Congenital lymphedema a literature review

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ABSTRACT

Congenital lymphedema is a rare and chronic medical condition characterized by abnormal development or function of the lymphatic system, resulting in localized edema and enlargement of tissues, usually in the extremities. This condition is present from birth or becomes evident during childhood. It can be classified into primary and secondary types, with primary congenital lymphedema being linked to genetic mutations affecting the lymphatic vessels and secondary congenital lymphedema due to other congenital conditions or developmental problems. The diagnosis of congenital lymphedema is typically based on clinical examination and may be supported by imaging studies such as lymphoscintigraphy. Management and treatment aim to relieve symptoms and improve patients' quality of life. Therapeutic approaches often include manual lymphatic drainage, compression therapy, and skin care practices to reduce swelling and prevent complications such as cellulite. Genetic counseling may be relevant for cases of primary congenital lymphedema, while treatment of secondary congenital lymphedema may address the underlying causes. In summary, congenital lymphedema is a genetic condition that requires early diagnosis, multidisciplinary treatment, and a thorough approach to lessen its impact on affected individuals. Understanding its genetic and secondary causes is essential for providing appropriate care and support to people living with this condition.

Keywords: Lymphedema, Genetic, Oedema, Ends, Multidisciplinary.

1 INTRODUCTION

Lymphedema is defined as the abnormal accumulation of interstitial fluid and fibrofatty tissue resulting from injury, infection, or congenital anomalies of the lymphatic system. This system is a circulatory network of vessels, ducts, and nodules that filters and distributes certain protein-rich fluids (lymph) and blood cells throughout the body. In congenital lymphedema, lymphatic fluid accumulates in the subcutaneous tissues under the outermost layer of the skin (epidermis) due to obstruction, malformation, or underdevelopment (hypoplasia) of several lymphatic vessels. As a result, swelling (lymphedema) and thickening occurs, as well as hardening of the skin in the affected areas, most commonly in the legs and feet (BRANDÃO et al., 2020).

The formation of interstitial fluid results from the movement of intravascular fluid through the capillary membranes due to arteriolar blood pressure. Much of the interstitial fluid returns to the intravascular fluid via the postcapillary venules. The dynamics of fluid production are influenced by arterial and venous hydrostatic pressures, tissue pressure, intravascular and interstitial fluid oncotic pressure, and membrane permeability. Normally, the dynamics favor an interstitial gain, and the excess is removed by the lymphatic channels. Because lymphatic vessels often lack a basement membrane, they can also reabsorb molecules that are too large for venous uptake. In summary, the lymphatic system controls the pressure, volume, and composition of interstitial fluid (BETHESDA, 2023).

Lymphatic obstruction leads to accumulation of interstitial fluid, which often contains large proteins and cellular debris. By mechanisms not fully understood, the increase in interstitial fluid induces inflammation, destruction or sclerosis of lymphatic vessels, fibrosis, and, ultimately, hypertrophy of adipose tissue (BETHESDA, 2023).

Lymphedema is etiologically classified into two groups: primary lymphedema and secondary lymphedema. The secondary occurs due to injury, obstructions, or other damage to the lymphatic system. Although filariasis caused by Wuchereria bancrofti infection is the most common cause of lymphedema worldwide, in developed countries, most cases of secondary lymphedema are related to malignancies or their treatment. This includes lymph node removal surgery, radiation therapy, or medical therapies (SLEIGH; MANNA, 2022).

Primary lymphedema can be divided into three types: congenital lymphedema, which is present at birth or detected up to two years later; early lymphedema, which appears during puberty or at the beginning of the third decade of life; or late lymphedema, which appears after the age of 35 years (SLEIGH; MANNA, 2022).

Regarding congenital lymphedema, Milroy's disease is its main presentation, it is the mutation in locus q35.3 of chromosomes 5, and the gene related to this area, known as FLT-4, responsible to produce VEGFR-3 is its characteristic pathophysiology. (KORHONEN et al., 2022).

