findings[1]. Patient with PIL often presents persistent diarrhoea and peripheral pitting oedema (in 95% of PIL cases) as the most frequent initial clinical manifestation[10,12]. Hypoalbuminemia, lymphopenia, and hypogammaglobulinemia are observed as constant biological findings in cases of PIL[1]. The cause of hypoalbuminemia appeared to be lymphatic leakage and diarrhoea, in absence of liver synthesis dysfunction or renal protein leakage in the patient[21]. Low oncotic pressure due to hypoalbuminemia often leads to peripheral pitting oedema[8]. Hypogammaglobulinemia may give rise to complications like opportunistic or recurrent infections due to the impairment of both humoral and cellular immunity as a result of lymphocytes and gamma-globulins leakage[1]. These biological findings may be complicated by lymphedema, chylous ascites, pleural effusion, pericarditis, steatorrhea, abdominal pain, chronic fatigue, weight loss, inability to gain weight, or growth retardation in children[3,8–10,12].

### *Metabolic complications of PIL*

The inability to absorb fat and fat-soluble vitamins including vitamin $B_9$ and $B_{12}$, and persistent diarrhoea secondary to PIL give rise to hypocalcemia, hypomagnesemia, hypolipidemia, iron deficiency anaemia, vitamin D deficiency, and convulsions[1,8,12,22].

Vitamin D deficiency is considered when its serum concentration falls below 12 ng/ml (< 30 ng/ml)[23]. When vitamin D deficiency persists for a prolonged duration, it results in osteomalacia or rickets, while less severe deficiency, accompanied by secondary hyperparathyroidism, leads to osteopenia[24]. Moreover, severe vitamin D deficiency impairs calcium and phosphate absorption from the small intestine[25] leading to hypocalcemia and ultimately to recurrent episodes of tetany[21]. Tetany is unlikely to occur unless the ionized calcium concentration drops below 4.3 mg/dl (1.1 mmol/l), which typically corresponds to a serum calcium concentration of 7.0–7.5 mg/dl (1.8–1.9 mmol/l)[23]. Tetany can manifest with various symptoms, ranging from mild, such as muscle cramps, paraesthesia of the hands and feet, and perioral numbness, to severe with carpopedal spasm, laryngospasm, and focal or generalized seizures[23]. Insufficient circulation of 25(OH)D is linked to elevated PTH levels[23]. In some cases, the PTH level found to be within the normal range. It may be due to suppression of PTH secretion caused by hypomagnesemia[26].

In PIL, hypomagnesemia may result from insufficient magnesium absorption, secondary to persistent diarrhoea[21]. As one-third of serum magnesium binds to albumin, hypoalbuminemia could further disturb magnesium transport and equilibrium, exacerbating the hypomagnesemia[27]. Hypomagnesemia in IL can lead to various clinical consequences. Severe reductions in serum magnesium may result in arrhythmias, such as prolonged PR intervals, widening QRS complexes, and notably, torsades de pointes[21]. Additionally, it can induce neuromuscular hyperactivity, contributing to tetany and seizures[21,28]. Magnesium plays a crucial role in potassium and calcium metabolism. Thus, hypomagnesemia could have potentially exacerbated these two-electrolyte imbalances[21]. A diminished level of serum magnesium (< 0.8 mEq/l) further precipitates hypocalcemia by reducing the sensitivity of calcium-sensing receptors[26]. Hypomagnesemia

