Primary Lymphedema in Children and Adolescents: A Follow-up Study and Review

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ABSTRACT. Primary lymphedema, a disorder causing persistent swelling in an extremity, is rare in children and adolescents; it affects 1.15/100,000 persons less than age 20 years. It primarily affects girls near menarche. The records of 125 children and adolescents, aged 0 to 20 years, who were examined at the Mayo Clinic were analyzed; 99 of these patients were contacted to obtain follow-up data. The influences of estrogen and inflammation are thought to be important etiologic factors in primary lymphedema. The diagnosis can be made on the basis of a thorough history and physical examination. Lymphangiograms, venograms, and biopsies add nothing to the diagnosis because of the low incidence of tumor in children and adolescents. Conservative treatment is recommended: a Jobst-type stocking, elevation, and proper foot care. Diuretics are not recommended. Careful psychologic counseling, especially in adolescents, is highly recommended. *Pediatrics* 1985;76:206–218; *primary lymphedema, lymphedema praecox, congenital lymphedema.*

Primary lymphedema has been studied as a clinical entity since 1934 when Allen[1] described its classification. Most of these studies have concerned lymphographic findings, associations with other disorders or congenital anomalies, and treatment. However, there have been few reports on the disease in children.[2–6]

Primary lymphedema in children and adolescents does not shorten the patient's life expectancy[7] but does influence the quality of life. The swelling generally persists for life, and sometimes it progressively worsens and is complicated by lymphangitis.

This paper describes the experience with primary lymphedema in children and adolescents at the Mayo Clinic between 1955 and 1974. It details the disease's presentation, prognosis, and treatment and includes a review of the literature.

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DEFINITION

Lymphedema is defined as a swelling of a part of the body caused by accumulation of interstitial fluid secondary to a malformation or malfunction of the lymphatic system.[8–11] Lymphedema is separated into secondary and primary forms. Secondary lymphedema includes all those cases in which a cause for the damage to the lymphatic system has been identified. These causes include infection (predominately from recurrent lymphangitis or cellulitis in this country), surgical excision (mostly postmastectomy), neoplasms, irradiation, and trauma. Primary, or idiopathic, lymphedema is swelling for which none of the above causes can be found.

Allen's classification[1] of this disease in 1934 used the age at onset as a criterion. He coined the term "lymphedema praecox" to describe those cases in which swelling developed after birth, because many of the patients were adolescent girls. Kinmonth et al[12] later narrowed the term to include patients only up to age 35 years and used the term "lymphedema tarda" for those older than age 35 years. The term "congenital lymphedema" has referred to patients with edema present at birth or shortly thereafter,[1,3,13] In this paper, all cases in which swelling developed up to age 3 months will be included under the heading congenital lymphedema. Milroy's disease[7,14] is defined as edema that is congenital and familial. The term lymphedema praecox will be used to describe patients between ages 4 months and 20 years; Meige's disease[15] refers to familial lymphedema praecox.

Kinmonth et al[12] have proposed a second way to classify primary lymphedema, by using lymphographic findings. Their original classification included categories of aplasia (no lymph trunks found), hypoplasia (lymph trunks deficient in size, number, or both), and hyperplasia (lymph trunks broader and more tortuous than normal). With improved techniques, it was later possible to divide the hypoplastic category into proximal obstructive and distal hypoplasia.[13,16–18] However, Kinmonth's classification was found not to correlate with clinical presentations and subsequent treatment of primary lymphedema.

MATERIALS AND METHODS

The medical index and record retrieval system at the Mayo Clinic was used to obtain all records for patients with diagnoses of lymphedema praecox, primary lymphedema, congenital lymphedema, or Milroy's disease for review. Between 1955 and 1974, 125 such children and adolescents aged 0 through 20 years were seen at the Mayo Clinic; 23 of these patients had been included in a previous study.[19] A follow-up letter was mailed to these patients, and 88 patients responded; 11 other patients had returned for a follow-up examination 5 years or more after the initial diagnosis. Analysis of these records concentrated on the history and presentation of the patients, laboratory procedures performed, operations done, and follow-up data.

RESULTS

The incidence of primary lymphedema in the population of Rochester was determined from the Rochester Group Study data.[20] During the 20-year period 1955 to 1974, four cases of primary lymphedema were diagnosed in persons less than age 20 years in the population of Rochester, Minnesota. This population averaged 17,800 during that period, providing 355,470 person-years of observation. The average annual incidence rate was calculated to be 1.15/100,000 population less than age 20 years.

