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Invited Review

Clinical features and management of pediatric lymphedema

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ABSTRACT

Lymphedema in children and young people (CYP) is a complex condition which impacts multiple aspects of their lives. Addressing these challenges requires a multidisciplinary approach, including medical treatment, psychological support, and social inclusion strategies. By understanding and managing the physical symptoms and providing emotional and social support, healthcare providers, families, and communities can help improve the quality of life for CYP living with lymphedema. Early intervention and ongoing care are crucial to minimizing its impact and supporting their overall wellbeing.

Keywords: Diagnosis, lymphedema, management, pediatrics.

Lymphedema is a chronic and progressive disease resulting from a dysfunctional lymphatic system due to abnormal lymphatic development, dysplastic valves, or obstruction in the lymph vessels. The typical finding of lymphedema is chronic swelling and accumulation of interstitial fluid in the periphery due to impaired return from the periphery to the central lymphatics (i.e., the thoracic duct).[1,2] While commonly associated with adults, lymphedema can also occur in children and young people (CYP), presenting unique challenges which can have a significant impact on their physical, psychological, and social well-being. The true prevalence of CYP remains uncertain; however, it is estimated to be based on an average annual incidence of 1.15 per 100,000.[3] This condition has a significant impact on the quality of life (QoL) of the children and families affected, yet awareness is still low in both developed and developing countries. This lack of knowledge often results in misdiagnosis or delayed diagnosis, thereby exacerbating the child's condition and complicate treatment.[4,5]

It is critical to implement effective strategies to prevent progression, facilitate early diagnosis, and ensure proper treatment in the management of pediatric lymphedema. Improving understanding of lymphedema in CYP is key to reducing the associated burden and disability.

Lymphedema is classified as primary and secondary. Although primary lymphedema is less common in the overall population, it constitutes the majority of lymphedema seen in the pediatric population. Primary lymphedema affects 1 in 100,000 children in the United States.[6]

Classification

In the past, primary lymphedema was classified as lymphedema congenita (from birth to 2 years of age), lymphedema praecox (2 to 35 years old), and lymphedema tarda (after 35 years of age).[6] Since this traditional classification is insufficient, primary lymphedema is further divided into four categories: infant-onset before one year of age, childhood-onset between the ages of one to 12, adolescent-onset between the ages of 13 to 21, and adult-onset after the age of 21.[7]

In primary lymphedema, genetic abnormalities affect the development or function of the lymphatic system, and clinical features may become apparent in infancy, childhood, or adolescence.[2] Although

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genetic causes of some primary lymphedema are known, it is not known exactly why clinical findings appear at different ages in patients.[7] In primary lymphedema, lymphatic vessels may be aplastic or hypoplastic, or there may be insufficiency or reduced contractility of the lymph vessels.[8] Primary lymphedema can occur either alone or as part of hereditary congenital disorders such as Milroy's disease and Meige's disease or genetic disorders such as Turner and Noonan syndrome.[9,10] "Milroy disease," or hereditary congenital lymphedema type 1A, is caused by an autosomal dominant missense mutation in the vascular endothelial growth factor receptor-3 (VEGFR-3) gene.[11] Hereditary congenital lymphedema type 2, also called Meige's disease, is caused by mutations in the forkhead box protein C2 (FOXC2) gene.[12]

Secondary lymphedema occurs as a result of an injury or obstruction affecting the lymphatic system. Although the most common cause worldwide is Wuchereria bancrofti infection, in developed countries, it is most commonly caused by malignancies or malignancy-related treatments.[6,13] Secondary lymphedema is rarely seen in the pediatric population.