The diagnosis of lymphatic system alterations can be made using lymphoscintigraphy. This is a procedure that uses a small amount of radioactive dye protein injected into the space between the first and second digits of the affected limb. The limb is photographed with a gamma camera to observe the dye as it moves through the lymphatic system. Images showing dye outside the lymphatic structures suggest edema of lymphatic origin (BROWNELL, 2022).

Despite advances in the understanding of the disease and in the standardization of the physical therapy approach, the treatment of lymphedema remains a challenge and requires a multidisciplinary approach. In addition, the treatment is expensive and requires a lot of time and effort from both the patient and the medical team in charge. The main goal of therapy is to reduce swelling and restore the function and appearance of the affected limb. However, one of the biggest obstacles is the lack of comparative protocols between the different forms of treatment, as many reports in the medical literature are based on uncontrolled and non-randomized case series (BROWNELL, 2022).

2 LYMPHANGIOGENESIS

The lymphatic system appears in the 6th or 7th week of embryonic development, about four weeks after the appearance of the first components of blood circulation. There is no definition for the formation of the lymphatic system. However, there are several theories for this formation and among all of them there are two that are more accepted: the first is Sabin's that says that early in fetal development, primitive lymphatic sacs would be originated by the sprouting of endothelial cells from the veins of the embryo. The other accepted theory is Huntington & McClure. This suggests that primitive lymphatic vessels arose in the mesenchyme from lymphangioblasts independent of the veins, growing centripetal and establishing connections with them later (PETRONA et al., 2020).

Although there are recent reports supporting Sabin's centrifugal theory, studies in birds have observed the existence of primitive lymphangioblasts in the mesenchyme. It is possible that both theories are combined, with lymphatic vessels originating from the venous endothelium and anastomosing with other lymphatics originating from mesenchymal tissue cells (KORHONEN et al., 2022).

The development of the lymphatic and blood systems is controlled by a complex network of cell signalers and receptors. Among these signals, the most important are a family of glycoproteins called vascular endothelial growth factor (VEGF). VEGF is responsible for endothelial cell regulation, angiogenesis, vasculogenesis, and vascular permeability. This family of proteins is divided into five types: VEGF A, B, C, D, and E, which bind to membrane-specific tyrosine kinase receptors, known as vascular endothelial growth factor receptor 1 (VEGFR-1/Flt1), 2 (VEGFR-2/Flk1/KDR), and 3 (VEGFR-3/Flt4). Activation of the VEGFR-2 receptor by VEGF is considered the primary pathway for endothelial cell angiogenesis and mitogenesis (KORHONEN et al., 2022).

Mutations in the genes that control vascular endothelial growth factor (VEGF) or its receptors (VEGFR-1/Flt1, VEGFR-2/Flk1/KDR or VEGFR-3/Flt4) can lead to a failure in the development of blood vessels, leading to embryonic death. When there is an overexpression of these signals and receptors, an abnormal expression of the lymphatic system occurs, while their decrease results in the reduction of the lymphatic system. Such results are observed in experiments (PETRONA et al., 2020).

Neuropilins 1 and 2, abbreviated as NRP-1/2, are receptors that have a strong affinity for vascular endothelial growth factor (VEGF) and are found in the cell membranes of both the vascular and nervous systems. In addition, NRP-2 can also bind to VEGF-C, resulting in activation of the VEGFR-3 receptor in lymphatic endothelial cells (ANDRADE, M., et al 2008).

Other important regulators of vascular remodeling are angiopoietins, which include Angiopoietins 1 to 4. They play a crucial role in the process and act through the receptor tyrosine kinase known as Tie-2. Although the function of the Tie-1 receptor is still unknown, it is important to highlight that Angiopoietins 1 and 4 act by activating the Tie-2 receptor, while Angiopoietins 2 and 3 exert an inhibitory effect, blocking the action of Angiopoietin 1. This complex balance of interactions plays a key role in the regulation of angiogenesis and vascular remodeling (ANDRADE, M., et al 2008).

