The management of childhood and adolescent lymphedema presents challenges unique in the developing youngster. Most of the affected children and adolescents have primary lymphedema caused by maldevelopment of the lymph vascular system and not by secondary causes, such as trauma, surgery, radiation or infection. Synonyms for primary lymphedema include idiopathic lymphedema, intrinsic lymphedema and spontaneous lymphedema. Lymphedema is an accumulation of protein-rich lymph in the interstitial spaces and results in thickening of the skin and fibrofatty deposition in the tissues.

Classification of Primary Lymphedema

Primary lymphedema can be classified by age of onset. Congenital lymphedema is present at birth and is often a lymphostatic, non-pitting edema that developed in utero. Lymphedema praecox develops after birth and before age 35 years and, by definition, lymphedema tarda after age 35. Lymphedema praecox frequently appears after puberty and predominantly affects women. The hereditary form of congenital lymphedema is known as Nonne-Milroy syndrome. Frequently, clinicians incorrectly call any form of congenital lymphedema Milroy’s disease. Meige’s disease is hereditary lymphedema praecox.

Kinmonth classified primary lymphedema based on lymphographic findings. Browse, et al., refined the classification of the lymphatic abnormalities that cause lymphedema based on recent genetic research and updated imaging studies. The genetically determined abnormalities are: (1) Aplasia, malformations and valvular incompetence of the central lymphatic ducts; and (2) Aplasia, hypoplasia or dilatation and valvular incompetence of the collecting ducts in the subcutaneous tissues of the limb and trunk. This group includes the familial conditions and the congenital, but sporadic lymphedemas are associated with other congenital abnormalities. The latter group includes Klippel-Trénaunay-Weber syndrome, Turner’s syndrome, Noonan’s syndrome and intestinal lymphangiectasia.

In recent years, there have been advances in understanding the genetics of some of the hereditary lymphedemas. There are several excellent reviews of this subject (see the reference list).

Embryology and Genetics

Knowledge of the development of the lymph vascular system and hemangiogenesis is important to understanding primary lymphedema. Lymphatic vessels arise by vasculogenesis and angiogenesis either from venous channels and/or mesenchymal precursors in the fifth week of gestation. Six primary lymph sacs are formed: two jugular, two iliac, one retroperitoneal and the cisterna chilii. Within a few days, axillary lymph sacs develop and fuse with the jugular sacs. Mesenteric and lumbar lymphatic plexuses develop. Right and left thoracic ducts are formed between 6-8 weeks, most likely from the postcardinal vein. The ducts then form anastomoses. A single thoracic duct develops from the cranial portion of the left thoracic duct, the anastomoses and the caudal portion of the right thoracic duct. The thoracic duct empties into the left subclavian vein. The right lymphatic duct develops from the cephalad portion of the right thoracic duct and empties into the right subclavian vein. The distal portion of this duct becomes the distal portion of the thoracic duct. Lymph nodes appear in the early fetal period as aggregations of lymphoblasts in the axillary and inguinal region. The development of lymphatic valves in the dermis continues throughout the early postnatal period. Venous and lymphatic vessels maintain a close relationship after birth. The major lymph vessels run parallel to the major veins. Twenty per cent of the lymph drains into the venous system through anastomoses between the two vascular systems.

Central to vascular development are the vascular endothelial growth factor receptors (VEGFR) and their ligands, the vascular endothelial growth factors (VEGFs). Through linkage analysis – a comparison of DNA between family members with and without lymphedema – Ferrel, Levinson, et al., were able to determine the location of the first lymphedema gene in chromosome 5 in some families with Milroy’s disease. In 1998, they reported lymphedema-causing mutations in the VEGFR-3 gene. They observed several lymphedema-causing mutations in the VEGFR-3 gene in different families. The mutations prevented the receptor from responding to
the messages it received from certain growth factors (VEGF C&D) that signal development of lymphatic vessels, resulting in hypoplasia.

Milroy’s disease has a dominant mode of inheritance, but there are other familial and environmental determinants. The genetic characteristics of the majority of lymphedema patients with a familial history have not yet been determined.

**Diagnosis of Primary Lymphedema**

The diagnosis of primary lymphedema is often delayed due to the medical profession’s low level of lymphedema awareness. Lymphedema may be present at birth and involve one or more extremities, even the face. In lymphedema praecox or tarda, spontaneous onset is common; however, lymphedema may present as a groin mass due to enlarged lymph nodes or edema may occur after major or minor trauma. An episode of cellulitis may herald the onset of lymphedema.