Presentation of Lymphedema

Infants and children

Males are more likely to present in infancy, whereas females are more commonly diagnosed with lymphedema in adolescence.[14] Congenital lymphedema may present as isolated edema of one or more extremities or as generalized edema with systemic involvement. Prenatally, generalized lymphedema may manifest as hydrops fetalis, a condition associated with mutations in the Ephrin type-B receptor 4 (EPHB4) gene or genetic syndromes such as Turner, Noonan, and Hennekam.[10] Milroy disease can be identified prenatally or manifest as bilateral lower limb lymphedema after birth.[15]

Adolescents

Primary lymphedema is common in adolescence, particularly in females. Although the swelling in Meige's disease is typically not noticeable until puberty, the abnormalities of the lymphatic system are present from birth (congenital). Swelling usually starts in the ankles and feet and progresses up the legs to the knees.

Differential Diagnosis

In the pediatric population, there are several causes other than lymphedema which can cause swelling in the extremities or other parts of the body. Approximately one-fourth of these patients are misdiagnosed with lymphedema.[10] However, although vascular anomalies are the most common underlying causes, lipedema, hypoalbuminemia, tissue overgrowth, and cardiac diseases can also be seen.[16] In this context, while diagnosing lymphedema, it is crucial to do a thorough anamnesis, a physical examination, and any required radiological tests. If necessary, venous Doppler ultrasound (US) can be performed for venous insufficiency and deep vein thrombosis (DVT), echocardiography for congestive heart failure, blood and urine tests and ultrasound for kidney and liver diseases. If abdominal or pelvic pathologies (tumor, thrombus, etc.) are suspected, Magnetic resonance imaging (MRI) and computed tomography (CT) scans may be performed.

Lipedema is another important condition in differential diagnosis. Pure lipedema, at least in its early stages, is a disorder of aberrant fat accumulation rather than a disease related to the lymphatic system.[17] Unlike obesity, which is widespread, real lipedema frequently runs in families and affects young women. The lower extremities are disproportionately affected by lipodystrophy in patients, while the rest of the body is comparatively spared from excessive adipose tissue.[16,18] Lipedema differs from lymphedema in that it is characterized by pain, easy bruising, and foot sparing with an ankle demarcation.[19] It should be noted that the onset of lipedema is typically associated with the onset of puberty.[20]

Children and young people with lymphedema and any of the subsequent characteristics should undergo genetic testing: congenital onset lymphedema, systemic and/or visceral involvement (e.g., chylous, ascites, and pulmonary/intestinal lymphangiectasia), altered growth, syndromic phenotype, cutaneous involvement; vascular abnormalities, learning difficulties, distichiasis, and family history of lymphoedema.

Anamnesis and Physical Examination

The majority of primary lymphedema cases are diagnosed clinically. A comprehensive patient evaluation should begin with a detailed history of the swelling, including its time of onset, whether it has developed suddenly or gradually, and whether it is unilateral or bilateral. It is also critical to figure out whether the edema varies with body posture. A thorough examination should be done for any

related symptoms, such as pain or changes in the skin. Physicians should ask about any history of trauma to the affected area, recent travels to tropical countries, or prior surgeries involving the dissection of lymph nodes. Furthermore, it is necessary to consider underlying systemic disorders such as liver, renal, or cardiac illness. Finally, a family history of comparable presentations can provide valuable information about possible genetic factors.

Early onset of the disease is associated with systemic involvement. In patients with an earlier onset before one year of age, the likelihood of lymphatic comorbidities such as chylothorax and chyloabdomen is as high as 75%.[21] Yellowed nails, several warts, vascular abnormalities, limb length hypertrophy and/or asymmetry, facial dysmorphism, and/or intellectual impairment should also be evaluated to determine syndromic involvement.[22] All children should have a hematological evaluation, which includes recording albumin levels, thyroid function, renal and hepatic function, and a full blood count.[23]