2.1 CONGENITAL LYMPHEDEMA

Lymphedema is defined as the abnormal accumulation of interstitial fluid and fibroadipose tissue resulting from injury, infection, or congenital abnormalities of the lymphatic system. Lymphedema is classified as primary or secondary depending on etiology and presentation (SZUBA; ROCKSON., 2018)

In primary lymphedema, the cause is a congenital change in the development of the lymphatic vessels and lymph nodes or an unknown preservation of the lymphatic vessels, also known as idiopathic lymphedema. In secondary lymphedema, on the other hand, there is an anatomical dysfunction of normal lymphatic tissue that has been affected by surgery or radiotherapy, the most common example being post-surgical or post-radiotherapy lymphedema (BROUILLARD et al., 2017).

Primary lymphedema is categorized based on the age at which the swelling manifests and is divided into congenital, early, and late. Early lymphedema is the most common form, accounting for the majority of cases, about 77% to 94%. Although it can appear between the ages of 2 and 36, it is more frequent during early puberty, usually manifesting as unilateral swelling, especially in the foot and calf. Women are more often affected, with a prevalence 10 times higher compared to men. The underlying cause is unknown in most cases, although there is speculation about the possible role of estrogen, given that the condition is more common in girls during puberty (VALENTINI; MATTOO; HOPPIN, 2022).

Although most cases are sporadic, 10% of cases of early lymphedema are hereditary, known as Meige's disease, with an autosomal dominant inheritance pattern. This type of early lymphedema is associated with distichiasis, which is the growth of double rows of eyelashes, and is called lymphedema-dysticiasis syndrome. A mutation in the FOXC2 gene, located at 16q24.3, has been identified in families with this syndrome. Mutation in FOXC2 leads to the absence of lymphatic valves and increased migration of muscle cells to lymphatic capillaries. In addition, FOXC2 is highly expressed in venous valves, which may explain why about half of patients with lymphedema-dysticiasis also have venous insufficiency (VALENTINI., et al 2023).

On the other hand, congenital lymphedema, which presents before the age of two, occurs due to congenital and/or hereditary abnormalities associated with inadequate development of lymphatic vessels. This may include a reduction in the number of lymphatic collectors, a decrease in the diameter of the lymphatic vessels (lymphatic hypoplasia), an increase in the diameter of the lymphatic collectors (lymphatic hyperplasia), the absence of lymphatic system components (lymphatic aplasia), and fibrosis in the lymph nodes. Finally, late-onset lymphedema manifests after the age of 35 years, most often in women, and affects the lower extremities (VALENTINI., et al 2023).

2.2 PATHOPHYSIOLOGY OF LYMPHEDEMA

The lymphatic system has a large functional reserve, that is, it is capable of transporting a much larger amount of lymph than the physiological need of the body. Under normal conditions, the lymphatic output, which is the amount of lymph transported per unit of time, is equal to the lymphatic load, which corresponds to the amount of fluids and lymphatic transport substances present in the tissues. However, when there is an increase in the lymphatic load, the lymphatic output also increases, until the maximum transport limit is reached. From this point on, edema arises (ASHINOFF et al., 2021).

When there is a loss of normal function of the lymphatic vessels, even with lymphatic loads within normal physiological values, there is an accumulation of fluids and macromolecules in the tissues. This type of edema is known as true lymphedema, which is characterized by having a high protein content. The amount of fluid associated with edema, at least in its initial phase, is due to the osmotic power of this system. Classically, the chronic presence of proteins in the extravascular space can cause a painful and fibrous process, giving rise to some characteristics of the disease. Recently, it was discovered that hyaluronic acid, an essential component of the extracellular matrix, also accumulates in the tissues of patients with lymphedema (BRICE, G; MANSOUR, S; BELL, R., et al., 2018)

