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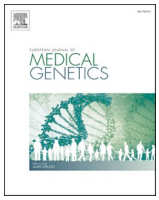

The VASCERN PPL working group patient pathway for primary and paediatric lymphoedema

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ABSTRACT

Lymphoedema is caused by an imbalance between fluid production and transport by the lymphatic system. This imbalance can be either caused by reduced transport capacity of the lymphatic system or too much fluid production and leads to swelling associated with tissue changes (skin thickening, fat deposition). Its main common complication is the increased risk of developing cellulitis/erysipelas in the affected area, which can worsen the lymphatic function and can be the cause of raised morbidity of the patient if not treated correctly/urgently. The term primary lymphoedema covers a group of rare conditions caused by abnormal functioning and/or development of the lymphatic system. It covers a highly heterogeneous group of conditions. An accurate diagnosis of primary lymphoedema is crucial for the implementation of an optimal treatment plan and management, as well as to reduce the risk of worsening. Patient care is diverse across Europe, and national specialised centres and networks are not available everywhere. The European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN) gathers the best expertise in Europe and provide accessible cross-border healthcare to patients with rare vascular diseases. There are six different working groups in VASCERN, which focus on arterial diseases, hereditary haemorrhagic telangiectasia, neurovascular diseases, lymphoedema and vascular anomalies. The working group Paediatric and Primary Lymphedema (PPL WG) gathers and shares knowledge and expertise in the diagnosis and management of adults and children with primary and paediatric lymphoedema. The members of PPL WG have worked together to produce this opinion statement reflecting strategies on how to approach patients with primary and paediatric lymphoedema. The objective of this patient pathway is to improve patient care by reducing the time to diagnosis, define the best management and follow-up strategies and avoid overuse of resources. Therefore, the patient pathway describes the clinical evaluation and investigations that lead to a clinical diagnosis, the genetic testing, differential diagnosis, the management and treatment options and the patient follow up at expert and local centres. Also, the importance of the patient group participation in the PPL WG is discussed.

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1. Introduction

Lymphoedema is caused by an imbalance between fluid production by the blood capillaries and transport by the lymphatic system. Accumulation of fluid in the interstitial space can be caused by either too much fluid production by the blood system (raised preload) or reduced transport capacity of the lymphatic system (raised afterload). It manifests in swelling, which is generally present in the extremities (usually in the legs), but also in other regions of the body such as the upper limbs, face, trunk or genital area. Lymphatic fluid stasis leads to tissue changes including skin thickening and fat deposition. Lymphoedema remains a chronic disease and worsens if left untreated (Grada and Phillips, 2017).

Another common complication associated with the dysfunction of the lymphatic system is the increased risk of developing cellulitis/erysipelas in the affected area. Cellulitis/erysipelas can be responsible for worsening the dysfunction of the lymphatic system, and it may even lead to sepsis. Another important aspect is the presence of skin lesions in patients with lymphoedema. These can be present in patients with primary lymphoedema and in secondary paediatric lymphoedema. Patients with wounds will experience delayed wound healing due to the dysfunction in the lymphatic system. An appropriate care of the wounds is crucial to avoid further complications (Damstra et al., 2008).

The term primary lymphoedema covers a group of rare conditions caused by an abnormal functioning and/or development of the lymphatic system (ISL Consensus Document, 2020). It represents a heterogeneous group that includes sporadic, hereditary and syndromic forms. In contrast, secondary lymphoedema is oedema developed after injury of the lymphatic system, especially after trauma or infection. Lymphoedema affects both adults and children. In children, it is known as paediatric lymphoedema, which can be primary or, more rarely, secondary (Devoogdt et al., 2022).

The first classification algorithm for primary lymphatic diseases was the St George's Classification for lymphatic anomalies, developed in 2010 and further updated in 2013 and 2020 (Connell et al., 2013; Gordon et al., 2020). This classification is based on the clinical features, the localisation of the oedema and the associated phenotype. According to it, primary lymphoedema is divided into five groups:

1) The syndromes (conditions with a constellation of malformations where lymphoedema is not the dominant feature)
2) Lymphoedema with systemic or visceral involvement (this includes foetal hydrops, pleural effusions, pericardial effusions, intestinal or pulmonary lymphangiectasia, ascites)
3) Lymphoedema with a congenital onset (<1.0 year).
4) Lymphoedema with a late onset (≥1.0 year)
5) The vascular and lymphatic malformations

Overall, this classification has the objective of providing an accurate diagnosis, as well as facilitating research into the genetic causes of the different phenotypes.

The diagnosis of primary lymphoedema can be challenging, and some individuals remain undiagnosed for years. It is important to receive a diagnosis as soon as possible after the appearance of the symptoms, in order to consider concomitant medical conditions, facilitate treatment and reduce the risk of progression (ISL Consensus Document, 2020). An accurate diagnosis and understanding of the cause of lymphoedema are important for the implementation of an optimal patient care and management (Devoogdt et al., 2022). Patient care is diverse across Europe, and diagnosis may vary according to the centre, indicating different referral criteria. Moreover, specialised centres and networks are not available in all countries. Therefore, there is a need for a statement describing the optimal strategies on care and management defined by experts and patient representatives in the field of primary and paediatric lymphoedema.

1.1. VASCERN PPL overview, goals, and delivery methods

At the European level, selected centres of expertise are united in European Reference Networks (ERNs), with the aim of increasing knowledge on rare diseases and taking better care of patients through collaboration. VASCERN, the ERN on Rare Multisystemic Vascular Diseases, gathers the best European expertise to help patients with rare vascular diseases. There are six different working groups within VASCERN, which focus on arterial diseases, hereditary haemorrhagic telangiectasia, neurovascular diseases, lymphoedema and vascular anomalies.

The Paediatric and Primary Lymphedema Working Group (PPL WG) is one of those groups, and it covers primary lymphoedema in children and adults, and secondary lymphoedema in children up to 18 years of age. This working group is composed by 8 healthcare providers, representing 7 EU countries (Belgium, Denmark, Finland, France, Germany, The Netherlands, Slovenia) and is supported by experts from the UK. A multidisciplinary panel of experts (dermatologists, vascular surgeons, geneticists, physiotherapists, nurses, plastic surgeons, internal and vascular medicine physicians) and patient representatives are part of PPL WG.

The objective of PPL WG is to gather expertise across Europe, in order to provide optimal guidance in the diagnosis and management of primary and paediatric lymphoedema.

The present document is an expert opinion statement reflecting strategies and have been put forward by medical experts and patient representatives involved in PPL WG. The aim of this document is to propose a pathway to:

1) Improve patient care and management by reducing time to diagnosis
2) Facilitate the establishment of a correct diagnosis
3) Define the best management and follow-up and
4) Ensure the efficient use of financial and personnel resources.

It can be used by non-specialised healthcare providers (HCPs) to guide them in choosing which patient has to be referred to a specialised centre. It also can be used by HCPs in specialised centres to help in the standardisation of care across Europe.

2. Results

Hereunder, the following steps of the patient pathway are discussed (see also Fig. 1): 1) clinical evaluation (blue), 2) additional clinical investigations (yellow), 3) genetics (green), 4) diagnosis (green) and 5) treatment and management (red). These steps are performed by the multidisciplinary expert centre, in cooperation with the first line HCP and local centres.