In our series, 78% of the patients were female; the range of female patients in other studies was 64%[13] to 90%[21] (Table 1). Only one study[22] was out of this range for percentage of female patients. For congenital lymphedema specifically, 59% of our patients were female compared with 25%[19] to 59%[12] female patients in other studies. The ratio of unilateral to bilateral extremity involvement varied from approximately 1:1 to 3:1.

Occurrence of familial lymphedema (Meige's disease) has been rare (Table 1). In the current series, only three of 20 patients with congenital lymphedema had Milroy's disease, and only seven of 105 patients with lymphedema praecox had Meige's disease. Overall, among the accumulated series of 291 patients, only 42 (14%) had a family history of lymphedema.

Of our 101 patients with lymphedema praecox, 76 were first seen with unilateral leg involvement; seven of the 20 patients with congenital lymphedema were initially seen with unilateral leg involvement. Most of the patients with lymphedema praecox had swelling only to the knee or ankle (80/98); in contrast, half of the patients with congenital lymphedema (7/13) had whole leg involvement. Furthermore, 16 of 26 boys were initially seen with whole leg involvement in contrast to only 18 of 96 girls. Arm involvement alone occurred only in congenital lymphedema; some arm involvement was present in six of 20 patients with congenital lymphedema compared with only eight of 105 patients with lymphedema praecox. Thus, the average pediatric patient with lymphedema praecox is female with unilateral leg involvement, whereas the patient with congenital lymphedema often is male with bilateral whole-leg swelling.

The mean age at onset in patients with lymph-

TABLE 1. Distribution of Children and Adolescents by Sex and Age: Literature and Present Series

Study	Sex (M/F)	Unilateral/ Bilateral	Age 0–3 mo		Age 4 mo to 20 yr		Infection Rate (%)
			Simple Congenital	Milroy's Disease	Lymphedema Praecox	Meige's Disease	
Allen[1]	14/91	73/32	12	0	93	NR*	13
Brunner[21]	28/257	137/148	9	NR	225†	NR	18
Feins et al[2]	15/24	NR	NR	NR	NR	NR	28
Fonkalsrud[5]	13/15‡	11/13‡	24	4	33	NR	(Rare)
Gough[13]	9/16	≈1:1	9	2	9	5	NR
Kinmonth et al[12]	30/77	37/44	10	2	66†	16†	22
Saijo et al[22]	18/18	24/12	4	3	19	NR	NR
Schirger et al[19]	17/114	≈1:1	8	NR	52	NR	24
Present series	28/97	92/33	17	3	98	7	31

* NR, Not reported.
† Patients up to age 35.
‡ Ages 0 to 2 years only.

edema praecox was 10.5 years for males and 13.0 years for females (Figure). The overall mean age at onset was 12.5 years.

Other data collected from the record of the patient's initial visit include causative factors for the swelling and diagnostic measures used. Spontaneous onset (no cause remembered) was by far the most common comment (104/125 patients), but 18 patients reported a history of minor trauma such as ankle sprain or deep laceration, and three patients had a history of cellulitis or lymphangitis preceding the swelling.

Of the 21 venograms recorded in Table 2, 20 had been done prior to the patient's visit to the Mayo Clinic; 19 had normal findings and two studies showed minor venous abnormalities unrelated to the lymphedema. Eleven of the 20 lymphangiograms had been performed elsewhere: two had normal findings, nine were unsuccessful, four showed hypoplastic or aplastic lymphatics, three showed an obstructive process, and two showed dilated lymphatics. The high percentage of unsuccessful lymphangiograms was probably caused by technical difficulties or aplastic lymphatic trunks.[22] The 11 successful studies, however, did nothing to alter the diagnosis or treatment plan at this institution. Most lymphangiograms were performed to satisfy the patient and, whether the result was hypoplasia or dilation, it only confirmed a preexisting diagnosis. Furthermore, several patients had delayed wound healing of the cutdown site, and two patients had mild hypersensitivity reactions to the contrast agent (which responded quickly to antihistaminics). Of the eight biopsies (all performed elsewhere) four resulted in findings consistent with lymphedema, one showed normal findings, one showed lymphangiectasia, and two had nonspecific findings.