Table 1

**Genetic mutations during lymphangiogenesis and their implications for PIL development**

| Genes involved | Physiological roles | Implications of mutations | Roles in PIL |
|---|---|---|---|
| Vascular endothelial growth factor receptor 3 (VEGFR3) | Lymphatic vessel sprouting and proliferation facilitated by VEGFC and its receptor, VEGFR3, expressed on lymphatic endothelial cell (LECs)[13]. | Inactivates VEGFR3 → prevents interaction and activation with VEGFC and VEGFD →disrupt Lymphangiogenesis → leads to abnormal lymphatic vessels in the intestines[13]. | Disrupt lymph flow → leads to fluid accumulation in tissue → primary lymphedema[13]. |
| Prospero homeobox 1 (PROX1) | Regulates lymphatic endothelial cell (LEC) specification, maintenance, and sprouting contributing to lymphangiogenesis[14,15]. | Decrease in LEC numbers followed by absence of lymphovenous valves[15]. | Impairs lymphatic function → hinder fluid drainage and compromise immunosurveillance, exacerbating existing pathological conditions[15]. |
| Forkhead box C2 (FOXC2) | Development of lymphatic valves and smooth muscle cells[13]. | Loss of function mutation results in defective lymphatic remodelling, absence of lymphatic valves, and increased pericyte coverage in lymphatic vessels[16,17]. | Lymphedema—distichiasis[17] |
| SRY—box transcription factor 18 (SOX18) | Formation of lymphatic network via the JAK2/STAT3 signalling[18], development of blood vessel and hair follicles[19]. | SOX18 gene mutations induce vascular, lymphatic, and hair follicle defects leading to hypotrichosis-lymphedema-telangiectasia (HLT) syndrome[19,20]. | Chylous ascites secondary to fluid extravasation and impaired lymphatic vascular resorption[19]. |

PIL, primary intestinal lymphangiectasia.

Table 2

**Clinical, biochemical, radiological, endoscopic and histological biopsy findings of patients of PIL diagnosed with hypocalcaemic tetany or osteomalacia**

| | | | | Clinical presentation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | OEdema | | | | | |
| Patient | Article name | Sex | Age at time of diagnosis | Chronic diarrhoea | Generalized | Localized | Tetany | Extraintestinal lymphatic malformations | Initial Dx | Final Dx |
| 1 | Primary intestinal lymphangiectasia diagnosed by endoscopy following the intake of a high-fat meal[30] | Female | 11 years | Yes | Yes (Ascites + LL oedema) | No | Yes | No | Eosinophilic gastroenteropathy | PIL |
| 2 | Hypocalcemia and tetany caused by vitamin D deficiency in a child with intestinal lymphangiectasia[24] | Female | 4 years and 8 months | Yes | Yes (Ascites + LL oedema) | No | Yes | No | PIL at 8 months age | Tetany secondary to PIL |
| 3 | Everolimus for primary intestinal lymphangiectasia with protein-losing enteropathy[31] | Male | 12 years | Yes | Yes (Puffy face + LL oedema) | No | Yes | No | PIL | PIL and secondary PLE |
| 4 | Complicated primary intestinal lymphangiectasia (Waldmann's disease) in a child successfully treated with octreotide: a case report from a low-resource setting[1] | Female | 11 years | Yes | Yes (Ascites + Pleural effusion + LL oedema + Lymphedema of U/L) | No | No | Yes | Coeliac disease at 6 months age | PIL |

(—) indicates the data not documented in literature; CT, computed tomography; LL, lower limb; PLE, protein-losing enteropathy; PTH, parathyroid hormone; U/L, upper limb.

may directly enhance the activity of potassium channels in the cells of the ascending limb, consequently resulting in hypokalemia[29]. Hyponatremia and hypokalemia could also be the result of intestinal secretions as a result of increased frequency of diarrhoea. This electrolyte imbalances may exacerbate the neurological manifestations in the patient with PIL. Thus, blood tests for magnesium, calcium, and vitamin D, along with specialized neuromuscular assessments, is crucial to establish the nutritional status and offer insights into PIL's impact on the nervous system.

### *Diagnostic evaluation in PIL*

The presence of intestinal lymphangiectasia is confirmed through endoscopic findings and the corresponding histology of intestinal biopsy specimens[2]. During the endoscopic examination, multiple whitish mucosal spots or creamy yellow jejunal villi are observed, which correspond to markedly dilated lymphatics[8] as seen in the first and second parts of the duodenum. The serological tests and endoscopy may not be sufficient for a definitive diagnosis of PIL. In this situation, histopathology remains the hallmark in identifying IL, and it exhibits similarity in both primary and secondary forms of the disease[8]. The aspect that confirms the diagnosis in the patient is the presence of characteristic histology that reveals grossly dilated lymphatics in the lamina propria of the small bowel (duodenum/jejunum/ileum), with distorted and enlarged villi but typically no atrophy[11]. The diagnostic evaluation of PIL has been summarized in detail in flowchart 1.