2.1. Clinical evaluation

A patient or their guardian contacts a general practitioner or other first line health care provider with the symptom of swelling. This care provider performs an adequate clinical evaluation and is the first step in diagnosing lymphoedema.

The initial evaluation requires a detailed family and travel history as well as a systematic clinical examination (Fig. 1). The physical examination must include evaluation of the skin. To investigate the degree and stage of oedema, palpation of the affected areas is mandatory. It should be noted if there is pitting oedema and/or signs of skin thickening. Pitting oedema can be demonstrated by applying firm pressure to the oedematous tissue. If this pressure causes an indentation in the tissue that remains after the pressure is released, pitting oedema is then present (Yale and Mazza, 2001) (Fig. 2A).

Subcutaneous fat and fibrosis can ensue after prolonged lymphoedema due to the accumulation of protein-rich interstitial fluid, which may elicit an inflammatory response. This response leads to lipogenesis,

fat deposition and dermal fibrosis (Grada and Phillips, 2017). Consequently, patients develop skin thickening, pitting decreases, and there is hypertrophy of the adipose tissue. The first site where fibrosis typically develops is on the feet or hands. Hence, examining for a positive Stemmer sign is mandatory in patients who are suspected to have lymphoedema. The Stemmer sign is positive if the skin on the dorsum or the base of the second toe of the foot or finger of the hand cannot be pinched as a fold by the fingers (Fig. 2B) (Pannier et al., 2007).

Common causes of swelling must also be ruled out by a physical examination that may need to be supplemented with relevant investigations such as venous doppler/duplex (venous insufficiency or deep venous thrombosis), echocardiography (congestive heart failure), blood tests, urine tests and ultrasound (kidney and liver disease). If abdominal or pelvic pathology (e.g. a tumour or thrombus) is suspected an MRI, ultrasound or CT scan may be performed.

We recommend to use the following criteria for referral to an expert centre for primary and paediatric lymphoedema (stated in the blue boxes of the Patient Pathway Flowchart, Fig. 1): *Patients with oedema for more than* 3 months *in combination with one or more of the following:*

1. congenital onset
2. family history of swelling
3. genital swelling, systemic involvement (e.g. intestinal lymphangiectasia, pleural effusions)
4. syndromic forms
5. recurrent cellulitis/erysipelas.

In the expert centre, a more detailed patient history should focus on age of onset of the oedema and the family history.

The physical examination should investigate the degree and stage of oedema in the different body parts (e.g. legs, arms, genitalia, face) and inspect whether the oedema is symmetrically distributed (Gordon et al., 2020). Moreover, the examination must include weight, size and BMI in adults and children, while in children, height and weight centiles and head circumference should be measured as well.

Lymphoedema patients may develop skin problems such as warts, lymphangiectasia (lymph blisters), papillomatosis, hyperkeratosis, nail abnormalities (upstanding toenails) and bacterial and fungal infections.

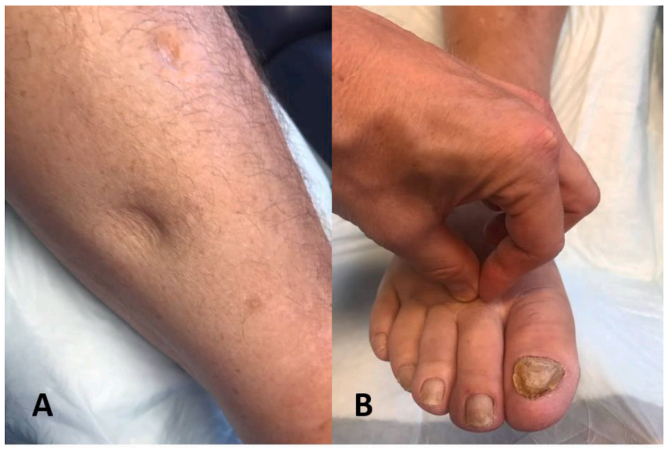

Fig. 2. Pitting oedema (A) and positive Stemmer sign (B) in a patient with primary lymphoedema.

Most of these skin conditions cause a breach in the epidermis and therefore predisposes patients to an increased risk of cellulitis/erysipelas, which often worsens the lymphoedema. Research shows a strong correlation between cellulitis/erysipelas and tinea pedis in particular, making it imperative to examine the skin carefully during clinical evaluation (Roujeau et al., 2004). On the other hand, many patients with lymphoedema and cellulitis/erysipelas cannot recall a skin defect at all (observations of members of PPL WG). The presence of oedema is strongly related to attacks of cellulitis/erysipelas (Burian et al., 2021).

Most cases of primary lymphoedema solely affects the extremities, but some patients may present with systemic involvement that gives rise to symptoms from the abdomen and/or heart/lungs (e.g., intestinal lymphangiectasia, pleural effusions, pericardial effusions, ascites and chylous reflux) (Vignes and Bellanger, 2018). If suspected, further investigations (e.g. radiographs, echocardiogram, MRI) should be requested.

Since primary lymphoedema is a genetic disease it is important to screen patients for associated problems such as venous insufficiency,

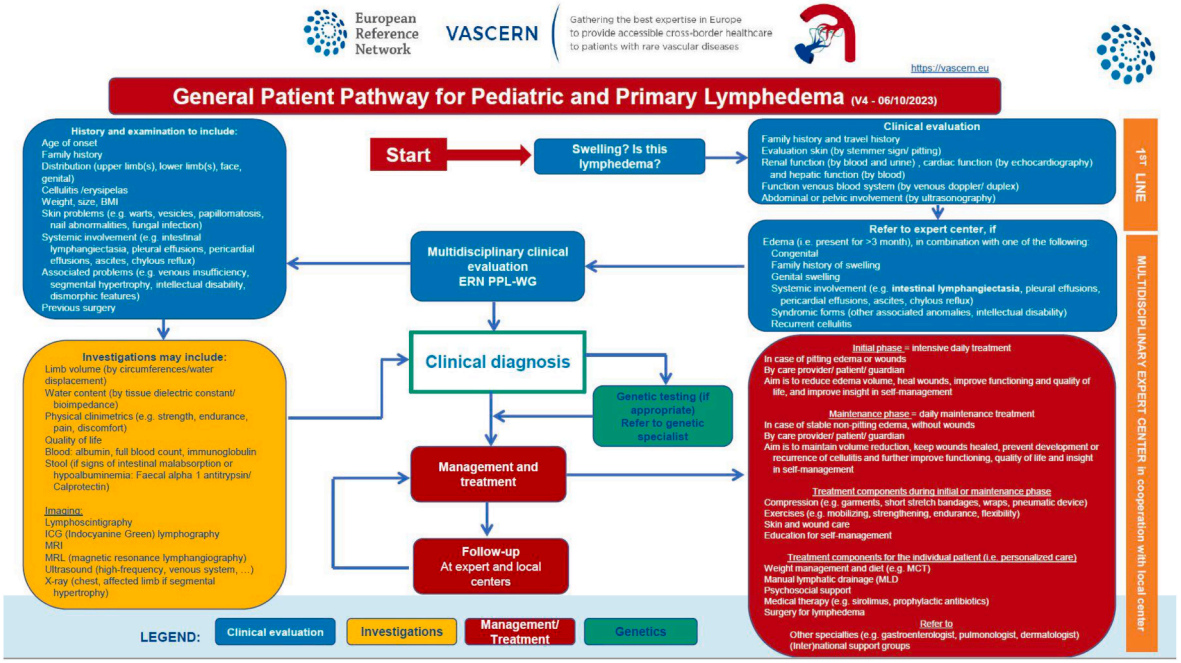

Fig. 1. General Patient Pathway for paediatric and primary lymphoedema. It includes the key aspects of the 1st line clinical evaluation and referral to the multidisciplinary expert centres and the further clinical evaluation, investigations, genetic testing, management and treatment, and follow up at expert and local centres.

segmental hypertrophy, intellectual disability and dysmorphic features, during the diagnostic work-up.