In addition, the development of swelling requires changes in the way the capillaries work, so as to favor an increase in the amount of fluid that is filtered and, at the same time, an inefficient removal

of this excess fluid through the lymphatic drainage system. Swelling can arise as a result of an increase in hydraulic pressure in the capillaries, which creates a "hydraulic pressure difference," or due to an increase in capillary permeability (Lp). It can also be caused by the breakdown of the endothelial glycocalyx layer, reduced flexibility of the interstitial space, decreased plasma osmotic pressure (which decreases the "osmotic pressure difference"), or a combination of these factors. In addition, swelling can be caused by obstruction of the lymphatic system, preventing the filtered fluid from returning to the systemic circulation as it normally would (STERNS., et al 2023)

2.2.1 Pathophysiology of congenital lymphedema

Milroy's disease is a dominantly inherited condition characterized by a lymphatic hypoplasia or aplasia. Genomic studies have identified a mutation in the q35.3 locus of chromosomes 5, and the gene related to this area, known as FLT-4, is responsible for the production of VEGFR-3 (KORHONEN et al., 2022).

An experimental model of hereditary type I lymphedema in rats was developed through mutagenesis, which resulted in the inactivation of the VEGFR-3 gene. The mutant rats showed hypoplasia of the lymphatic vessels of the skin and lymphedema in the paws, but no alteration in the lymphatic tissue of the internal organs (HO; GORDON; MORTIMER, 2018).

Patients with primary lymphedema were found to have increased levels of VEGF-D in their blood. This can be explained by the absence of stimulation in VEGFR-3, which leads to a higher production of VEGFR-D as an attempt to compensate for the deficiency in lymphatic vessel formation caused by the lack of VEGFR-3 (Hwang, J. H; Cha, J. H.; Han, Y. D; & Kang, H. 2019).

Meige described hereditary lymphedema type II, an early-onset condition with a family history, which is transmitted in an autosomal dominant manner. However, the clinical manifestation can vary greatly, with low penetration and variable phenotype. The most frequent symptom is bilateral and symmetrical edema below the knees, which is more common in women (3:1). Some experts suggest that Meige's disease can be seen as a subcategory of lymphedema patients, without the presence of other common features of the syndrome, such as distichiasis, ptosis, cleft palate, yellow nails, and congenital heart disease (KORHONE et al., 2022).

3 EPIDEMIOLOGY

Primary lymphedema is rare, affecting 1 in every 100,000 individuals. Secondary lymphedema is the most common cause of the disease and affects approximately 1 in every 1,000 Americans (SLEIGH; MANNA, 2022).

Milroy's disease shows an autosomal dominant inheritance pattern with penetrance of 80-90%. A first type of Milroy's disease was mapped to the telomeric part of chromosome 5q (5q34-q35) in

several families, while a second locus was mapped to chromosome 6q (6q16.2-q22.1) in a single inbred Pakistani. Ferrell et al. were the first to identify a mutation in Milroy's disease in the FLT4 gene (also known as VEGFR3) located at 5q34-q35. Subsequently, more mutations of the FTL4 gene were identified in a study of patients with this pathology. In this, they found a mutation in the FTL4 gene in 75% of typical Milroy patients with a positive family history and 68% of sporadic patients (BORNAR, 2018)

Mutations in patients who have a phenotype that is not typical of this disease (lymphedema of the lower limbs, unilateral or bilateral, but symptoms not seen at birth and the presence of other features not previously associated with Milroy's disease) is very small (<5%). Most FLT4 mutations are autosomal dominant, but a single homozygous hypomorphic mutation was found in an autosomal recessive form of nonsyndromic primary congenital lymphedema (MEHRARA et al., 2022).