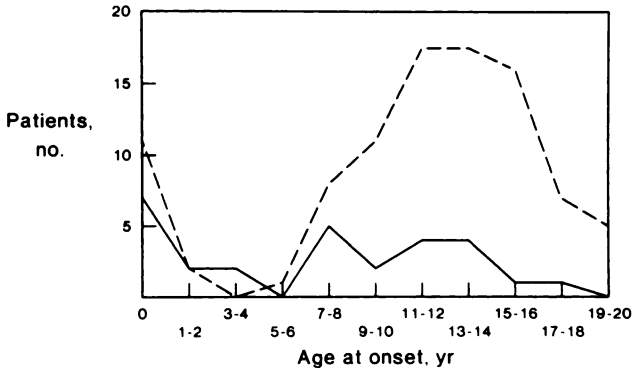

Figure. Age distribution at onset of lymphedema praecox in males (solid line; mean, 10.5 years) and females (dashed line; mean 13.0 years); overall mean, 12.5 years.

Other negative diagnostic measures included: excretory urograms to rule out pelvic and retroperitoneal masses (15 patients); urinalysis to rule out nephrotic syndrome (120 patients); serum chemistry groups (78 patients); hematology groups (120 patients); chest roentgenograms (120 patients); roentgenograms of extremities to rule out skeletal abnormalities (73 patients); and pelvic examinations to rule out gynecologic abnormalities (26 patients).

The treatments recommended at initial diagnosis also are shown in Table 2. Use of either a Jobst or Ace bandage compression with or without diuretics was recommended for 99 patients. Most of these patients were hospitalized for two to three days of bed rest and elevation of the affected extremity to minimize the swelling prior to measurement for the Jobst stocking.

Only 13 of the 125 patients had even minor associated abnormalities at the time of initial diagnosis: three had Noonan's syndrome, three had distichiasis (a double row of eyelashes)-lymph-

TABLE 2. Diagnostic Studies, Complications, and Recommended Treatments for Primary Lymphedema

	Congenital Lymphedema	Milroy's Disease	Lymphedema Praecox	Meige's Disease	Total
Sex (M/F)	7/10	1/2	17/81	3/4	28/97
Diagnostic measures					
Lymphangiogram	0	0	19	1	20
Venogram	0	0	21	0	21
Biopsy	1	0	7	0	8
None	16	3	57	7	83
Complications					
Infection	6	2	18	1	27
Malignancy/tumor	0	0	0	0	0
Recommended treatment					
Jobst	3	2	22	3	30
Ace	2	0	23	1	26
Jobst/diuretics	3	0	34	1	38
Ace/diuretics	1	0	4	0	5
Diuretics	0	0	3	0	3
Surgery	1	1	6	3	11
None	7	0	5	0	12

TABLE 3. Types of Surgical Treatment and Results

Operation	No. of Operations	Result			Infection Rate		
		Good/ Excellent	Fair	Poor	Decreased	No Effect	Increased
Homans procedure	7	0	3	4	1	4	2
Thompson buried flap	7	3	4	0	0	3	4
Charles procedure	3	1	2	0	0	2	1
Genital procedures	4	2	2	0	0	4	0

edema syndrome, one had petit mal and grand mal seizures, and six had minor vascular and dermatologic abnormalities. Five of the 20 patients (25%) with congenital lymphedema had abnormalities, in contrast to only eight of 105 patients (8%) with lymphedema praecox with abnormalities.

A total of 21 operations were performed, counting multiple-stage operations as a single procedure (Table 3). These operations were performed on 16 patients. They included operations to remove excess edematous tissue, such as the Charles and Homans operations, and to attempt restoration of physiologic drainage of lymph, such as the Thompson buried flap. A "good/excellent" result was one in which there was a marked reduction in the size of the swelling; a "fair" result was one in which the operation only produced a slight reduction in the swelling; and a "poor" result was one in which there was no change or increased swelling postoperatively. The Thompson buried flap, Charles, and genital operations gave better results than the Homans procedure, the currently recommended operation.[2,7,23-27] Furthermore, infections were increased in one third of the patients and decreased in only one. Most authors[2,24,28] report a decrease in the infection rate after surgery.

Besides infection, other complications were present in these patients. The major postoperative complication was a below-the-knee amputation caused by massive ischemic necrosis. Other postoperative complications included ischemic necrosis requiring skin grafts in three patients, delayed wound healing in four patients, and poor cosmetic results in virtually all the patients. Other authors have reported skin grafting for ischemic necrosis,[9,24] poor cosmetic results and scarring,[2,24,29] delayed wound healing,[30] and hematoma.[28,30]

In Table 4, the results of surgery in this series are compared with results in other series for which reported data are adequate. Good or excellent results occurred in approximately 30% of the cases, but these good results were balanced by poor results in about 20% of the cases.