Finally, it is essential to have information about previous surgical history (e.g. lymphadenectomy, trauma) and medical history (e.g. cellulitis/erysipelas, cancer, radiation therapy) in the assessment of secondary paediatric lymphoedema.

2.2. Additional investigation

In many cases, an accurate diagnosis can be made by conducting a proper clinical evaluation. However, in some patients with primary or paediatric lymphoedema, one or more additional investigations are needed to come to a complete overview of their clinical situation.

2.2.1. Measurements related to volume and water content

The first step to quantify the oedema in patients with primary and paediatric lymphoedema is performing limb volume measurements. To have an idea of the amount of oedema, the excessive volume (i.e. difference in volume/circumference between the affected and the non-affected limb) is calculated. This is only possible if a patient has unilateral lymphoedema. Obviously, in patients with bilateral primary lymphoedema it is not relevant to evaluate this excessive volume. In these cases, lymphoedema is objectively detected by performing direct measurements of water content or extracellular fluid (see below). Limb volumes can be determined by performing the water displacement method and/or opto-electronic volumetry (with a perometer ®), and/or circumference measurements using the truncated cone formula (ISL Consensus Document, 2020). Since oedema of the foot (and sometimes hand) is also frequently present in patients with primary lymphoedema, it is also important to evaluate the volume of the foot/hand separately. This can be performed with the water displacement method or figure of eight method (Devoogdt et al., 2019).

Tissue dielectric constant devices are useful tools to evaluate the water content in the skin using electromagnetic waves. Bio impedance analysis/spectroscopy is a method to estimate the body composition. Alternating currents of a range of frequencies are passed through the body. By measuring the resistance that the current experienced at the level of the tissues, it is possible to estimate, the amount of body fat, the muscle mass and the water in the body (both intra- and extracellular) (Mulasi et al., 2015).

The clinimetric properties of methods determining volume and of devices measuring tissue dielectric constant and bio-impedance have been investigated in adults, and especially in patients with upper limb lymphoedema, but not yet in children with lymphoedema (Hidding et al., 2016). Whether these methods/devices are useful in children as well is currently unknown.

2.2.2. Evaluation of functioning, problems in functioning and quality of life

A complete overview of the clinical situation of the patient should be established. Oedema is often accompanied by other problems. As a consequence, the measurement of only the limb volumes is not sufficient to develop a holistic treatment plan.

The International Classification of Functioning, disability and health (ICF) is a valuable instrument for mapping the patient's functioning and problems in functioning (World Health Organization, 2001). Table 1 gives an overview of the instruments that have to be used for detection of the problems in functioning (Damstra et al., 2017). To have a general overview of the lymphoedema-specific quality of life, patients with primary lymphoedema may complete the Lymph-ICF questionnaire. Specific questionnaires for patients with upper limb lymphoedema or with lower limb lymphoedema exist. The questions within the questionnaires are categorised into 5 domains: 1) physical function and 2) mental function 3) household, 4) mobility and 5) life & social activity (Devoogdt et al., 2014; De Vrieze et al., 2019). More information about the questionnaire and available translations can be found on the website: https://www.caredon.org/researchers/tools. Another lymphoedema-specific quality of life questionnaire that can be used is the LYMQOL questionnaire that also exists for patients with upper limb or lower limb lymphoedema. The questions are categorised into following groups: function, appearance, symptoms, emotional and overall quality of life (Keeley et al., 2010). These questionnaires can be used in adult patients with primary lymphoedema. A lymphoedema-specific questionnaire for children with primary or secondary lymphoedema is being developed by the International Lymphoedema Framework (i.e. LYMPHOQOL for children). To understand the impact of lymphoedema in children, it is important to measure the quality of life with tools that are disease specific and age related. The LYMPHOQOL questionnaires are for age group 6–12 years and age group 13–21 years. The clinimetric properties of both questionnaires for children are currently under investigation.

On the level of impairments in function, besides limb volume, the following physical impairments may be objectively evaluated as well

Table 1
Overview of the outcomes and measurement methods which are recommended to be evaluated in patients with primary and paediatric lymphoedema.

Outcome	Measurement method	At baseline (for detection of problems in functioning)	During follow-up	Also in children
Local water	Pitting test	X	X	X
Skin condition	Inspection, photograph	X	X	X
Swelling midline	Inspection, photograph	X	X	X
Limb volume	Water displacement method, Perometer ® or measuring tape	X	X	X
Foot or hand volume	Water displacement method or figure-of-eight	X	X	X
Episodes of cellulitis/ erysipelas	Anamnesis	X	X	X
Body weight	Scales	X	X	X
Body length	Stadiometer	X	X (in children)	X
Muscle strength	Medical Research Council Scale, hand-held dynamometer	On indication	On indication	On indication
Endurance and gait pattern	6-min walking test, steep ramp	On indication	On indication	On indication
Physical activity level	Subjective, objectively by e.g. International Physical Activity Questionnaire	On indication	On indication	On indication
Pain	Visual Analogue Scale or Numeric Rating Scale	On indication	On indication	On indication
Discomfort	Distress thermometer	On indication	On indication	On indication
Joint range of motion	Goniometer	On indication	On indication	On indication
Fatigue	Visual Analogue Scale or Numeric Rating Scale	On indication	On indication	On indication
Lymphoedema-specific quality of life	Lymph-ICF for upper or lower limb lymphoedema, LYMQOL for upper or lower limb lymphoedema	X	X	X

(Table 1): muscle strength, cardiovascular endurance and gait pattern, physical activity level, pain, discomfort, limited joint range of motion and fatigue (Damstra et al., 2017). These aspects may be evaluated where indicated, depending on the clinical situation of the adult or child. It is recommended to involve a paediatric physiotherapist for the evaluation of children and babies.

Special attention should be paid to the evaluation of environmental factors (such as the compression garment, support of the patient, aids to daily living) and personnel psychological and emotional factors (such as anxiety, depression).

2.2.3. Laboratory tests

It is important to differentiate between isolated peripheral lymphoedema and central lymphatic forms of lymphatic impairment. The diagnosis of a central lymphatic disorder with systemic involvement may be supported with blood tests (Gordon et al., 2020). We advise in restricted cases to perform a full blood count (e.g. to detect lymphopenia or monocytopenia) or to determine lymphocytes subsets for CD4/CD8 ratio, immunoglobulins and albumin levels. For example, monocytopenia is a key feature of Emberger syndrome.

