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PrimeView
Primary lymphoedema

Primary lymphoedema (PLE) includes developmental anomalies in the structure and/or function of the lymphatic system. PLE can manifest as swelling in any part of the body (although it typically affects limbs), is sometimes associated with other clinical syndromes, and can be present at birth or develop later in life.

Epidemiology

Each PLE phenotype has a prevalence of ≤5 per 10,000 individuals and, therefore, is a rare disease. Accurate estimates of PLE epidemiology are further complicated by the variability in the penetrance of pathogenetic variants and clinical presentation.

- A causative genetic variant is identified in only ~30% of affected individuals.

Diagnosis

Diagnosis can be based on clinical examination; in addition to swelling, various PLE phenotypes exist, depending on the organs affected by the lymphatic defects, for example, lung effusions, intestinal lymphangiectasias (overt proliferation of lymphatic vessels) and ascites. PLE onset can occur at different ages, and the disease can worsen, improve or fluctuate with time and can be unilateral or bilateral. Lymphatic function and structural abnormalities can be assessed with isotopic lymphoscintigraphy or non-contrast magnetic resonance lymphangiography. Genetic analyses are available at specialized centres and can be an important resource to improve our knowledge on PLE.

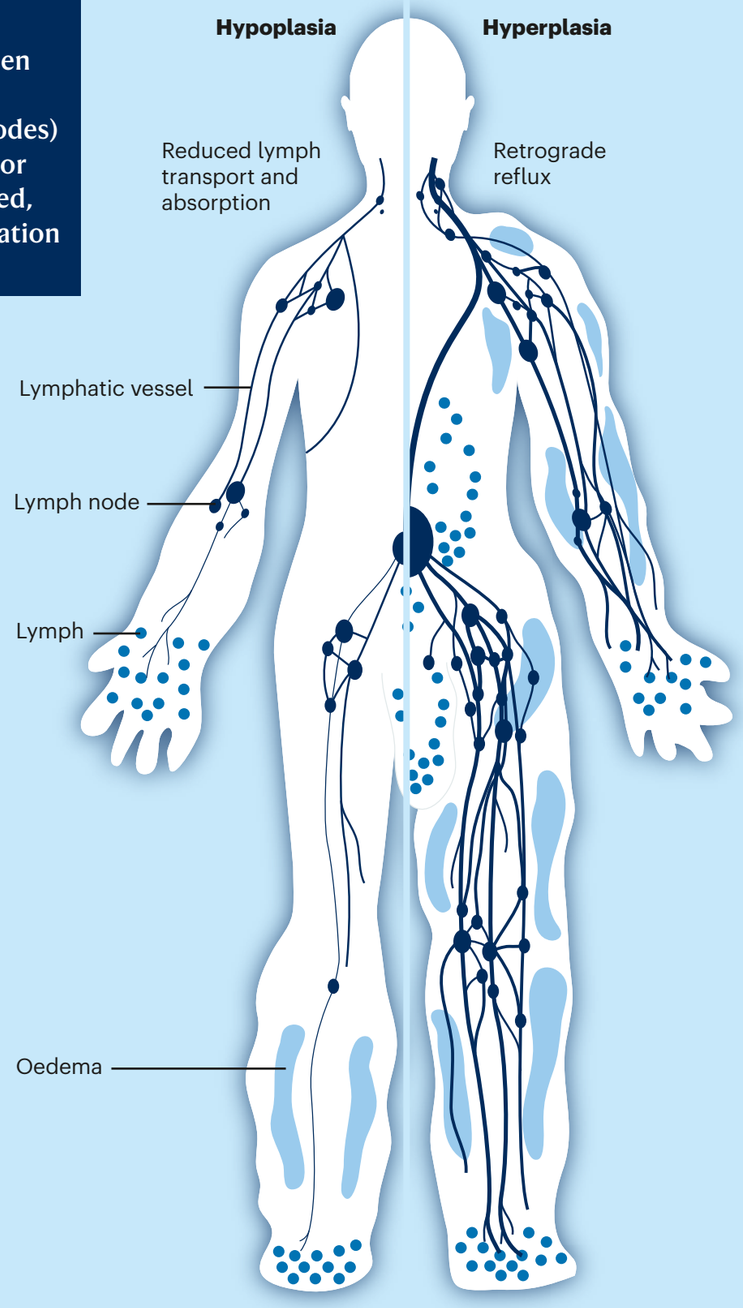
- PLE is distinct from secondary lymphoedema, in which normal lymphatics have been damaged by infections, such as filariasis, or invasive surgery.

Screening

Individuals at risk of developing PLE and who might benefit from screening are relatives of a person diagnosed with PLE, as well as patients with a syndrome known to be associated with PLE but who do not present with PLE. In addition, individuals who develop erysipelas (an infection of the superficial layers of the skin) without having any preceding risk factors should also be monitored for PLE development.

Pathophysiology

PLE is classified as hypoplastic (when the underlying defect impairs the growth of lymphatic vessels and nodes) or hyperplastic (when the number or size of lymphatic vessels is increased, and in which lymphatic valve formation or function can be affected).



Alterations (mostly loss-of-function) in 31 genes or loci have been confirmed to cause PLE, and an association with PLE has been suggested for another 18 genes.

Complicated lymphatic anomalies (CLAs) are localized lymphatic malformations occurring in various organs or tissues; some CLAs can be associated with PLE, such as central conducting lymphatic anomaly and disorders caused by mutations in genes encoding proteins of the RAS pathway (RASopathies).

Vascular endothelial growth factor C (VEGFC) is one of the main drivers of lymphatic development; inactivating mutations in *FLT4*, encoding the receptor for VEGFC and part of the RAS–MAPK signalling pathway, are frequently found in PLE.

In addition to VEGFC, several signalling molecules and their receptors are involved in lymphatic development and function, including ephrin, angiopoietin 2 and hepatocyte growth factor.

Management

The goal of PLE management is to reduce symptom burden and prevent complications. Compression of the affected areas, skin care to prevent infections and weight control are recommended non-invasive approaches to reduce and control swelling. Decongestive therapy can include wearing compressive garments, compression bandaging, manual lymphatic drainage and decongestive exercises. Patients with a known causative genetic mutation may benefit from off-label use of cancer drugs targeting the dysfunctional signalling pathway. Surgical procedures aiming to remove excess tissue (for example, liposuction) or to restore lymph flow (reconstructions creating lympho-venous anastomosis, as well as lymph node transfer) can be considered for severe disease.

Quality of life

The physical and aesthetic effects of PLE can be associated with psychological issues and further affect quality of life. Although decongestive therapy effectively improves quality of life, PLE is a chronic disease requiring lifelong management, which makes treatment compliance challenging.

Outlook

Identifying new causative genetic variants and understanding the effects of variants of unknown significance that are often detected with genetic screening will be key to an improved understanding of the underlying pathogenetic mechanisms of PLE, faster diagnosis and personalized treatment.

Written by Lucia Brunello; designed by Laura Marshall