Finding the location and distribution of the swelling should be the first step in a physical evaluation. Primary lymphedema frequently affects the lower extremities, starting from the foot and spreading proximally. Due to the swelling, the skin on the dorsum of the patient's foot cannot be pinched by the examiner's thumb and index finger, a so-called positive Stemmer's sign.[24] The Stemmer sign displays a sensitivity of 92% and a specificity of 57% for lymphedema.[23] Although lymphedema mostly affects the extremities, the face and genital area may be solely affected or generalized lymphedema involving the face and trunk may occur.[25] In the pediatric population, genital lymphedema is frequent. According to earlier studies, 8 to 18% of children with primary lymphedema had genital lymphedema.[14,26,27] Most of the investigations showed a male preponderance in genital involvement, and the majority also showed concurrent involvement of the lower extremities (Figure 1).[27]

Next, pitting and fibrosis should be evaluated and any indications of skin infection should be recorded. Skin problems such as warts, lymphangiectasia, papillomatosis, hyperkeratosis, nail abnormalities (upstanding toenails), and bacterial and fungal infections may be seen in lymphedema patients. Many of these skin conditions cause weakening of the epidermis and, therefore, predispose patients to the risk of cellulitis/erysipelas, which often worsens lymphedema.[28] Prolonged lymphedema may result in fibrosis of the subcutaneous tissue due to the accumulation of protein-rich interstitial fluid, which may elicit an inflammatory response.[29] As a result, patients develop skin thickening, reduced pitting, and hypertrophy of adipose tissue. Fibrosis typically starts first in the hands and feet.

In addition, the examination should include measurements of height, weight, and body mass index. In children, height and weight percentiles and head circumference should be measured.

Staging of Lymphedema[17]

Stage 0: This stage is the latent, subclinical stage. Although there is impaired lymph flow and changes

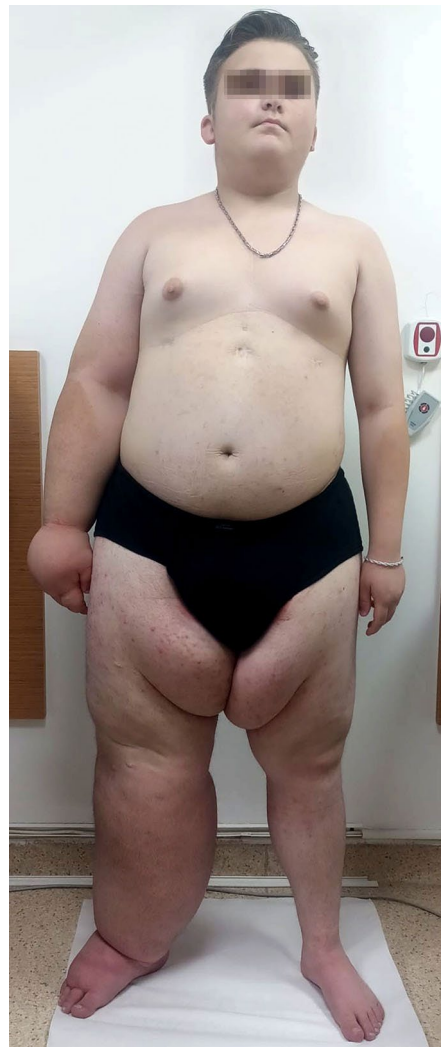

Figure 1. A male adolescent patient with unilateral lymphedema of the right upper and lower extremities and genital area.

in the fluid component in the tissue, swelling is not yet evident. This stage may be transient, or patients may remain in this stage for months or years before progressing to other stages.

Stage 1: In this stage, protein-rich fluid accumulation starts, but edema decreases with limb elevation. Pitting can happen. Increased proliferation of various cells can be seen at this stage.

Stage 2: At this stage, there is persistent protein and fat accumulation and fibrosis in the affected area. Reduction in edema with elevation is less common. Tissue stiffness increases compared to the previous stage.

Stage 3: This stage includes lymphostatic elephantiasis. Pitting may be absent. The skin character changes with more fat and protein accumulation, and trophic skin signs are seen.