Furthermore, the increase of alpha 1-antitrypsin clearance in the stool confirms a protein losing enteropathy. This can be related to lymph leak into the gastro-intestinal tract (primary intestinal lymphangiectasia).

2.2.4. Imaging techniques

Due to the small diameter of lymphatics, it is difficult to directly visualise the lymphatic system. Some specific imaging techniques are developed to investigate the lymphatic system: lymphoscintigraphy, ICG lymphography and MR lymphangiography. Table 2 shows an overview of imaging techniques that may be applied in a patient with primary or paediatric lymphoedema.

Lymphoscintigraphy is one of the most frequently used imaging techniques for the diagnosis and evaluation of primary lymphoedema. It offers both dynamic imaging of the superficial lymphatics and lymph nodes, as well a semi-quantitative data of the lymphatic transport. Lymphoscintigraphy can be used to support a diagnosis and it can show typical features for primary lymphoedema, such as decreased inguinal uptake, visualisation of popliteal lymph nodes as a sign for rerouting into the deep system, dermal backflow indicating reflux of the lymphatic flow and absence of the lymphatic flow (Szuba et al., 2003). For example, in subjects with lymphoedema distichiasis syndrome typically dermal backflow due to lymphatic valvular incompetence is seen.

Another technique is the ICG lymphography, which also can be used to visualise the superficial lymph transport and architecture in patients with primary lymphoedema (Suami et al., 2022).

Leakage may occur into the abdomen or into other body cavities. Intranodal lymphangiography (or MR-lymphography) is used for imaging of central abdominal and thoracic lymphatic vessels directly by injecting an MR contrast medium (i.e. gadolinium) into inguinal lymph nodes. It is used to diagnose leakage out of the central lymphatic system, lymphatic malformations or to diagnose chylous reflux or leakage (Arrivé et al., 2018). Non-contrast MR lymphography is able to classify primary lower limb lymphoedema into hyperplastic, aplastic, hypoplastic and normal patterns. These patterns indicate the severity of the condition. (Arrivé et al., 2018).

Magnetic Resonance Imaging (MRI) is of additional value in certain (genetic) disorders to distinguish bone structure changes, overgrowth syndromes and vascular malformations. Furthermore, by performing MRI, abnormalities in lymph nodes and causes for lymphatic obstruction (e.g. abdominal masses compromising lymph flow) may be detected. Finally, certain characteristics of the lymphoedema, such as fluid accumulation in soft tissue, fat hypertrophy and skin thickening may be visualised as well. A (duplex) ultrasound may also be performed for several purposes: 1) to investigate the presence and extent of oedema in the epifascial spaces; 2) to determine a venous origin of the oedema by

Table 2
Additional investigations of the lymphatic system in patients with primary or paediatric lymphoedema.

Type	Description	Indication	Advantage	Disadvantage	Also in children
Lympho-scintigraphy	Injection of radio-isotope into the dermis to investigate the superficial and deep lymphatic system; qualitative and semi-quantitative evaluation	If primary lymphoedema is expected	Besides visualisation, it provides also information about function of the lymphatic system; also information about severity of disturbance of lymphatic system	Invasive technique; time consuming; patient must be able to walk and lay down for at least 30 min; radioactivity	Performed when the child understands the procedure and only if indicated (e.g. if diagnosis is not clear)
ICG lymphography	Injection of indocyanine green (ICG) or other fluorescent agent into the dermis to investigate the superficial lymphatic system; qualitative evaluation	On indication, e.g. if localised oedema of foot, to check indication for surgery and prepare it, if no stabilisation of oedema unless good conservative treatment	Detailed information of superficial lymphatic architecture; real time imaging	Minimally invasive; only superficial visualisation of the lymphatic system (up to 2 cm); operator dependent	Performed when the child understands the procedure and only if indicated (e.g. if diagnosis is not clear)
MRI/MR lymphography	Visualisation of lymphatics with or without gadolinium injection	If central lymphatic disturbance (e.g. chylous syndrome) or evaluation of lymphatic system of limbs (e.g. indication for surgery; no stabilisation unless good conservative treatment)	Diagnosis of central lymphatic disturbance; direct treatment of leakage is possible	Invasive; difficult to perform and interpret, need expertise; time consuming	Only in severe cases with central lymphatic disorder

mapping the venous system for superficial and deep insufficiencies (useful in some types of primary lymphoedema, e.g. lymphoedema distichiasis syndrome); 3) antenatal examination e.g. for hydrops fetalis; 4) in combination with elastography, to measure the dermal (tissue) stiffness with shear waves; and 5) to visualise enlarged lymph nodes and to detect abdominal masses that compromise lymph flow. Pleural and pericardial effusions can be demonstrated with an X-ray (chest) radiograph. Effusions can be exudates or transudates. These effusions may be suspected in patients who present with shortness of breath, coughing and chest pain or fatigue. It can result from leakage out of the lymphatic system into the pleural/cardiac space. They may also be chylous i.e. have a milky appearance due to the presence of chyle derived from intestinal lymphatics. Leakage of chyle is caused by damage to the thoracic duct, congenital abnormalities or excessively high venous pressure.

2.3. Genetic testing

Primary lymphatic anomalies are a highly heterogeneous group of conditions. A discussed in the introduction, the classification of these conditions has been published (St. George's classification algorithm), with its latest update in 2020. Genetic causes and testing can be structured around this classification. Genetic testing is appropriate and helpful in the diagnosis and management of children and adults with primary lymphatic disorders, so the patient may need to be referred to a genetic specialist. This field is developing rapidly and a growing number of genetic causes are being identified each year (Gordon et al., 2020).

A specific genetic diagnosis can inform about the natural history and prognosis of the condition, surveillance for associated complications and recurrence risk for offspring or siblings of the proband. Availability of genetic testing varies from one centre or country to another, although this is rapidly improving.

Genetic testing is not usually indicated in those with secondary lymphoedema with clear causes. However, some cases of primary lymphoedema may occur after minor trauma e.g. a sprained ankle, which leads to persistent swelling, where the degree of trauma would not usually be expected to cause chronic swelling. Similarly, persistent swelling after an episode of cellulitis/erysipelas may indicate an underlying primary lymphatic dysplasia (Keeley, 2008).

Many of the primary lymphoedemas are single gene disorders. These can be diagnosed on DNA extracted from blood lymphocytes from an affected individual. Testing can either be for single genes (targeted) or a panel of genes including many or all the genes currently known to be associated with lymphoedema. This is usually done by next generation sequencing, also known as massive parallel sequencing.

Some examples of primary lymphoedema are listed below:

1. Milroy Disease (see Fig. 3)

Milroy disease is often caused by pathogenic variants in The FLT4 gene which encodes for the Vascular Endothelial Growth Factor Receptor 3 (VEGFR3). This condition presents with congenital lymphoedema, particularly of the dorsum of the feet – usually bilateral, but may be asymmetrical. Other typical characteristics are prominent veins at the level of the leg(s) and upward-pointing nails of the toes. Males have an increased risk of hydroceles (at any age) and minor urethral abnormalities (e.g. hypospadias). There is rarely swelling of any other extremity. This condition is autosomal dominant.