### *Diagnostic challenges in PIL*

Four paediatric cases with PIL have been reported in literature till date to have hypocalcaemic tetany or osteomalacia as initial clinical manifestations alongside typical clinical symptoms of diarrhoea and oedema. Three of them are female. The mean age at the time of diagnosis was 10 years (Range: 5–12 years). The

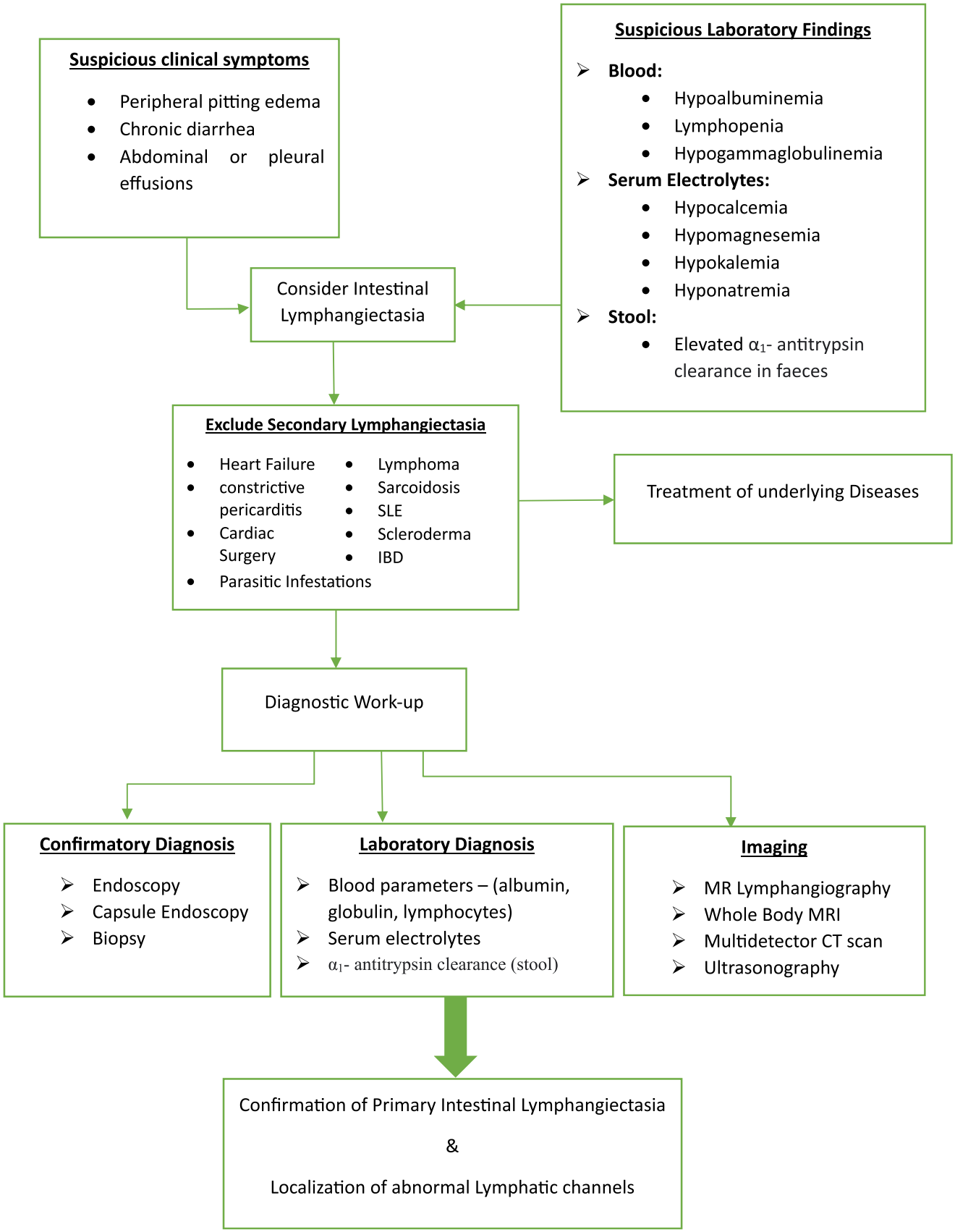
Table 2
**(*Continued*)**

| | Examination | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Growth chart | | | | | | | |
| **Past history** | **Findings other than oedema** | **Height for age** | **Weight for age** | **Laboratory findings** | **Imaging findings** | **Endoscopic findings** | **Histological biopsy findings** | **Treatment** | **Outcomes** |
| None | None | 158 cm (90–97th percentile) | 40.5 kg (50th–75th percentile) | Low serum protein, albumin, and calcium levels, lymphocytopenia, elevated α-1-antitrypsin in faeces, | None | Whitish dot-like patches scattered across the second part of the duodenum; | Intestinal mucosa with dilated lymphatics; | Dietary therapy | Full recovery |
| PIL | Genu valgum | 100 cm (10th–25th percentile) | 17 kg (50th–75th percentile) | Lymphopenia, hypoalbuminemia, hypogammaglobulinemia, elevated liver enzymes, low serum $Ca^{2+}$, Mg or phosphorus; elevated PTH, very low serum 25-hydroxy vitamin D [25(OH) D] concentration (< 12.48mmol/l) | mild periosteal elevation at both distal femurs on Knee X-ray films; low bone density; | Both acute and chronic inflammatory changes, and dilated lymphatic channels in the duodenum filled with proteinaceous material. | Dilated lymphatic spaces that involved the lamina propria and muscularis mucosa of duodenum; | IV multivitamins' supplements + Oral vitamin D supplementation | Improvement of symptoms |