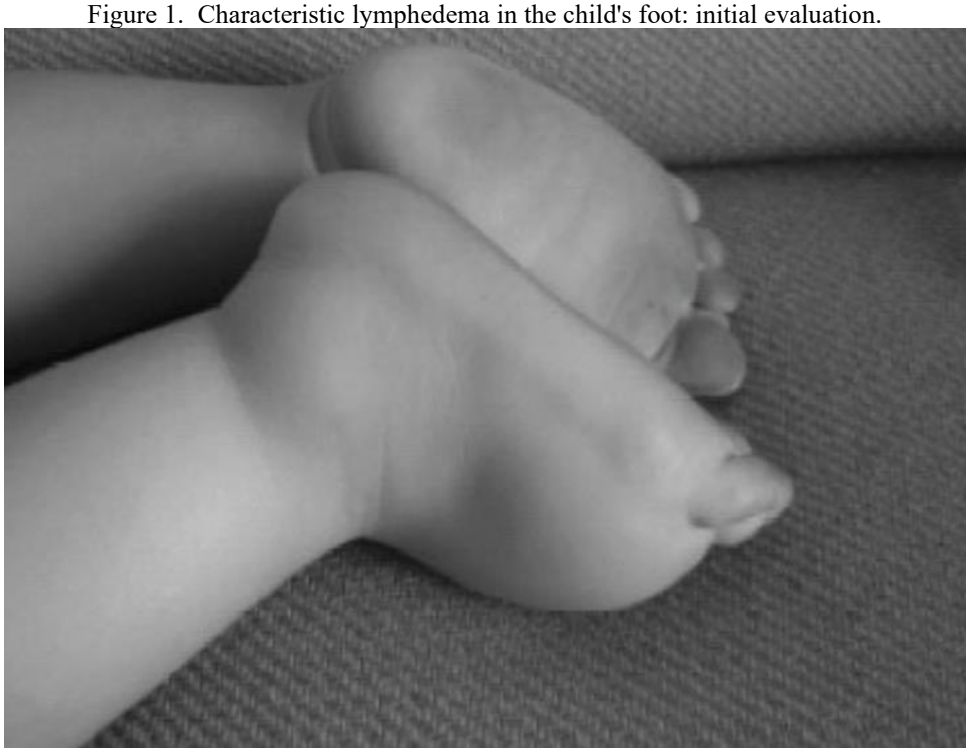
4 CLINICAL MANIFESTATIONS

The most common finding in the disease is bilateral congenital lymphedema of the lower limbs. Edema is usually present from (or before) birth. Rarely, prenatal pleural effusion and hydrops fetalis have been reported. In neonates, swelling tends to mainly affect the dorsum of the feet (foot edema). Anecdotal evidence suggests that, on rare occasions, it develops later in life (JIANG et al., 2018).

The amount of edema varies within and between families. The swelling is usually bilateral, but may be asymmetrical (Figures 1 and 2). The degree of edema sometimes progresses, but in some cases it can improve, especially in the first few years. Other features are associated with Milroy's disease: Hydrocele (37% of men); Prominent veins (23%) below the knees (with or without venous reflux seen on Doppler imaging); Inclined toenails (spoon-shaped and/or dysplastic) (14%); Papillomatosis located in the toes and/or forefoot (10%); Urethral abnormalities, such as hypospadias or urethral stricture, in men (4%) (JIANG et al., 2018).

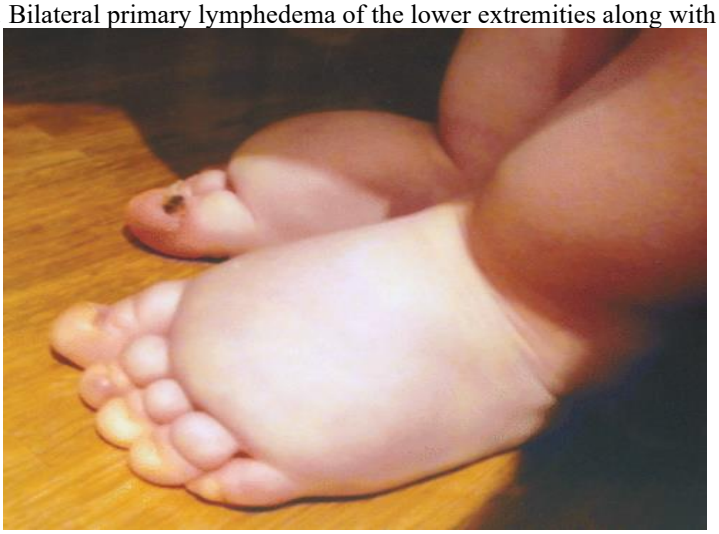
Cellulitis occurs in approximately 20% of affected individuals, with infection significantly more likely in men than in women. Cellulitis can damage existing lymphatic vessels, resulting in an increase in the degree of swelling (VALENTE et al., 2021)

Figure 1. Characteristic lymphedema in the child's foot: initial evaluation.