2. Lymphoedema Distichiasis syndrome

Pathogenic variants in the FOXC2 gene cause lymphoedema distichiasis syndrome (LDS). This presents with lymphoedema of the lower limbs in late childhood or adulthood, varicose veins at a young age of onset, distichiasis from birth (extra eyelashes arising from the inner aspect of the eyelids) and an increased incidence of congenital heart disease, renal abnormalities, cleft palate and spinal cysts. This condition is also autosomal dominant.

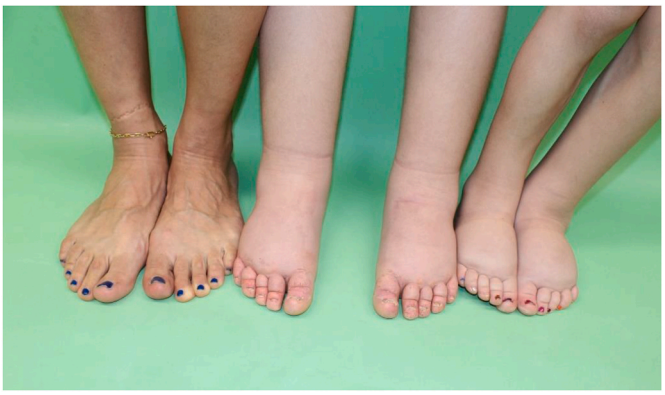

Fig. 3. Mother with two children who genotypically have Milroy disease, but phenotypically are very different.

3. GATA2-deficiency (Emberger syndrome)

Pathogenic variants in the gene, GATA2 may present with childhood onset of lymphoedema, often in one leg and the genital area. This condition is particularly important to diagnose, as it can be complicated by immunodeficiency, myelodysplasia and leukaemia. Surveillance for these complications is indicated.

4. Generalised Lymphatic Dysplasia

There are a number of genes resulting in a generalised lymphatic dysplasia (GLD) (swelling of all four limbs, genitals and face) with internal (systemic) lymphatic problems (intestinal lymphangiectasia, pleural or pericardial effusions or may present antenatally with fetal hydrops). These genes are usually inherited in an autosomal recessive manner. These genes include CCBE1, FAT4, ADAMTS3, FBXL7 and PIEZO1.

A child (or adult) may present with lymphoedema of the extremities but also with intellectual disability, autism, structural malformations and or dysmorphic features (unusual facial features). These patients should be carefully evaluated for the underlying cause. It is possibly due to a chromosome abnormality – which would be detected by a test called an array CGH (comparative genomic hybridisation). However, some other single-gene disorders may present in this way (e.g. Noonan syndrome). In some centres, the genes for these syndromic conditions may be included in the 'lymphoedema gene panel'.

Finally, some patients may have a localised genetic disorder presenting with swelling, segmental overgrowth and vascular malformations (e.g. Klippel Trenaunay syndrome). Testing the DNA extracted from blood lymphocytes rarely identifies the underlying genetic cause. In this group, DNA extracted from a skin biopsy from the affected limb is much more likely to identify the cause, e.g. gain of function pathogenic variants in *PIK3CA*. These patients are seen by the VASCERN vascular anomalies working group.

2.4. Differential diagnoses

Although the diagnosis of the different types of primary lymphoedema is largely based on the St. George's algorithm (with appropriate investigations and genetic testing), secondary lymphoedema may need to be considered and excluded in the differential diagnosis following a detailed assessment of the patient's medical history, complete physical examination and complementary investigations (see 'clinical evaluation').

For example cardiac, renal or hepatic diseases (with hypoalbuminemia) have to be excluded. Chronic venous insufficiency with

oedema, including post-thrombotic syndrome, can sometimes be mistaken for primary lymphoedema but does not usually engender a positive Stemmer's sign. Chronic venous insufficiency is diagnosed with venous Doppler ultrasonography. Advanced forms of chronic venous insufficiency may cause lymphatic overload, but its specific signs are at the forefront with skin changes (pigmentation/eczema, lipodermatosclerosis or atrophie blanche, corona phlebectatica, active or healed ulcer) (Lurie et al., 2020). In post pubertal teenagers or adulthood, lipoedema, often confused with lymphoedema, is the main differential diagnosis (Vignes et al., 2017). Lipoedema is defined as an abnormal accumulation of adipose tissue from the hips to the ankles, initially sparing the feet (Bertsch et al., 2020). Lipoedema almost exclusively affects women, who are often obese, and usually begins at puberty. The tissue feels soft, the limb is spontaneously painful, when pinched or after (minor) physical contact and pitting oedema is absent. Signs of obesity-related venous hypertension may be present.

Primary lymphoedema in infants is sometimes difficult to diagnose when the foot and lower leg are chubby but the diagnosis may become clearer over the following months or years. Hamartomatous or vascular anomalies, especially cystic lymphatic malformation on the dorsal aspect of the foot, may mimic lymphoedema. Ultrasound or magnetic resonance imaging (MRI) are required to confirm the diagnosis.

In children, the main differential diagnoses are limb hypertrophy, especially those entities attributable to the segmental overgrowth syndromes caused by gain of function somatic/mosaic (PIK3CA)-gene mutations and called PIK3CA-related overgrowth spectrum (PROS)

Table 3
Overview of the treatment modalities for paediatric and primary lymphoedema.