It should be taken into account that more than one stage may appear in an affected area at the same time due to changes in different lymphatic territories.

Only the physical state of the extremities is mentioned at these stages. Improved knowledge of the pathogenic mechanisms of lymphedema (such as the type and severity of lymphangiodysplasia, lymph flow abnormalities, lymphatic valve maldevelopment, and nodal dysfunction as determined by anatomic features and physiologic imaging and testing) and underlying genetic disorders, which are gradually becoming clearer, demands the development of a more thorough classification.

Simple excess volume differences have been used for a limited but functional severity assessment for each stage. These variations are classified as minor (>5 to <20% increase in limb volume), moderate (20 to 40%), or severe (>40%). In certain clinics, >5 to 10% is considered minimal, while >10 to <20% is considered mild.

The most common approach for determining volume differentials is circumferential measurement, since it is inexpensive and widely accessible. For volume calculations, the truncated cone formula is utilized, and a flexible non stretch tape is recommended. Certain clinics use water displacement volumetry to measure the volumes of the arms, full legs, or lower legs, but there are some practical restrictions such as limb size, measuring areas close to the limb root, and hygiene difficulties.

Finally, it is critical to evaluate volume discrepancies between the limbs cautiously in cases of bilateral lymphedema.[17]

Imaging Methods

The diagnosis of lymphedema is usually made by anamnesis and physical examination; however, various methods can be used to confirm the diagnosis. Lymphoscintigraphy is the gold-standard diagnostic method with 92% sensitivity and 100% specificity in the diagnosis of lymphedema.[24] It is usually preferred after the age of seven to eight years, as cooperation is required during lymphoscintigraphy.[22] On lymphoscintigraphy, delayed transit time, dermal backflow, asymmetry in nodal involvement, and the presence of collateral lymphatic channels are findings in favor of lymphedema.[8] Although particular patterns are distinctive, such as lymphatic aplasia/hypoplasia vs. hyperplasia in primary lymphedema, the cause cannot always be ascertained from the imaging alone. Lymphoscintigraphy is safe and useful in the diagnosis of primary lymph edema in CYP as young as newborns.[30]

In recent years, indocyanine green (ICG) lymphography has become a popular imaging technique for diagnosing lymphedema. It has the ability to map lymphatic vessels in real time.[31] Compared to lymphoscintigraphy, this method is less invasive and less expensive. It is comparable to lymphoscintigraphy in its diagnostic capacity to assess the severity of the disease and has a high sensitivity and negative predictive value for precise diagnosis.[24] This method is usually considered safe for use in pediatric patients.[32] The primary limitation of ICG lymphography is that it only makes the superficial lymphatics visible.[24]

Magnetic resonance imaging is one of the more recent diagnostic, investigative, and potentially interventional techniques used to clarify structural changes in the lymphatic system as well as lymphangiodysplasia/lymphedema syndromes, particularly in infants and children. The MRI repertoire includes MR lymphography (MRL) and MR angiography (MRA) procedures, which are being refined and used more often in specialized locations worldwide. These techniques can be performed non-invasively without contrast or with peripheral and intranodal injections. These methods and specialized protocols produce high-spatial-resolution images that show deep-seated bodily structures, such as the thoracic duct.[17]

One in four cases of lower limb swelling in children is misdiagnosed as lymphedema. History, examination, and often imaging are required to differentiate this from other conditions.[14]

Treatment

The main goal of treatment is to minimize and stabilize lymphedema as much as possible, as well as to improve the patient's functioning and QoL. According to the International Society of Lymphology (ISL), the gold-standard treatment is non-operative therapy.[33] Treatment of lymphedema should be started immediately after diagnosis. This would reduce the risk of infection and prevent reversible skin changes.