The follow-up data included 99 patients. In our series, after up to 27 years of follow-up, 59 of 99 patients (60%) had swelling that remained unchanged, 28 (28%) had increased girth in the affected extremity, and 12 (12%) had swelling in another extremity. In regard to the incidence of infections at follow-up, 36 of 99 patients (36%) had at least one attack of cellulitis or lymphangitis and 19 patients had recurrent infections. In all of these patients with complicating infections, recovery was uneventful.

TABLE 4. Reported Results of Surgical Treatment of Lower Extremity

Study	Good/ Excellent	Fair	Poor
	No. (%)	No. (%)	No. (%)
Kinmonth et al[30]	16 (22)	45 (61)	13 (18)
Sakulsky et al[28]	27 (71)	5 (13)	6 (16)
Tanabe[31]	4 (31)	3 (23)	6 (46)
Taylor[32]	16 (31)	27 (53)	8 (16)
Present series	4 (24)	9 (53)	4 (24)
Total	67 (35)	89 (46)	37 (19)

Some (15) of the 68 patients initially advised to use Jobst stockings had refused; 39 patients were still using them at follow-up. Ace bandages were initially more appealing to patients, but not many patients continued to use them at follow-up. Patients using a form of compressive stocking actually had a slightly higher infection rate than those who used diuretics or no treatment (Table 5). Furthermore, control of increased girth in the affected extremity with compressive stockings was no better than with no treatment at all. The patients who used diuretics had about the same infection rate and slightly more progression than the no-treatment group.

The probable reason for the poor results obtained with compressive stockings is that, in a retrospective study such as this, patients who have little residual swelling will stop using any treatment and those who have increased swelling will use any treatment that they can find. The variable course of primary lymphedema makes a stereotyped treatment protocol useless.

An aspect of lymphedema often neglected by physicians is the psychologic effect of the swollen extremity. Narrative comments received in the replies to our follow-up letters illustrate this point.

TABLE 5. Follow-up Data for Patients with Primary Lymphedema

Treatment in Use at Follow-up	No. of Patients	Finding			
		Infections	Increased Swelling		Swelling Unchanged
			Same Extremity	Another Extremity	
		No. (%)	No. (%)	No. (%)	No. (%)
Jobst	25	11 (44)	10 (40)	4 (16)	11 (44)
Ace	6	2 (33)	1 (17)	1 (17)	4 (67)
Jobst/diuretics	14	5 (36)	2 (14)	2 (14)	10 (71)
Ace/diuretics	1	0 (0)	1 (100)	0 (0)	0 (0)
Diuretics	13	5 (38)	4 (31)	5 (38)	4 (31)
Machine	6	5 (83)	4 (67)	0 (0)	2 (33)
Unknown	2	0 (0)	0 (0)	0 (0)	2 (100)
None	32	8 (25)	6 (19)	0 (0)	26 (81)
Total	99	36 (36)	28 (28)	12 (12)	59 (59)

One patient wrote, "I don't like people looking at my legs and making comments. Every woman likes to have pretty legs and I'm no different." Another stated that she experienced "embarrassment, self-consciousness, and an unwillingness to have others notice [her] condition." A third patient wrote, "Thank goodness school teachers can wear pants. I sometimes feel . . . my feet must belong to someone else. Most of the effects of the edema have been emotional."

Lymphedema sometimes affected a patient's job and leisure opportunities. Twelve patients could work only at desk jobs or jobs that allowed frequent sitting. One patient felt he had been refused higher-paying jobs because of his edema. Other patients reported limitation of participation in exercise and sports because of the uncomfortable heavy feeling in the leg.

DISCUSSION

Pathology

Schirger et al[19] described the gross and microscopic features of congenital and later-onset lymphedema. Grossly, the skin is roughened like a pig's skin, and the subcutaneous tissue is filled with watery fluid and abundant fat lobules. Curiously, the deep tissues and muscles are never affected by primary lymphedema.[2,5,24-26] Microscopically, frequent acanthosis and hyperkeratosis of the epithelium, thickened dermal papillae, and fibrokeratotic proliferation and collagenization of the dermis, subcutaneous septa, and deep fascia are present. The superficial lymphatic vessels are sparse with fibrosis and lymphocytic infiltrate, and the deep lymphatics are dilated and seemingly unaffected by the fibrosis.

Etiology

The actual etiology of primary lymphedema is still unknown. The basic problem is known: an overproduction or decreased removal of lymph, which causes stasis.[9,11,12,33] How this lymph excess develops is not known.