Treatment modality	Goal	Description	Specific for patients with primary and paediatric lymphoedema	Level of evidence in lower limb lymphoedema[a]
Compression therapy (compression garments, short-stretch bandages and velcro wraps)	1) To increase tissue pressure, which result in an increase of the resorption by the lymph system and a decrease of the filtration by the blood system; 2) To displace the oedema to a region where less/no compression is applied; 3) To create a stiff wall around the limb and, if combined with muscle contractions, to stimulate lymphatic and blood transport; 4) If padding (with or without structure) is used, a higher local pressure is created and tissue fibrosis is reduced.	The preference of material goes towards inelastic material. In addition, for garments compression class 2 for upper limb (20–30 mmHg) and class 3 (35–45 mmHg) or 4 (>45 mmHg) for lower limb, custom-made and flat knitted is recommended. The choice of the type of compression differs according to the clinical state of the oedema, the shape of the region with oedema, the location of the oedema, the preference of the patient/care provider, the phase of treatment (initial or maintenance) and the reimbursement policies. The different compression methods can be combined as well.	A first difficulty in children with primary lymphoedema is that they grow fast. The consequence is that the compression garment has to be replaced regularly. A second difficulty is that the toes and feet in young children are small, which makes that it is more complex to produce a toe cap or knee stocking or to bandage the toes, foot and limb. A third difficulty is that the optimum time to start compression treatment in children with congenital lymphoedema has not been established: one year after they are born, after two years or even before? In children, the recommended compression level (mmHg) of compression garments is lower than for adults	Primary lymphoedema: - no studies about compression garments and velcro wraps - short-stretch bandages (level IV, Benoughidane et al., 2018) Secondary lymphoedema: - compression garments (level III-3, Brambilla et al., 2006) - short stretch bandages (level II, Badger et al., 2000) - Velcro wraps (level II, Borman et al., 2021)
Compression therapy – pneumatic compression	To increase tissue pressure and to displace the oedema proximally	Pneumatic compression uses a compressor and a cuff with air chambers (Phillips and Gordon, 2019). The cuff is wrapped around the limb and intermittent compression is generated. It can be used as an adjunctive therapy or if conventional compression therapy is not possible/effective	If applied in children, a smaller cuff is needed	Adults and children with primary lymphoedema, upper & lower limb (level I, (Phillips and Gordon, 2019)
Exercises	1) To reduce the oedema volume by stimulating the muscle pump and obtain a pump-effect in the epifascial space. 2) To improve joint mobility, muscle strength, cardiovascular endurance and muscle flexibility	Mobilising, breathing, strengthening, endurance and flexibility exercises, while wearing compression		Primary lymphoedema: no studies Secondary lymphoedema: level II, Do et al., 2017; level III-1, Fukushima et al. (2017).
Skin and wound care	1) To improve or maintain the condition of the skin 2) To reduce the risk of cellulitis/erysipelas	Patients often have a dry skin, caused by the compression material and the increasing tension of the skin (due to swelling). Some patients also have skin irritation because of the friction of the compression material. Adequate skin care with hydration is important. If a wound is present, local wound care according to the Tissue Infection Moisture Edges (TIME) management is advised	Wounds do not occur because of the impaired lymphatic system (as in primary or secondary lymphoedema), but rather because of venous insufficiency.	Primary lymphoedema: no studies Secondary lymphoedema: no studies
Education and self-management	To facilitate patients to play an active role in their own management and be better able to stabilise the oedema	The patient/caregiver can be taught the method and reason of putting on a garment, bandage or wraps, performing self-exercises, taking care of the skin and evaluating the region with lymphoedema. Providing information on the prevention of infections is also very important.	Try to involve children as much as possible in self-management (such as skin care, compression)	Primary lymphoedema: no studies Upper and lower limb lymphoedema (level IV, Blaise et al., 2017)

[a] According to the National Health and Medical Research Council; level I = systematic review of level II studies; level II = randomized controlled trial; level III-1 pseudorandomised controlled trial; level III-2 comparative study with concurrent controls; level III-3 comparative study without concurrent controls; level IV case series.

(Keppler-Noreuil et al., 2014). For the differential diagnosis with primary lymphedema, PROS includes CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Skeletal and spinal anomalies), and Klippel–Trenaunay syndrome. In this context, complementary investigations (e.g. MRI, cutaneous biopsy with genetic analyses) are required. Germline pathogenic variants of the RASA1 gene and EPHB4 (ephrin type-B receptor 4) may present with arteriovenous malformations (Parkes Weber syndrome) (Amyere et al., 2017).

2.5. Management and treatment of lymphoedema

The main therapeutic goal is to maximally reduce the lymphoedema, stabilise it and improve the functioning and quality of life of the patient. According to the International Society of Lymphology, the gold standard in the treatment of lymphoedema is a non-surgical treatment (ISL Consensus Document, 2020). A surgical treatment is only offered in certain cases (this is discussed further below).

The management of the lymphoedema needs to start as soon as possible after its occurrence. This reduces the risk of infections and avoids the development of reversible tissue changes. A multidisciplinary approach for the management of lymphoedema is needed, not only involving different specialised medical doctors and physical therapists, but also nurses, psychologists, dieticians, social workers and compression specialists. If a multisystemic disease is present, the patient has to be referred to other specialists, such as the gastro-enterologist, respiratory physician or dermatologist.

2.5.1. Decongestive lymphatic therapy

Every patient with primary or paediatric lymphoedema is effectively treated by the decongestive lymphatic therapy (Lasinski et al., 2012). This is a two-stage treatment programme consisting of an initial (intensive) phase and a maintenance phase. The decision of the kind of treatment phase is based on the clinical state of the lymphoedema. If there is pitting oedema, the treatment is started with the initial intensive phase. During this phase, patients are treated daily by a care provider or guardian, and the patient performs self-management. The aim of the initial phase is to maximally reduce the lymphoedema, heal the wounds and skin lesions (if present), improve physical and mental functioning and quality of life, and improve the patient's insight in self-management. Abakay et al. compared the effect of the intensive phase of decongestive lymphatic therapy between 20 patients with primary lower limb lymphoedema and 20 patients with secondary lower limb lymphoedema (Abakay et al., 2021). In both groups, the oedema volume and lymphoedema-specific quality of life improved significantly. However, the change of the oedema volume was not significantly different between both groups. In contrast, lymphoedema-specific quality of life improved significantly more in patients with secondary lymphoedema than in patients with primary lymphoedema. Moreover, Vignes et al. have shown in a retrospective study in patients with primary lower limb lymphoedema, that being older, having a BMI >40, having a history of cellulitis/erysipelas and a lower initial lymphoedema volume was associated with a larger decrease of the oedema volume during an intensive treatment phase (Vignes et al., 2021).

In case of stable non-pitting oedema and no presence of skin lesions/wounds, the maintenance phase is started. During this phase, the patient or guardian performs daily (self-)management, which is supervised by the care provider. The aim of the maintenance phase is to conserve and optimise the result obtained in the initial phase, keep wounds closed, prevent development or recurrence of cellulitis/erysipelas and further improve functioning and quality of life and insight in self-management.

The initial and maintenance phase consist of several components: compression, exercise therapy, skin and wound care, and education for self-management. See Table 3 for the goal, the description, specific information for patients with primary and paediatric lymphoedema and the level of evidence for every component of the decongestive lymphatic therapy.

Besides the decongestive lymphatic therapy, some patients may also benefit from other treatment modalities, such as weight management and diet, manual lymphatic drainage, psychosocial support, medication and surgery.

2.5.2. Weight management and diet

Attention should be given towards a healthy life-style with a daily focus on healthy food, sufficient drinks, sufficient sleep and avoiding stress. No specific diet is currently recommended (ISL Consensus Document, 2020). The goal is maintaining a healthy stable weight through a healthy lifestyle. If the patient is overweight or obese, losing weight is likely to improve the condition of the lymphoedema (level of evidence II (Shaw et al., 2007). However, the effectiveness of weight management and diet has only been demonstrated in patients with breast cancer-related arm lymphoedema, and not in patients with primary and/or paediatric lymphoedema.

In cases of chylous effusion (or protein-losing enteropathy), a strictly low-fat diet supplemented with medium chain triglycerides diet (MCT) will diminish the production of chylous fluid, and therefore, lymph leakage (Al-Busafi et al., 2014). This may also improve hypoalbuminaemia associated with intestinal lymphangiectasia.

2.5.3. Manual lymph drainage

Manual lymph drainage (MLD) is a massage technique that aims to stimulate the resorption of lymph by the lymph capillaries and the transport of lymph through the lymph collectors. Worldwide different schools of manual lymph drainage exist. The most well-known are the manual lymph drainage schools of Casley-Smith, Leduc, Vodder, Földi or Belgrado (Fill & Flush).