Treatment of lymphedema requires a multidisciplinary team approach. At the center of this team is the patient and their family, as their participation in the treatment is of utmost importance. Since lymphedema requires lifelong follow-up, it is of utmost importance for the patient to comply with the treatment and follow-up. In addition, it is recommended that conditions such as depression and anxiety, and QoL, should be monitored at regular intervals in pediatric lymphedema patients.

Complete Decongestive Therapy

Complete decongestive therapy (CDT) is the main treatment for lymphedema and includes manual lymphatic drainage (MLD), compression bandaging, exercise, weight loss, skin care, and patient education. The CDT consists of two stages. The first stage aims to maximally reduce edema and strengthen the skin barrier, while the second stage aims to maintain the achieved level and prevent progression.[24] In the first stage, patients receive skin care, MLD, and occasionally deeper methods that involve muscle-pumping movements and compression, usually applied with multilayered bandage wrapping. Stage 2 includes skin care, ongoing exercise, compression with a low-stretch elastic stocking or sleeve, and MLD as required.[17] In a retrospective study by Vignes et al.,[34] including patients with primary lower extremity lymphedema, there was a greater decrease in edema volume in the first stage of CDT with older age, body mass index >40 kg/m^2, and a history of cellulitis/erysipelas.

Manual Lymphatic Drainage

Manual lymphatic drainage is a massage technique applied with specific and rhythmic, gentle hand movements to drain accumulated excess lymph fluid. It should be applied by a certified physiotherapist. With this technique, drainage of the lymph fluid in the affected area is achieved by stimulating the lymphatic system, thus reducing edema.[35] Most importantly, this is a light-touch, superficial massage rather than a deep tissue massage, which could be harmful. The MLD starts proximally in the abdomen, gently massaging toward the thoracic duct to remove fluid from the abdominal lymphatics. After that, the upper legs are massaged before going on to the distal extremities. This method causes the lymphatics to temporarily lose fluid. Following it, compression bandaging or the proper use of specialized compression garments must be applied.[17] According to a study by Ali et al.,[36] children with complex lymphatic abnormalities can benefit from MLD as a reliable noninvasive technique for decongestion and analgesia to postpone the development of lymphedema-associated fibrosis and long-term impairment.

Compression Therapy

A bandage or a compression garment is used to apply compression therapy to the affected area. This technique applies external pressure, supports the lymphatic system, facilitates lymphatic drainage, and prevents fluid buildup. The pressure garment should be specially planned according to the patient's needs and preferences. The children and their families should be educated about the care of the pressure garment. And the patient should be checked periodically to evaluate whether it maintains its optimal properties.[37] It is necessary to resize compression garments frequently during childhood to compensate for normal growth. The type of activities CYP engage in, and growth must be taken into account while determining the frequency of compression fittings and the number of sets of compression garments required every six months, as recommended by the International Lymphoedema Framework (ILF) (2010).[38] Each child and young individual's needs should be assessed on an individual basis. For toilet-training children, for example, more sets may be required. Compressive dressings for newborns and babies have not yet been proven to be effective (Figure 2).[22,39]

However, unlike adults, extra care is required in children during the bandaging process. Change in skin color and capillary refill should be monitored to assess overpressure. Additional indicators to

Figure 2. An infant with unilateral lymphedema has compression bandaging on the afflicted upper limb.

look out for include fussiness or crying which are indications of pain. As these individuals are more susceptible to cellulitis, fungal infections, and skin damage, careful skin care is crucial.

Gentler textiles are used for bandaging pediatric patients to prevent trauma or skin irritation. Cotton or cotton-like padding, lambswool, soft roll gauze, and terry cloth stockinette are examples of possible fabrics. For smaller hands and feet, a multilayered soft roll gauze can be used as a compression wrap on its own. Also, small fingers can be kept from pulling or picking by wrapping them with a tubular stockinette.