| None | None | — | — | Decreased levels of serum albumin, total protein, magnesium, and corrected calcium, Hypogammaglobulinemia; high faecal α-1-antitrypsin clearance rate; | 99mTc human serum albumin (99mTcHSA) scintigraphy revealed albumin leakage from colon; no leakage in stomach or small intestine | Whitish villi and chyle leakage in the mucosa of the distal duodenum and ascending colon to the transverse colon | Diffusely dilated mucosal and submucosal lymphatic channels along the villi of duodenum and ileum; | Everolimus (mTOR inhibitor) + Dietary therapy + antidiarrheal agents | Improvement of symptoms |
| Stature-ponderal delay and coeliac disease at age of 6 months; | Genu Valgum + wart type molluscum contagiosum in perioral region and fingers of both hands | -4 standard deviation (SD) | -3 Standard deviation (SD) | microcytic hypochromic anaemia, hypoalbuminemia, hypocalcemia, hypogammaglobulinemia, low serum cholesterol, elevated PTH, hypophosphatemia; chylous ascites on ascitic fluid analysis; elevated faecal alpha 1-antitrypsin level; | Signs of osteomalacia on X-ray of lower limbs; Inflammatory digestive thickening associated with sclerolipomatosis without visible lymphatic obstruction on abdominopelvic CT scan; Peritoneal effusion on abdominal USG; | congestive gastritis without villous atrophy on fibroscopy; | Histopathological study of Duodenal biopsy was normal; | Dietary therapy + i.m. slow-release octreotide; | Respond well to treatment |