Most investigators agree that congenital underdevelopment of the lymphatic system underlies all cases of primary lymphedema.[19,33,34] This original hypothesis was proposed by Allen et al in 1946.[35] With Kinmonth's lymphographic studies[12] showing objective "proof" of this underdevelopment, the earlier theory of increased capillary permeability and an overload on the lymphatic system was all but forgotten.

Kinmonth's lymphographic classification of primary lymphedema, which is the main support of the maldevelopment theory, has been inadequate to explain the various presentations seen in patients. Abnormal lymphangiograms can be obtained from perfectly normal limbs, and patients with clinical lymphedema can have normal lymphangiograms.[36] Problems such as these in the lymphographic classification led Kinmonth et al[17,37,38] to hypothesize that the lymph nodes originally become fibrotic, causing secondary obstructive changes in the lymph trunks. Interestingly, Price[39] proposed the same hypothesis 4 years earlier, and Olszewski et al[40] have also found similar fibrosis. These recent changes cast doubt on Kinmonth's original theories, and one wonders whether there are additional etiologic factors present in primary lymphedema.

If it is assumed that there is some sort of development insufficiency of the lymphatic system in the patient who develops primary lymphedema, why are there such varied presentations of the edema? Congenital lymphedema and lymphedema praecox are two clinical presentations on a continuum of lymphatic maldevelopment, with congenital lymphedema simply more severe than lymphedema praecox. Thus, in congenital lymphedema, noticeable swelling is present at birth or shortly thereafter, and the incidences in boys and girls are approx-

imately equal because no additional stimulus is needed to cause the edema to begin. In lymphedema praecox, some factor is needed to overstress an insufficient lymphatic system.

The preponderance of girls in the lymphedema praecox group can be explained by several factors. One is that subcutaneous tissue pressure is approximately 7 mm Hg greater in boys than in girls.[41] This difference may be enough of an extrinsic component of lymph flow to prevent lymphedema in many instances. A second factor is the difference in estrogen levels between boys and girls, which is especially evident at puberty. Estrogen influences retention of salt and water.[42] Other investigators[1,33,34] have postulated a hormonal cause for lymphedema because of its exacerbation by pregnancy, menses, and menarche. Peak estrogen levels in girls occur at approximately age 14 years, 18 months after menarche. The peak age for onset of lymphedema praecox occurs at ages 11 to 14 years in girls (Figure), encompassing the average age of menarche which is 12.5 years.[42] Estrogen levels begin to increase at ages 6 to 8 years, when gonadotropin levels increase in both boys and girls.[42] Lymphedema praecox also begins increasing at age 6 years (Figure).

Besides being produced in the ovary, estrogen is produced by a P450 enzyme in the liver and in peripheral fat tissue in both sexes; 80% to 90% of the male level and 30% of the female level of circulating estrogen is derived from an androgen precursor in this way.[43] This enzymatic conversion may explain why some patients with lymphedema are obese. Some authors[5,6] noted that all their patients were in the 75th percentile or higher in weight and that in several of their patients the edema disappeared after they went on a weight-reduction program. Others[44] also reported that 25% of their patients were obese. In the current series, 24% of the patients were obese, but another 27% were slender. Obesity may aggravate the swelling in some patients, but its presence is probably often secondary to inactivity.

The possible role of estrogen in causing primary lymphedema may cause some important rethinking about the earlier theory that increased capillary permeability causes edema. Besides the female predominance and peak onset near puberty, the relationship of infection and trauma to lymphedema can be explained by the earlier theory. Both infection (either lymphangitis or a subclinical infection through a break in the skin as seen in tinea pedis) and trauma (even unrecognized by the patient) can cause inflammation, and inflammation increases vascular permeability. This increase in interstitial fluid may then overload the lymphatic system. Several investigators have reported that minor trauma and infection are important "causes" of primary lymphedema.[1,9,12,13] In our series, in all 18 patients who reported trauma or infection prior to the onset of swelling, the lymphedema began with unilateral edema; only one of these patients later had bilateral swelling.

Some authors still believe that elephantiasis nostras is the sole cause of primary lymphedema.[45,46] This idea, popularized by Muller and Jordan[47] in 1933, stated that an episode of cellulitis or lymphangitis precedes all cases of lymphedema. Many have disputed this theory,[1,9,12,13,48,49] and it is now thought that these infections are a minor cause of primary lymphedema, but they often complicate cases of lymphedema.

Basically, we think that a combination of factors, including tissue pressure, inflammation, and estrogen, acts on a congenitally maldeveloped lymphatic system to cause stasis of interstitial fluid and subsequent lymphedema. Estrogen and inflammation (caused by trauma or infection) increase capillary permeability, overloading an insufficient lymphatic system. Lymphedema results from an imbalance between inflow and removal of interstitial fluid and protein.