Fonte: Artíbale., et al (2005, p 02)

Figure 2. Bilateral primary lymphedema of the lower extremities along with toenails



Cast iron: KITSIOU-TZELI., et al (2010, p 3)

5 DIAGNOSIS

A history and physical examination with typical clinical features consistent with lymphedema and asymmetric limb measurements can usually establish a diagnosis of lymphedema. For newborn patients, the suspicion of congenital lymphedema arises from delivery or in the first days of life, because many patients with the disease already have changes in the symmetry of the limbs at the time of delivery or days after. (MEHRARA et al., 2022).

Different imaging methods have been used to diagnose lymphedema, such as lymphoscintigraphy, computed tomography (CT), magnetic resonance imaging (MRI)/MR

lymphography, and indocyanine green lymphangiography (ICG). Unfortunately, the lack of standardization in the techniques used results in variable outcomes, especially for lymphoscintigraphy. However, in centers specializing in lymphatic disorders, different techniques can be used in a standardized way to portray specific lymphatic dysfunction (MEHRARA et al., 2022).

Lymphoscintigraphy shows the flow of macromolecules and interstitial fluid from the skin to the lymph nodes, particularly at the extremities. Subcutaneous or intradermal radioactive tracers are injected into the extremities, and imaging is obtained 30 to 120 minutes after injection. The patient then performs a stressful activity (such as walking, massaging or squeezing a ball for approximately 20 minutes), which is followed by repetition of the image. Criteria for lymphatic function impaired by qualitative lymphoscintigraphy include delayed, asymmetrical, or absent visualization of regional lymph nodes and dermal reflux. Quantification of the marker's regional lymph node accumulation appears to be more sensitive than qualitative lymphoscintigraphy (RANZENBERGER, 2023).

ICG lymphangiography is a technique in which an infrared dye is injected intradermal (Figure 3). The dye is bound to albumin after injection and therefore absorption is restricted to the lymphatic vessels. The lymphatic vasculature can then be visualized directly with specialized sensors. Anatomy of the lymphatic vessels, leakage, pumping capacity, and dermal reflux can be seen. This is currently an off-label use of ICG; however, many lymphatic surgeons rely on ICG imaging for preoperative analysis and staging of lymphedema (BRORSON, H., & SVENSSON, H. 2007).

Clinics and hospitals use imaging techniques, such as CT scans and MRIs, to detect fluid overload in the soft tissues of the extremities of patients with lymphedema. Studies report that CT has good sensitivity and specificity, with a sensitivity of 93% and specificity of 100% in patients detected by CT and lymphoscintigraphy. The main CT findings in patients with lymphedema include thickening of the skin (95%), accumulation of subcutaneous edema (95%), and "honeycomb" appearance (41%). On the other hand, MRI has advantages in demonstrating lymphatic channels, but the injected contrast material can be captured by nearby veins, requiring discernment to distinguish from lymphatic vessels, which generally have a contoured appearance and higher signal intensity (MEHRARA et al., 2022).

For patients diagnosed with primary lymphedema or suspected late lymphedema, referral to a medical geneticist or genetic counseling service is suggested for evaluation of family history and recommendations for further testing (ZANTEN et al., 2021).