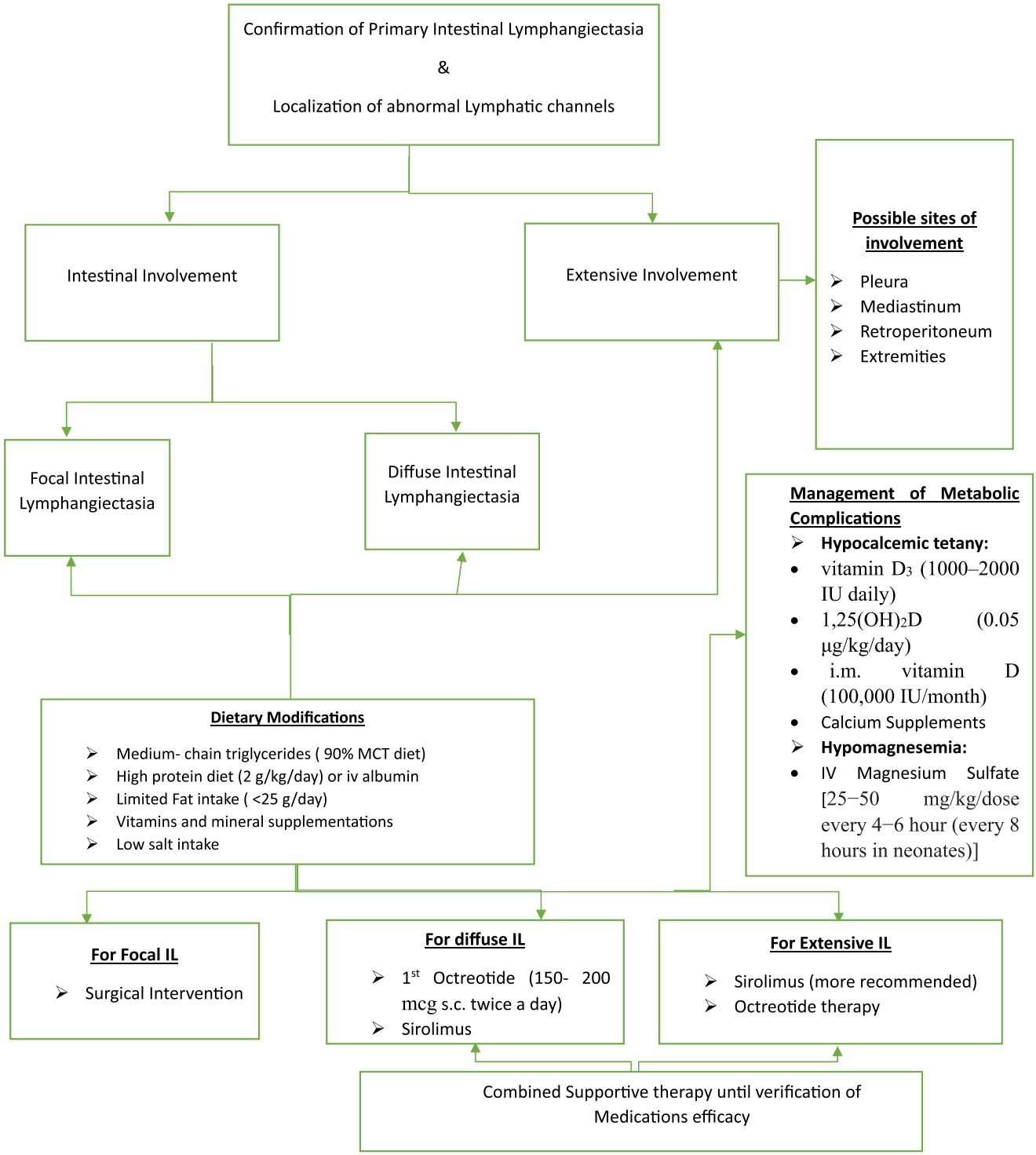
(Source: https://www.ncbi.nlm.nih.gov/pmc/).

clinical manifestations, biochemical, radiological, endoscopic and histological biopsy findings are shown in Table 2.