This theory, however, is not without problems. One problem is the fact that 57 patients in our series had unilateral swelling not caused by trauma or infection. Another problem is explaining why lymphedema keeps developing years after the estrogen peak. A multifactorial cause of primary lymphedema comes closest to explaining all aspects of this disease.

Congenital Anomalies

The association of primary lymphedema with congenital anomalies and genetic syndromes has been overemphasized in the past. Considering that there are hereditary forms of both congenital lymphedema and lymphedema praecox, it is not surprising that investigators have searched for and found genetic syndromes associated with the disease. Some of these include intestinal lymphangiectasia and protein-losing enteropathy,[50-52] chylous ascites and chylothorax,[9,53-56] hypoplasia of the nails,[3] lymphaticovenous communications and lymphangiomatosis,[57] xanthomatosis,[58-61] congenital heart disease,[62] pericardial effusion,[63,64] Fabry's disease,[65] and conjunctival lymphedema.[66]

Genetics

Primary lymphedema has also been associated with several genetic syndromes including Noonan's syndrome,[67-69] distichiasis-lymphedema syndrome,[70-75] Aagenaes' syndrome,[76-80] yellow nail syndrome,[81-92] Turner's syndrome,[93,94] pes cavus,[95]

ptosis,[96] and cerebrovascular malformations.[97] These genetic syndromes have been shown to be transmitted in an autosomal dominant fashion[67]; only Aagenaes' syndrome (autosomal recessive) and Turner's syndrome (XO chromosomal abnormality) are exceptions.

Hereditary primary lymphedema was first described by Letessier in 1865[98] and was discussed by Nonne,[99] Milroy,[7,14] and Meige.[15] Nonne and Milroy described families with familial congenital lymphedema; Meige described a family with familial lymphedema praecox. Additional families with the same features have been reported.[100–102] Inappropriate use of the term "Milroy's disease" has blurred its specific usage. One must be sure not to call congenital lymphedema "Milroy's disease" unless there is a hereditary component. All these forms of hereditary primary lymphedema are inherited in an autosomal dominant manner with incomplete penetrance.[67] Only two offspring of the patients in our study who responded to follow-up had developed lymphedema, both congenitally.

A major question that should be asked in all of the above associations is whether there actually is an increased rate of congenital anomalies in primary lymphedema. Various authors have estimated that the incidence of minor malformations ranges from 4% to 5%[103] to 13%[104] in live newborns and young schoolchildren. The 10% rate in our study lies within this range. Other studies on primary lymphedema have found the rate of anomalies to be within the 5% to 13% range,[9,12,13] but these studies have stated that these rates were higher than in the general population. Our data show that one must be careful in drawing the conclusion that there is an increased rate of anomalies in primary lymphedema compared with the general population; in fact, such a conclusion probably is unjustified.

Diagnosis

The diagnosis of primary lymphedema rests on a carefully taken clinical history and results of physical examination; diagnosis is confirmed by characteristic lymphangiographic findings in those cases in which this procedure is done.[105] The importance of the first two cannot be overemphasized. In 90% of the patients in the current series, the history and physical were the only diagnostic measures used. Recently, radionuclide lymphangiography using technetium-99m (^{99m}Tc) has been developed to aid in the diagnosis and to follow the progress of treatment in primary lymphedema.[105] Its relative simplicity may allow it to be used as a screening tool to differentiate primary, secondary, and nonlymphatic causes of peripheral edema. Lymphangiography has been given too much attention as a diagnostic technique, especially in children.[106] It adds little when a child or adolescent is initially seen with primary lymphedema, and it has inherent complications, including delayed wound healing at the cutdown site,[5] pulmonary complications,[9] and idiosyncratic hypersensitivity reactions.[9] Computed tomography also has been used as a diagnostic tool. However, a recent study concluded that its primary use would be in excluding secondary causes of the edema such as retroperitoneal masses rather than examining the affected extremity.[107] The results of our study also show that venograms and biopsies added nothing to the diagnosis. The distinction between venous stasis and lymphedema is usually quite simple. Edema that is nonpitting and resolves after elevation is lymphedema.[108]

In addition to these findings, one of the pediatric oncologists at this institution reviewed his records and found ten patients who possibly had initially been seen with lymphedema and had neoplasms. Only three of these patients actually had lymphedema, and these were all clearly cases of lymphedema secondary to obstruction by a tumor. The patients initially had symptoms and signs of a neoplasm–such as a mass on the leg or weight loss and fever—rather than isolated edema of an extremity as seen in primary lymphedema in children and adolescents.