To achieve a high working pressure and the greatest possible reduction in edema, it is crucial to establish enough gradient compression through layering; nevertheless, layering shouldn't restrict mobility. Compression bandaging shouldn't limit a child's or infant's capacity to play or move, since play is crucial to their development. If it becomes difficult to maintain a wrap during the day or if a "bandage break" is required during the day, a caregiver may choose to apply bandaging before bed. To avoid splay-toe deformity or limit a child's ability to walk or crawl, therapists should use additional attention while putting toe wraps on infants or young children.[40]

Exercise

In the treatment of lymphedema, the exercise program should be specifically planned according to the child's capacity and to prevent a possible injury. Exercise plays an important role in the treatment of lymphedema as it stimulates lymphatic flow, strengthens the pump function of the muscles, and often improves physical and mental health. Exercise is also recommended as it has an effect on weight control. Low-intensity aerobic exercise is usually safe and appropriate for people with lymphedema. Flexibility and resistance exercises can also be beneficial, but are recommended under supervision due to the risk of increasing lymphedema.[37,39] Additionally, with deep inspiration, negative intrathoracic pressure is generated, thus directing lymphatic flow proximally.[24] In infants, exercises can be done through play activities and tactile stimulation to stimulate the pump activity of the muscles.

Patient Education

Key patient education topics include the significance of maintaining clean skin in the affected areas using non-perfumed, dye-free emollients, protecting the skin from sunburn, insect bites, and puncture wounds, and understanding the warning signs, symptoms, dangers, and surveillance of

cellulitis.[10] Managing and accepting lymphedema is difficult and affects various aspects of a family's life. Self-control might be challenging. According to the study of Quéré et al.,[4] meeting with other children and their parents, as well as providing an educational program tailored to each child's needs and follow-up, should all be part of the lymphedema care. Of note, a systematic review examining the conservative treatment of lymphedema in CYP concluded that currently there is insufficient evidence to recommend specific parameters for any treatment modality in CYP.[41]

Lymphedema services for CYP have been established in the last five years. Based on the experience of these services, lymphedema in CYP appears to be more common than previously reported. Secondly, childhood and adolescent lymphedema services have revealed that these children experience delays in accessing treatment. Improving education and awareness of lymphedema in young people, and prioritizing CYP for assessment, has enabled lymphedema treatment services to be more efficient.[42]

Surgical Management

Since primary lymphedema is usually adequately treated conservatively, surgical treatment is rarely required. Surgical management of lymphedema in children is particularly influenced by factors such as growth, development, appearance, and postoperative compliance.[43] The two main goals of surgical management are either increasing lymphatic flow (physiological operations) or excising excess skin and subcutaneous adipose tissue (excisional procedures). Surgery is indicated when there is substantial psychological morbidity, infections, and decreased function of the affected area, even with the most conservative treatment. For symptomatic patients with increased extremity volume due to subcutaneous fibroadipose deposition by MRI, liposuction is the first-line treatment. Patients still need conservative treatments for the rest of their lives because the operation does not cure lymphedema.[10,44]

Prognosis

Once lymphedema develops, it is rarely cured. The progression of the disease can be slowed or stopped, symptoms can be reduced, and consequences can be avoided with careful treatment and prevention. The chance of having lymphangiosarcoma is 10% for those who have had persistent lymphedema for 10 years. This tumor has a very bad prognosis, is extremely aggressive, and requires the severe amputation of the affected extremity. Less than 10% survive for five years.[45]

Complications

Various complications can occur in patients with lymphedema. Cellulitis is among the most common and frequently recurring side effects. Other important complications include lymphangitis, superficial bacterial and fungal infections, lymphangioadenitis, and DVT. Patients may experience significant functional impairment, psychosocial difficulties, and cosmetic concerns.[6]

In conclusion, recognizing the symptoms of lymphedema in children is essential for early intervention and effective management. Families dealing with lymphedema in children can access a range of resources to support them. Local and national organizations provide educational materials, support networks and access to specialist healthcare providers. Using these resources can improve lymphedema management and enhance the quality of life for children and their families.

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