Limited medical literature discusses paediatric cases of hypocalcaemic tetany linked to severe vitamin D deficiency and hypomagnesemia in PIL. The Table 2 illustrates the unusual occurrence of hypocalcaemic tetany or osteomalacia as the initial clinical presentation of the disease despite hypocalcemia being a common laboratory finding[32]. Extraintestinal lymphatic malformation was observed in patient 4, involving lymphedema of upper limb. Patients 1 and 4 were initially misdiagnosed as eosinophilic gastropathy and coeliac disease respectively, but later when the disease progress, PIL emerges as definitive diagnosis. Patient 4 experienced stature-ponderal delay as a disease complication, due to the delayed diagnosis. Hypoalbuminemia, lymphopenia, hypogammaglobulinemia and elevated faecal clearance of α1- antitrypsin were observed in all patients. Patient 3 had hypomagnesemia in addition to hypocalcemia. Low bone density, suggestive of osteomalacia or bone disorders, was observed in X-rays of lower limbs in patients 2 and 4, which presented as genu valgum on physical examination. 99mTc human serum albumin (99mTcHSA) scintigraphy revealed albumin leakage from colon, suggesting Lymphangiography as a valuable tool for detection of lymphatic leakage[31]. Endoscopic and biopsy findings supported a diagnosis of PIL in all cases except patient 4, where a definitive diagnosis was made through abdominopelvic computed tomography (CT) scan, revealing inflammatory thickening of digestive mucosa with sclerolipomatosis[1]. A study by Zhang *et al.*[33] also revealed that PIL often presents with symptoms such as fatigue, lower abdominal pain, oedema, chylothorax, chronic diarrhoea, ascites, iron deficiency anaemia, and hypocalcaemic tetany, leading to misdiagnoses like Crohn's disease. The presence of symmetrical lower limb oedema poses a diagnostic challenge, resembling conditions like congestive cardiac failure, nephrotic syndrome, and protein energy malnutrition[34]. Kahana et al. also documented a case report of an infant initially misdiagnosed with cow's milk protein (CMP) allergy when presented with




**Flowchart 1.** Diagnostic evaluation of primary intestinal lymphangiectasia. CT, computed tomography; IBD, Inflammatory Bowel Disease, SLE, systematic Lupus Erythematosus.




**Flowchart 2.** Treatment Algorithm in primary intestinal lymphangiectasia based on severity and localization of disease. MCT, medium-chain triglycerides.

failure-to-thrive and chronic diarrhoea. However, later on, a definitive diagnosis of intestinal lymphangiectasia was established through endoscopic biopsy. Thus, there is high potential for misdiagnosis in PIL due to the mimicking behaviour of disease to other conditions due to overlapping clinical symptoms and laboratory findings[35]. It is crucial to rule out secondary causes of intestinal lymphangiectasia, including erosive and non-erosive intestinal disorders, conditions involving mesenteric lymphatic obstruction, and cardiovascular disorders that elevate central venous pressure before confirming PIL[2]. Clinicians should

always consider PIL as one of the differential diagnoses when the patient presents with overlapping signs and symptoms of the diseases.

### *Management of PIL and its metabolic complications*

The broad spectrum of presenting symptoms poses a challenge in determining the appropriate therapy. The treatment protocol relies on the specific symptoms, disease localization, and associated complications[2]. Initially , It is crucial to determine whether the disease is limited to the small intestine or extensively involves extremities or third spaces, with a particular focus on discerning the nature of intestinal lesions—whether focal and confined or diffuse[36]. Treatment algorithm used in PIL based on the severity and localization of the disease has been illustrated in a flowchart 2.

The management of all types of PIL depends on lifelong dietary modifications, including a high protein diet (2 g/kg/day), limited fat intake (< 25 g/day) replaced with over 90% medium-chain and short-chain triglycerides, along with vitamin supplementation[12,24,36]. Restriction to long-chain fatty acids prevents the engorgement and rupture of malformed lymphatics, while direct absorption of medium-chain triglycerides (MCT) into the portal venous circulation contributes to the treatment, thereby reducing intestinal lymphatic flow[15]. Enteral nutrition and total parenteral nutrition (TPN) can be beneficial[2,8]. However, implementing and sustaining this strict diet under clinical conditions can be challenging for patients[36].

Surgery is recommended for focal intestinal lymphangiectasia[2], with the extent of involvement accurately identified beforehand. The approach of surgery varies based on location of lesion; laparoscopic resection is suitable in absence of adjacent organs in the vicinity, while pylorus-preserving pancreaticoduodenectomy is required for duodenal involvement due to interconnected biliary and pancreatic ducts[36]. However, surgery is rarely indicated for widely distributed intestinal lesions due to the challenges associated with extensive resection and difficulties in embolization involving multiple lymphatic vessels[36].