Although the physiological effect of manual lymph drainage on the lymphatic system has been demonstrated (Tan et al., 2011), it has never been proven that it enhances the clinical situation of the patient with lymphoedema. Its added value to the other parts of the decongestive lymphatic therapy has extensively been investigated in patients with breast cancer related-lymphoedema. However, different systematic reviews had the same conclusion: the added value of manual lymph drainage is limited (Ezzo et al., 2015; Liang et al., 2020). Moreover, the added value of manual lymph drainage has never been investigated in patients with primary and/or paediatric lymphoedema.

2.5.4. Psychosocial support

In some patients, the presence of lymphoedema is associated with psychological distress, which has a negative impact on the patient's quality of life (Franks et al., 2006). Psychosocial support should be provided by the specialised centres. For children, psychological stress and uncertainty can be particular problems as they go through puberty and adolescence. Specific attention should also be given to developing sexuality. The added value of psychosocial support in patient with lymphoedema in general has never been investigated.

2.5.5. Medical therapy

There are a small number of drugs which may be helpful in the management of selected patients with specific conditions. In PIK3CA related overgrowth these drugs include mTOR inhibitors (e.g. sirolimus) (Venot et al., 2018) and a specific PIK3CA inhibitor, alpelisib. In Rasopathies, e.g. Noonan syndrome, MEK inhibitors, such as trametinib, may be useful in relieving the effects of severe lymphatic anomalies.

Antibiotics should be administered if a cellulitis/erysipelas is present. If repeated infections occur despite an optimal conservative treatment ($\geq$2 episodes/year), prophylactic antibiotics are recommended (ISL Consensus Document, 2020).

2.5.6. Surgery

In general, due to the large variation in aetiology, there is no routine indication for surgery in the treatment of primary lymphedema. Surgical

Table 4
Overview of studies about the effectiveness of surgery in patients with primary lymphoedema.

Author, country, design & level of evidence	Population	Surgical method	Assessment	Result
Reductive Procedures				
Karlsson et al., 2022 Sweden Retrospective study Level IV	n = 63 primary lymphoedema (15-77 y)	Liposuction, which is followed by wearing compression garment (panty CCL3 during day and panty CCL3 + leg CCL2 during night)	Infection rate 5-year follow-up	Before surgery: 0.17 bouts per person per year; post-surgery 0.04 bouts per person per year
Yu et al., 2020 China Retrospective study Level IV	n = 40 primary lymphoedema of genital region (18-68 y)	Complete excision of oedematous subcutaneous tissue and plastic reconstruction of penis or scrotum After care: 72 h antibiotics and hemostatics; compression garment for penis/scrotum and for leg if needed.	1) Magnetic resonance lymphangiography 2) Cosmetic result 3) Recovery of sexual function 4) Patient satisfaction 5) Complications 3.5 y follow-up	1) No recurrence of oedema; 62.5% had new formation and reopening of lymphatic drainage; 100% had decrease of dermal backflow 2) Improvement of appearance of the scrotum and penis 3) 100% had improvement of sexual function 4) 100% of patients were satisfied 5) 2.5% scrotal hematoma, 0% infection; 5% poor wound healing or skin necrosis
Damstra et al., 2020 The Netherlands Retrospective study Level IV	n = 28 primary lymphoedema and lymphatic verrucosa	Shaving and excision, followed by wearing toe caps (after the skin was healed)	1) Number of infections 2) Toecaps 5 y follow-up	1) Before surgery: 17.6 episodes of infection; post-surgery 0.6 episodes 2) Before surgery none of patients were able to wear toecaps; after surgery: 100% were able to.
Reconstructive procedures				
Drobot et al., 2021 Israel Retrospective study Level IV	n = 22 with primary lymphoedema of lower limb (34 y) (n = 48 with secondary lymphoedema)	LVA (3.1 anastomosis per patient) One week after surgery, patients returned to the preoperative conservative compression therapy protocol, which included compression stocking or wrap during the day or night. After 3 months, compression therapy was discontinued at the request of the patient.	1) Volume reduction 2) Adverse events 9 m follow-up	1) Compared to preoperatively: −28% at 3 months, −37% at 6 months, and −39% at 12 months 2) No
Hayashi et al., 2022 Japan Retrospective study Level IV	n = 45 primary lymphoedema and received already anterior LVA	Post LVA group: second LVA on posterior side Med LVA group: second LVA on medial and anterior sides	1) Lower extremity lymphedema index 2) Number of anastomoses 1.4 y follow-up	1) in Post LVA group: 10.5 vs in Med LVA group: 5.5 (p = 0.008) 2) in Post LVA group: 3.5 vs in Med LVA group: 4.6 (p = 0.038)
Cheng et al., 2018 Taiwan Prospective study Level IV	n = 17 with primary lymphoedema (2-57 y), 19 limbs	LVA: if patent lymphatic ducts on indocyanine green lymphography (n = 4) LNT: without patent lymphatic ducts (n = 15) No postoperative use of compression garments	1) Circumferential limb measurements 2) Body weight 3) Infection rate 4) Lymphedema Quality-of-Life (LYMQoL) questionnaire 20 m follow-up	1) After LNT: −3.7 ± 2.9 cm vs after LVA -1.9 ± 2.9 cm (p = 0.2) 2) After LNT: −6.6 ± 5.9 kg vs after LVA -1.7 ± 0.6 kg (P < 0.05) 3) After LNT: 5.1 ± 2.8 times/y vs after LVA: 4.2 ± 0.5 times/y (P = 0.7) 4) After LNT: improvement in overall score from 3.9 ± 1.2 to 6.4 ± 1.1 (P < 0.05) vs after LVA: from 3.0 ± 1.4 to 5.0 ± 2.4 (P = 0.07)
Cheng and Liu, 2020 Taiwan Retrospective study Level IV	n = 9 with primary paediatric lymphoedema (2-19 y), 11 lower limbs and 2 upper limbs	12	1) Volume 2) Infection rate 3) Quality of life with LYMQoL 38 m follow-up	1) In unilateral lymphoedema: −6.7%; in bilateral: −1.3 cm and −6.5 cm 2) Infection rate decreased 2.7 times 3) In 6 patients >7 y: LYMQoL improved by 3.2 points
Reisen et al., 2020 USA Retrospective study Level IV	n = 8 babies (1–9 months) with congenital or acquired obstruction of thoracic duct outflow	Thoracic duct-to-vein anastomosis under high-power microscopy		6 patients: successful reconstruction with restoration of lymphatic flow and clinical improvement 2 patients: technical adequate reconstruction without improvement of the flow 5 patients remained alive, 3 patients died

treatment in primary lymphoedema is a very complex therapeutic option and has to be performed in a centre or clinic where lymphatic surgery is routinely performed within an interdisciplinary programme (Lee and Chang, 2017).

Prior to evaluating possible (additional) surgical treatment options, maximal conservative treatment methods must be used to ensure there is no pitting oedema. Any surgical treatment should be combined with conservative treatment.

The structure and functionality of lymphatic vessels and the lymphatic transport should be evaluated with several complementary methods such as lymphoscintigraphy, ICG lymphography and/or MR lymphography (Fallahian et al., 2022). Another imaging technique is ultrahigh frequency ultrasound (with a frequency of 70 MHz or more) which is able to detect lymphatic vessels that are not seen by ICG lymphography (Hayashi et al., 2019).