Molecular genetic testing approaches may include a combination of gene-targeted testing (single-gene test, multigene panel) and comprehensive genomic testing, depending on phenotype (ZANTEN et al., 2021)

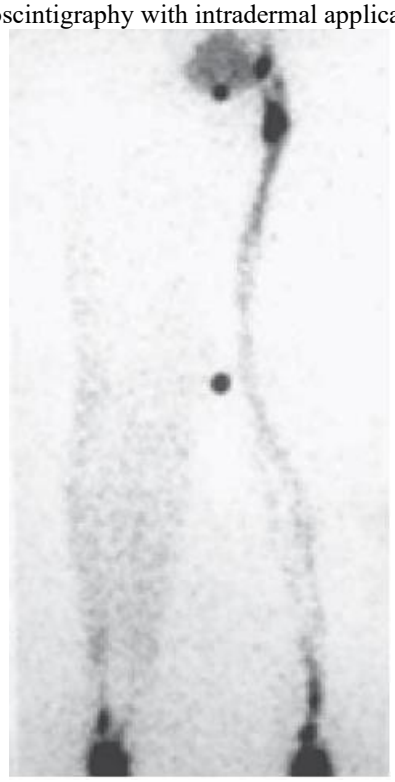
Gene-directed testing requires the clinician to determine which gene(s) are likely to be involved, while genomic testing is not. Because Milroy's phenotype is broad, individuals with the distinct findings are likely to be diagnosed using gene-directed tests, while those with a phenotype

indistinguishable from many other inherited disorders with lymphedema are more likely to be diagnosed using genomic testing (ZANTEN et al., 2021).

The single-gene test consists of the analysis of the FLT4 sequence. This test is capable of detecting small intragenic deletions/insertions and junction site variants. In Milroy's disease, most variants are pathogenic nonsense in the tyrosine kinase domain of the gene (SHIMTH et al., 2023).

A multigene lymphedema panel that includes FLT4 and other genes of interest is more likely to identify the genetic cause of the condition at the most reasonable cost, limiting the identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype (SMITH et al., 2023).

Figure 3. Lymphangioscintigraphy with intradermal application of 99 technology.



Source: DOMINGUES., et al (2011, p4)

5.1 DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lymphedema is comprehensive and based on the specific distribution of the edema (MEHRARA et al., 2022).

Chronic venous insufficiency: Lymphedema shares many clinical features with chronic venous insufficiency (CVI). Lymphedema is distinguished from CVI by the absence of typical varicose veins, absence of distribution of characteristic skin changes (i.e., severe discoloration in the medial region of the ankle in CVI), and relief of symptoms and reduction of swelling with elevation of the limb. Doppler ultrasonography will demonstrate typical findings of venous valve insufficiency. However, a subset of patients with severe and long-standing chronic venous insufficiency may develop concomitant

lymphedema; Acute deep vein thrombosis – Classic symptoms of a deep vein thrombosis (DVT) include acute edema, pain, and erythema involving a limb (MEHRARA et al., 2022).

The onset of oedema and associated symptoms (e.g., acute erythema, calf pain) easily distinguish DVT from lymphedema; Postthrombotic syndrome – Postthrombotic syndrome (PTS) is the development of chronic venous symptoms and/or signs secondary to DVT. These include pain, venous dilation, oedema, pigmentation, skin changes and venous ulcers. A previous history of DVT can distinguish this condition from lymphedema; Limb hypertrophy – Several syndromes are characterized by limb size discrepancies that may be due to hypertrophy of the soft tissues and bones (i.e., Klippel-Trenaunay syndrome) or disproportionate overgrowth of body parts (i.e., Proteus syndrome), which may affect one or more limbs (IANNIELLO et al., 2015).

These syndromes are associated with other clinical manifestations, such as capillary malformations, which may help differentiate them from lymphedema; Lipedema is a rare adipose disorder characterized as abnormal fat deposition with associated edema. A pedigree analysis suggests that it is inherited as an X-linked or autosomal dominant condition. It occurs almost exclusively in women. Patients with lipedema may have family members who also have abnormal patterns of fat deposition but usually have no history of lymph node resection or trauma as seen in lymphedema. Patients with lipedema may complain of pain, tenderness, and bruising easily (Rabe et al., 2018).