In cases of extensive and diffuse type PIL, where the patient does not respond to a low-fat and MCT diet, medical interventions like antiplasmin therapy and octreotide, a somatostatin analogue, should be considered as alternative treatments[8]. The property of systemic absorption makes medication suitable for patients with extensive and diffuse type PIL. Effective drugs can be employed when their mechanism is well understood[36].

It was reported that Octreotide causes a reduction in acetylcholine secretion in the intestinal plexus, impacting motility and intestinal absorption[1]. Long-term therapy often reduces stool frequency, helps maintain normal serum albumin levels, and consequently decreases the need for albumin infusions[37]. It also decreases the triglyceride absorption in the thoracic duct[2] leading to improvement in histological and endoscopic findings[8]. Octreotide, administered at 150–200 mcg subcutaneously twice daily, demonstrates positive outcomes; however, there is no standardized recommended dose or duration of therapy[37–39]. As an induction therapy, a subcutaneous injection of 1–10 mcg/kg/dose twice daily for 2 weeks is advised, followed by the same dose every 4 weeks for maintenance therapy[36]. Discontinuation of therapy often leads to disease recurrence, but remission can be achieved upon restarting the treatment. While regular administration is preferable, short-term use may be considered based on symptoms[37]. It is most effective in patients with solely intestinal involvement of abnormal lymphatics. A review of cases indicates therapeutic benefits only in patients with intestinal lesions but suboptimal effects in extensive type lymphangiectasia[36]. The slow-release form (Sandostatin LAR 20 mg) is effective but faces cost challenges for the prolonged use. A more extended follow-up is essential to confirm the adequacy and effectiveness of octreotide as a long-term therapy[37]. It may cause acute pancreatitis as a severe adverse effect in some cases[4]. Other side effects like hypertension, sinus bradycardia, and hyperglycaemia, should be closely monitored during the treatment process[36].

Oral fat-soluble vitamin supplements and electrolyte replacement therapy are considered important in the management of disease[2]. In cases with malabsorption syndrome, where tetany become unresponsive to calcium and vitamin D supplementation, it may suggest hypomagnesemia in the patient[28].

Magnesium replacement is indicated, when serum magnesium levels fall below 1.5 mEq/l. Oral replacement is suitable, except for severely low magnesium (< 1.0 mg/100 ml), suspected malabsorption, or persistent symptoms, where IV replacement is preferred. Thus, intravenous magnesium sulfate is the preferred option for the treatment of hypomagnesemia in these patients[25]. It is commonly administered at 25 – 50 mg/kg/dose (up to 2 g/dose) every 4 – 6 hour (every 8 hr in neonates) as needed for repletion of serum magnesium[40,41]. In life-threatening cases with severe symptoms like seizures, an IV push of magnesium sulfate at 50 mg/

Table 3

**Management guidelines for exogenous/iatrogenic vitamin D toxicity**

| Management guidelines | Therapy involved |
|---|---|
| First line treatment[42,44,46,47] | Discontinuation of Vitamin D supplementation |
| | Limited dietary Calcium intake |
| | Avoid Bed rest (prevent hypercalcemia due to immobilization) |
| | Administration of isotonic saline (correct dehydration and restore renal function) |
| | Medications |
| | Glucocorticoid Therapy - Hydrocortisone 100 mg/day or prednisone 40 mg/day for 5 days |
| | Antiresorptive therapy (for severe cases with severe hypercalcemia, serum $Ca^{2+}$ > 14 gm/dl) - |
| | Calcitonin – i.m. at 4U/kg in every 12 hours for 48 hours |
| | IV bisphosphonates – i.v. Pamidronate 90 mg over 2 hours and i.v. Zoledronic acid 4 mg over 15 minutes |
| Second line treatment[42,48–51] | Phenobarbital |
| | Ketoconazole |
| | Specific inhibitors of CYP27B1 (1α-hydroxylase) |

kg (up to 2 grams/dose) is given over 1–5 min. Subsequently, for patients with total body magnesium depletion, a regimen of 125 mg/kg/day over 24 h, followed by 75 mg/kg/day for 3 – 5 days is recommended[40]. Multiple days may be required to restore serum magnesium to normal levels as 50% of the injected magnesium usually lost from the urine[21]. Serum magnesium level should be monitored daily to prevent hypotension arising from high dose IV magnesium infusion and ensure the restoration of normal levels during therapy[40].