In summary, in uncomplicated cases of suspected lymphedema in a child or adolescent, the history and physical examination are the primary tools by which the diagnosis is established. The use of diagnostic measures such as venograms, lymphangiograms, and biopsies did not help make a diagnosis in any patient in this series. Children and adolescents initially seen with lymphedema thus should not undergo any of these unnecessary diagnostic measures.

Natural History

The natural history of primary lymphedema classically has been stated to be a slow, constant progression from a mild, painless swelling of an ankle to a huge, swollen extremity. Firm, nonpitting edema, fibrokeratotic skin, verrucous growths, squaring of the toes, lack of ulceration of the skin, and a tendency toward recurrent attacks of cellulitis and lymphangitis are common manifestations of primary lymphedema.[1,9,10,21] The chief complaint of the patient is often cosmetic. In more severe cases, the complaints include difficulty in wearing clothes and shoes, a heavy although not painful feeling in the limb, and interference with daily activities. But there are many exceptions to these generalizations.

The results of the present study emphasize that

the normal course of primary lymphedema is not necessarily inexorable progression. The swelling remained unchanged in 57% of the patients for up to 27 years. In the only other study with adequate follow-up data, Wolfe and Kinmonth[18] found that 62% of their patients had unchanged swelling up to 20 years later. In most patients, an equilibrium point is reached after several years of increased swelling and, irrespective of treatment measures, the swelling remains stable. Other patients, even when faithfully using all the best conservative and surgical treatment available, have an inexorable progression of their lymphedema. It is virtually impossible to predict the future course of primary lymphedema at the time of initial diagnosis if the swelling has only been present for 1 or 2 years. These uncertainties and individual variations have caused us to conclude that, in children and adolescents, surgical treatment should be postponed until after the edema has stabilized, which may take several years. Adequate conservative treatment should begin immediately.

Psychologic Aspects

The psychologic aspects of primary lymphedema have been neglected, both in the literature and in the physician's approach to the patient. Most of these patients are adolescent girls who are extremely conscious of their physical appearance, and this continues into adulthood. The edema obviously detracts from their self-image. These patients must be reassured that, although the swelling makes them different from others, it should not force them to lower their goals in life. Maintaining self-esteem is an important aspect of living with lymphedema.

Treatment

Although there are numerous methods of treating primary lymphedema, a cure is not yet available. The best conservative treatment available can only maintain the status of the swelling, reduce the incidence of infections, and stop the development of verrucous growths and hyperkeratotic skin. The best surgical treatment moderately reduces the size of the affected extremity but will leave a scarred extremity. Conservative treatment suggestions have not changed since Allen's recommendations in 1934,[1] and operations have not basically been improved since the Homans operation was described in 1936.[109] There are four common methods of treatment now in use: (1) compression—Ace elastic bandage, Jobst form-fitted pressure stocking, or pneumatic machine; (2) elevation; (3) medical treatment; and (4) surgery.

Compression is the treatment of choice in mild-to-moderate primary lymphedema, especially in children.[2,4,5,26,110,111] Since the development in the late 1950s of the Jobst-type high-pressure (up to 50 to 60 mm Hg) stockings, they have become the recommended method for compression. These stockings must be put on each morning before the patient arises; the stockings are expensive, and they are hot and uncomfortable to wear. These drawbacks are the chief reason for patient noncompliance with the Jobst stocking—the benefit of mildly decreased swelling does not seem to be worth the inconvenience. Ace-type elastic bandages, which have been available for a longer period of time, are easier to put on each day, are inexpensive, and are more comfortable. However, they lack sufficient pressure to decrease the edema significantly. Pneumatic pumps are a fairly new method of compression therapy.[110,112–117] The Jobst pump, Flowtron-Aire pump, Wright linear pump, and Lympha-Press are types of pumps now being used. They all work on the principle of sequential, intermittent, pneumatic compression of the limb—beginning at the hand or foot and ending with the proximal portion of the limb. They all must be used together with a support stocking such as a Jobst. They have produced good results in the studies so far, although no controlled studies in comparison with Jobst stockings have been done. Their major disadvantages are their cost and immobility—they are ineffective when the patient is away from home. Their advantage is the effective compression and decreased swelling achieved after just several hours of use.