Elevation of the limbs has no effect on lipedema. The feet are usually not involved, but they may or may not be involved in lymphedema. Physical examination will help differentiate lipedema from lymphedema; Patients with lipedema usually do not have pitting edema, whereas lymphedema may present with pitting edema. If doubt persists, imaging studies may help. Patients with lipedema usually have normal lymphatic function, whereas patients with lymphedema may experience dermal reflux and lack of lymph node uptake; Myxedema results from infiltration of the skin by glycosaminoglycans with associated water retention, leading to non-pitting edema. In particular, recurrence of breast cancer in the axillary area or the development of lymphangiosarcoma should be excluded (MEHRARA et al., 2022).

6 TREATMENT

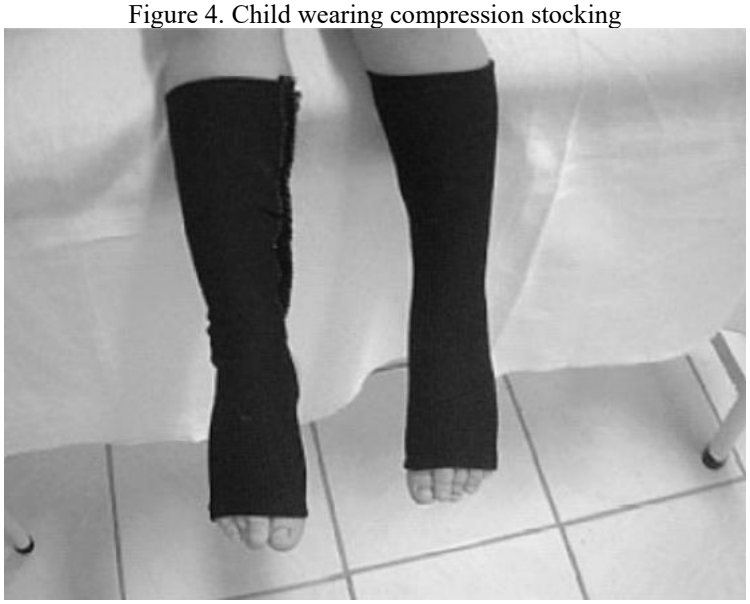
Congenital lymphedema is a condition in which there is an abnormal accumulation of lymphatic fluid in the tissues, causing prolonged edema, usually in the extremities of the body. Treatment for congenital lymphedema is directed toward symptom management and may involve a multidisciplinary approach that includes medical care, physical therapy, and supportive care. Some of the treatments that may be considered include compression therapy with the use of compression garments, such as compression socks, sleeves, or gloves (Figure 4). These can help reduce swelling

and improve lymphatic flow. Manual lymphatic drainage is a specialized massage technique that can help stimulate lymphatic flow and reduce fluid swelling. Exercise and movement, such as walking, swimming, or yoga, can help stimulate lymphatic flow and improve circulation. Skin care with this is important with this is to keep the skin clean and hydrated to prevent and other complications (KAUFMAN et al., 2016).

It may be necessary to use special creams or lotions to care for the skin healed by lymphedema. Additionally, physical therapy can be helpful in managing congenital lymphedema, with techniques such as strengthening exercises, joint alignment, and balance training helping to improve function and quality of life. Weight management is important to reduce the burden on the lymphatic system and improve the symptoms of lymphedema. Finally, surgical treatments may be considered in severe cases of congenital lymphedema, such as removal of excess affected tissue or lymphatic bypass surgery to divert lymphatic flow to healthy areas (Kaufman et al., 2016).

The indications for surgical treatment of lower limb lymphedema are: Lack of improvement or progression despite conservative measures; Non-operational management that has reached a plateau; Recurrent cellulite; Limitation of function (e.g., mobility, contracture); Lymph leakage into body cavities, organs, or externally; Deformity or disfigurement; Pain and decreased quality of life, including emotional or psychosocial distress (SCHAVERIEN; MUNNOCH; BRORSON, 2018).

Figure 4. Child wearing compression stocking



Fonte: Artíbale., et al (2005, p 02)

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