Vitamin D supplementation is the ideal approach to address tetany due to vitamin D deficiency, as solar radiation and dietary intake may not be sufficient due to malabsorption[24]. Conventional oral replacement therapy is effective, as it leads to a notable increase in 25(OH) D concentration regardless of fat malabsorption levels in PIL. 25(OH)D, 1,25$(OH)_2$D, and alfacalcidol are more effective than vitamin $D_3$ in malabsorption cases, with similar potency[24]. The recommended safe dose for vitamin $D_3$ is 1000–2000 IU daily and 0.05 μg/kg/day for 1,25 $(OH)_2$D. However, a higher dose may be necessary for malabsorption cases, and if oral supplements are ineffective, parenteral supplements like intramuscular vitamin D injections (100 000 IU/month), should be considered[24]. In severe hypocalcemia or tetany, intravenous calcium gluconate is generally preferred, followed by oral supplements once symptoms improve[29]. Vitamin D supplementation is frequently advised along with calcium to enhance absorption when hypocalcemia is due to vitamin D deficiency[29]. Failure to adjust doses according to requirements, poses a high risk of exogenous Vitamin D toxicity[42].

Clinical presentation in vitamin D toxicity results from hypercalcemia, presenting as nonspecific symptoms like weakness, fatigue, anorexia and bone pains. Severe cases may involve neurological symptoms (confusion, agitation, irritability, ataxia, stupor or coma), gastrointestinal issues (abdominal pain, nausea, vomiting, constipation, peptic ulcer and pancreatitis from malignant calcifications), and renal manifestations (polyuria, polydipsia, nephrolithiasis)[43,44]. Extreme hypercalcemia can lead to cardiac arrhythmias[44]. Physical examination findings of these patients are unremarkable, however, may reveal loss of skin turgor and dry mucous membranes due to dehydration, changes in mental status, and abdominal tenderness without rebound, rigidity, or guarding[44]. Thus, high clinical suspicion should be maintained based on historical information[42,44]. While current data suggests that a plasma 25(OH)D concentration above 750 nmol/l may lead to vitamin D toxicity, it is prudent to maintain a lower upper limit of 250 nmol/l for a wider safety margin[45]. Injectable vitamin D should be prescribed and administered within recommended pharmacological doses, based on laboratory evidence of vitamin D deficiency, and with regular serum monitoring to mitigate the risk of toxicity, and adjust the dose accordingly[24]. Awareness should be raised among healthcare providers about the potential for iatrogenic vitamin D toxicity associated with excessive doses, despite its generally wide safety margin[45,46]. Caution is crucial, as excessive use of any substance, even with a broad safety range, can pose risks.

Symptomatic exogenous vitamin D toxicity from active vitamin D metabolite therapy is marked by hypercalcemia, suppressed PTH (intact), 25(OH)D concentration greater than 150 ng/ml ( > 375 nmol/l), and normal or increased values of 1,25 $(OH)_2$D concentration[42,44]. Management primarily involves supportive measures with a focus on reducing elevated calcium levels in case of iatrogenic toxicity[44]. The detail management guidelines have been depicted in Table 3. Early appropriate management of PIL usually prevents hypocalcaemic tetany in the child.

## Conclusion

Diagnosing and managing PIL can be challenging due to its rarity and variable presentation. Paediatricians should consider PIL as a possible differential diagnosis when a child presents with peripheral oedema and tetany. Vitamin D deficiency and hypomagnesemia played a significant role in the tetany manifestation. Hence, screening for vitamin D deficiency and regular serum magnesium level monitoring is essential in PIL cases when present with associated neuromuscular or ionic abnormalities. Early recognition and management through nutritional support, vitamin supplementation, electrolyte replacement and octreotide therapy, are crucial for better patient outcomes in PIL.

## Ethical approval

None.

## Consent

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I.T. and J.Y. wrote the original manuscript, reviewed, and edited the original manuscript.

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