Kinmonth cautions that “no inguinal swelling of uncertain origin should be surgically explored or excised without prior imaging.” A mild edema can become severe after unnecessary lymph node excision. A common scenario is edema developing in a youngster after a minor sports injury such as an ankle sprain, the ankle edema persisting and spreading into the foot and up the leg. Often, a visit to three or four physicians is necessary before the lymphedema is diagnosed. A useful clinical finding is the presence of the Stemmer sign, a thickening of the skin of the involved digits making the skin difficult to pick up or pinch. This is a sign of lymphostatic edema and may not be present if the edema is mild. Other signs of lymphedema include increased firmness of the subcutaneous tissues, thickening of the skin (hyperkeratosis) and vesicles draining lymph fluid (lymphorrhea). There may be few symptoms. Achiness and heaviness are common complaints in moderate to severe lymphedema. Depending on the extremity involved, tightness of shoes, clothing and jewelry may be noted. Individuals with new onset leg edema usually have had a venous ultrasound examination and radiographic imaging by the time they are referred to a lymphologist or lymphedema therapist. The minimally invasive lymphoscintigram is a useful diagnostic study to evaluate lymphatic flow. The lymphoscintigram (LAS) assesses the time a radioactive substance requires for transport from the point of injection to lymph node arrival time in minutes. Early and late readings are taken (e.g., 30 and 120 minutes). Exercise is encouraged after injection to promote isotope transport. Normally, the lymph collectors are visualized in 5-10 minutes as band-like structures. The number and diameter of the vessels cannot be determined. In congenital and early-onset primary lymphedema, a typical pattern shows stagnation of the radioisotope in the involved distal extremity. Another pattern is delayed transport. Occasionally, there is clinical evidence of lymphedema but the lymphoscintigram is normal. Direct lymphography involves injection of an oily contrast agent containing iodine into a lymph vessel. Surgical exposure of the vessel is necessary. There are potential complications with this procedure—pulmonary embolism, pneumonia, contrast agent allergy—and direct lymphography is rarely used. Other imaging methods, such as CT scans and MRIs, can show edema, localized lymph fluid collections (cysts) or secondary causes, such as tumors. They do not image the dynamics of lymph flow.

**Treatment**

Treatment of primary lymphedema follows the principles of Complete Decongestive Therapy (CDT). Obviously, adjustments need to be made for younger children, generally shorter therapy sessions in a comfortable environment. Cooperation of the parents or other caregivers is essential. They need to be informed that there is, at this time, no cure for lymphedema but CDT is essential to reduce progression of the lymphedema. Formal therapy should continue for a finite period of time and a written home program developed. Some parents may even want to videotape therapy sessions to increase their comfort level with home therapy. In addition to MLD by the therapist and parents, bandaging can help reduce edema. Bandaging in infants and small children needs to be carefully supervised by an experienced therapist due to the small limb(s) and skin sensitivity. Infants need to have their hands and feet uncovered for several hours a day so normal sensorimotor skills develop. Also, children up to age 2 frequently put their hands in their mouth and wet bandages can lead to skin maceration. At ages three to four years, children begin demonstrating independent behaviors (“Let me do it”), and can be encouraged to participate in their lymphedema therapy. The home MLD treatment sessions should be short and can be incorporated into routine daily activities. The caregivers should not feel overburdened by the therapy routine. Specific issues, such as therapy for the child in daycare, relations with siblings and peers and coexisting medical problems, need to be addressed. The use of compression garments is important for controlling lymphedema. Generally, garments are not used before ages 2 to 3 years. Growth and wear can make for frequent replacement. Flat-knitted fabrics are effective and, at times, more comfortable than circular-knit garments. Low compression garments are usually advisable in younger children. At times, and to reduce cost, elasticized tubular bandages and foam padding can be used for auxiliary compression. Custom fit, directional flow poly/Lycra foam-filled quilted garments can simplify nighttime and nap time edema control. Preteens and adolescents will be subject to peer pressure and will want to “fit in.” Compression garments can be obtained in various colors and styles so as to be more acceptable. Older children may be able to use ready fit garments, which are generally less expensive than

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custom fit garments. Exercising is usually not a problem for young children since they are active. Recreational activities and sports are important to the preteen and teenager. The risk/benefit ratio of each activity must be assessed and discussed with the individual and caregivers. Approval for participation in some higher risk sports (e.g., hockey) may be necessary if the child’s peer group is involved in this activity and the child does not want to be socially isolated. Metatarsalgia caused by splay foot deformity may require orthopaedic or pediatric intervention. Weight control is important since lymphedema is more difficult to treat in overweight individuals.

Common sense measures to be followed include avoiding tight clothing, avoiding immersion of the limb in a hot tub, use of an electric razor by adolescent girls who shave their legs, and good hygiene. Antifungal powder in socks, especially for children using public facilities such as gyms and pools, is advisable to prevent fungal infections, which can result in cracks in the skin, bacterial invasion and cellulitis. Compliance with therapy may become a problem, especially in adolescents. Periodic visits to the therapist and/or lymphologist are advisable to reinforce the importance of treatment. Referral to the primary physician will be necessary if there are concerns about depression, anxiety, factitious lymphedema or withdrawal and/or substance abuse.

Compression pumps are not recommended for children and pose problems for adolescents. The pump can temporarily reduce edema and soften the tissues, but they are expensive and, if used improperly, may damage the tissues, cause genital edema, and leave a band of fibrotic tissue proximal to the pneumatic appliance.

A discussion of surgical intervention is beyond the scope of this article. Surgery is not a cure and most patients will need to continue wearing an elastic support. Surgery has been used in cases of recurrent attacks of cellulitis, severe genital edema not responding to CDT and massive limbs that need debulking. Genetic research offers the promise to develop therapy to stimulate lymphangiogenesis. Recent local VEGF-C gene transfer in animals with secondary acute/subacute lymphedema led to a decrease in lymphedema and attenuation of the fibrofatty changes of the skin.

Conclusion

The diagnosis and treatment of lymphedema in children and adolescents is challenging and rewarding. Early diagnosis and initiation of CDT is essential to reduce and control the lymphedema.

REFERENCES


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