There are several surgical techniques applied in patients with primary lymphoedema: reductive procedures such as circumferential suction assisted lipectomy ("liposuction" or "lympha-liposuction") or excisions, or reconstructive procedures such as lymphovenous anastomosis (LVA) or a vascularised lymph node transfer (LNT) (Lee and Chang, 2017). Table 4 gives an overview of several studies that investigated the different surgical procedures in adults or children with

primary lymphoedema.

If lymphoedema progresses to stage 3, it results in fat accumulation. The liposuction procedure for lymphoedema involves the removal of these excess fat deposits using a cannula, which is inserted through small incisions in the skin. The surgeon moves the vibrating or ultrasound-assisted cannula to break up and suction out the fat. Liposuction completely reduces the excess volume and significantly reduces the risk of cellulitis/erysipelas in patients with primary lymphoedema (and secondary lymphoedema). After the liposuction, to avoid recurrence, compression therapy has to be continued lifelong (Karlsson et al., 2022).

In patients with lymphoedema of the genital region, excision of the oedematous subcutaneous tissue and plastic reconstruction of the penis or scrotum can be performed. After the procedure, the patients have to wear compression garments. This procedure results in the long-term reduction of the oedema, the improvement of the appearance of the scrotum/penis and of the sexual functioning of the patient (Alnajjar et al., 2019; Yu et al., 2020).

Some patients with primary lymphoedema develop lymphostatic verrucosis (i.e. deposition of fat and fibrosis, and warty overgrowths) at the level of the forefoot and toes. Surgical excision and shaving of the verrucosis of the toes with secondary healing is an effective therapeutic modality as part of an integrated lymphoedema treatment program to restore the shape of the toes and enable the wearing of toecaps (Damstra et al., 2020).

The objective of LVA is to redirect the lymph to the venous stream directly, bypassing areas of obstruction, and without going through the thoracic duct (Lee and Chang, 2017). LVA is only applied if functional lymphatics can be localised, primarily by ICG lymphography and/or MR lymphography and/or (ultra)high frequency ultrasound. One must be aware that in most of the cases with primary lymphoedema, the lymphatic system is not locally obstructed. Many cases have a general dysfunction of the lymphatic system. The retrospective study of Drobot et al. showed a long-term volume reduction and no adverse events at 12 months post-surgery (Drobot et al., 2021). Hayashi et al. showed that - in patients with primary lymphoedema and a history of LVA on the anterior side of the lower leg - performing LVA at the posterior side of the calf also can be useful (Hayashi et al., 2022).

With LNT, orthotopically placed lymph nodes act as a sponge to absorb lymphatic fluid and direct it into the vascular network. The transferred lymphatic tissue may also induce lymphangiogenesis (Lee and Chang 2017). LNT is performed in patients without functional lymphatics. Cheng et al. prospectively followed 19 limbs with primary lymphoedema that were treated with LVA (n = 4) or LNT (n = 15) (Cheng et al., 2018). The average circumference of the legs did not change significantly and a significant change was only seen at 15 cm above the knee. Infection rate did not improve significantly, but quality of life improved significantly. Cheng and Liu also performed LVA or LNT in children with primary lymphoedema (Cheng and Liu, 2020). They concluded that it has a positive effect on volume, infection rate and quality of life.

In the different studies, compression was completely or partly stopped. However, according to Yamamoto, in the postoperative phase in patients receiving LVA, compression is critical to keep the lymphatic pressure higher than the venous pressure, allowing continuous lymph-to-venous bypass flow (Yamamoto et al., 2020).

For central lymphatic anomalies, visualisation of the thoracic duct through intranodal MR lymphography is necessary in deciding if a lymphovenous anastomosis is possible. Reisen et al. performed a thoracic duct-to-vein anastomosis in 8 babies with obstruction of the thoracic flow. In 6 babies, the reconstruction was successful and improved the clinical situation (Reisen et al., 2020).

The level of evidence of the 8 studies described in Table 4 was IV, which means that these studies were case series. None of the studies were randomised controlled trials comparing surgery and usual care with usual care alone. Therefore, it is not clear whether there is a cost effective value of surgery in addition to usual care. Furthermore, 7 studies had a retrospective design and only one study had a prospective design.

2.6. Follow-up

Appropriate follow-up at expert and local centres is necessary for all patients.

At follow-up visits, pitting status, swelling and skin condition of the limbs and the midline region must be evaluated (Table 1). In patients with unilateral lymphoedema the excessive volume of the limb/foot/hand is determined and compared with the previous values. In patients with bilateral lymphoedema, the limb/foot/hand volume is followed over time and is combined with body weight measurements. In children with lymphoedema, it is much more difficult to follow-up the amount of oedema, as the child (and so the limb) grows. Ask the patient or parent if the child is < 6 years to complete the lymphoedema-specific questionnaire (when available) to evaluate the evolution of the problems in functioning/quality of life. Record the frequency of episodes of cellulitis/erysipelas. If indicated, re-evaluate other impairments in function as well.

3. Discussion

3.1. Practical aspects/reimbursement

1. Most of the clinical studies about evaluation and treatment of lymphoedema have been performed in patients with breast cancer-related lymphoedema. The problem is that not all results can be translated from cancer-related lymphoedema to primary lymphoedema and from upper limb to lower limb. Therefore, more clinical studies about evaluation and management of primary and/or paediatric lymphoedema are needed.
2. A patient pathway is helpful to structure the care. However, there might be problems to implement this pathway because of non-reimbursement issues. For instance, in most of the countries, compression garments/wraps/bandages and wound care materials and products are only partly reimbursed or not reimbursed at all. Specific materials or products are not available in certain countries. Moreover, sessions of therapy (by different professions) are only partly reimbursed or not reimbursed at all.
3. Not every country has a multidisciplinary expert centre for primary and paediatric lymphoedema. If there is no local expert centre, a patient can be referred to a centre in another country (see the VASCERN website for the overview of the different expert centres: https://vascern.eu/groupe/pediatric-and-primary-lymphedema/).

3.2. Patient group participation

Patient participation is an integral part of the work of the PPL WG in VASCERN. The patient representatives, called the European Patient Advocacy Group (ePAG), come from different countries and patient associations. During the development of the pathway, they contributed to its design and advised on information which needed to be included. The process involved collecting information and discussing the different elements during the patient meetings, to derive a common view. The final patient pathway was also reviewed by the ePAG, ensuring it was clear for the patients and their families to read and use.

4. Conclusions

The term primary lymphoedema covers a group of rare conditions caused by abnormal functioning and/or development of the lymphatic system. The present document, developed by experts and patient representatives within the VASCERN PPL WG, is an opinion statement on how to approach patients with primary and paediatric lymphoedema. It describes the strategies to reduce the time to diagnosis and to implement

the best management, whilst ensuring the efficient use of resources. In conclusion, the expected outcome of the PPL patient pathway is to improve patient care across Europe through standardisation of the clinical diagnosis, treatment and follow up of patients with primary and paediatric lymphoedema.

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Data availability

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