The results of the current study did not appear to support the proposed advantages of the compressive methods of treatment. The retrospective patient selection bias probably explains these poor results. Comments made by patients who did use the Jobst stockings were mostly positive. Some patients thought that they could not live without the use of these stockings.

Elevation is routinely and universally recommended as one method to reduce lymphedema, and it is effective. No studies have specifically shown the value of elevation, but patients' histories consistently show that a night's sleep and hospitalization will decrease the swelling. To continue with normal lives, however, these patients must have their extremities in a dependent position for most of the day. Thus, although recommending that the patient sleep with his or her feet elevated 15 cm is a good idea,[10,53] it will not solve the problem of increased swelling during the day.

The medical treatment of primary lymphedema consists chiefly of diuretics. Other drugs have been tried experimentally, including anticoagulants[118]

and intralymphatic corticosteroids,[119] but the results so far do not merit their use. Diuretics have been recommended as a method of treatment for primary lymphedema since the early 1960s after Barker et al[120] described their usefulness. It was not until the study by Cattell et al[121] in 1965, however, that they became popular. The Cattell et al study is frequently cited as proof of the efficacy of diuretics, but only ten of 25 patients in that study showed marked relief of swelling after using diuretics.

In view of the somewhat disappointing results of diuretic therapy in our study and the inherent risks of long-term diuretic use, this form of therapy is best not used in children and adolescents with primary lymphedema. However, diuretics may be useful in some adults with primary lymphedema.

Surgical treatment is the most controversial area. New procedures are proposed nearly every year, but their efficacy often is not proved.[122] Most current operations date back to early treatment for filariasis. Charles[123] devised one of the first excisional operations in 1912. Sistrunk,[124] Kondoleon,[125] and Homans[109] later modified the Charles operation. These basic variations of the excisional operations have been performed for many years to treat primary lymphedema. They produce relatively good results in reducing the size of the extremity but often leave residual scarring and a "peg-leg" appearance postoperatively, thus diminishing their appeal.[32,126]

In the 1960s, the era of the physiologic operation, Thompson developed his buried dermal flap operation to enhance lymphatic drainage from the subcutaneous tissues to the deeper lymph trunks.[127-129] Initially the results were encouraging, but later investigators[24,130] have shown that the operation's success was caused by the removal of lymphatic tissue only. Goldsmith et al[131,132] developed an omental transposition procedure using the lymphatic-rich omentum to drain the involved extremity. Results of this operation have been poor,[24,27,30,111] in contrast to the Goldsmith group's original results. The latest physiologic operation uses microsurgery to create lymphaticovenous anastomoses in an attempt to bypass "blocks" in the lymphatic system.[133,134] Although this operation has been used with some success to treat patients with secondary lymphedema,[135,136] poor results have been obtained in patients with primary lymphedema,[24,135] and currently it is not recommended for treatment of congenital lymphedema or lymphedema praecox.[137]

Miller et al[24,25,67] and others[23,26,27] have tried to improve the excisional operations. Although some think it is not radical enough,[23] Miller's staged subcutaneous excision has been fairly successful. This operation is basically a modified Homans procedure, similar to the one used by Feins et al.[2] Good cosmetic results and reduced swelling have been obtained. Miller[138] also recommended that the Charles procedure should use a skin graft from the tissue excised, rather than from the other limb. With this modification, Miller thought that the Charles procedure and his operation should be the only types used in patients with primary lymphedema.

Operation is recommended only for patients with uncontrolled swelling, excessive disfigurement, or decreased mobility because of the size of the extremity.[2,5,10] Adequate preoperative and postoperative care is important for all patients. The patient should be hospitalized with the extremity elevated for several days to eliminate all residual edema prior to the operation. If necessary, a pneumatic pump should be used.[2,117] Postoperatively, the patient should always wear adequate support and take proper care of the feet to avoid infections.[10,24,33] Surgical treatment is not advised for infants less than age 2 years.[5] Occasionally, the edema will diminish once the child begins walking.

It is clear that the results of surgical treatment have been less than satisfying (Table 4). Furthermore, the minimal benefits of operation are often outweighed by the many complications. However, there is one area in which surgical treatment had obtained good results—in operations on the genitals. Bulkley[139] devised the currently used debulking procedure for scrotal edema, and it has been used successfully.[140,141] Removal of penile and vulvar edema has had similarly good results. Some controversy does exist about the scrotal operation. Malloy et al[142] recommended a complete excision of the scrotal skin, rather than Bulkley's posterior skin flap, because it may produce better long-term cosmetic results.

In summary, surgery on the extremities should be reserved as a last-ditch effort when conservative measures have failed. Premature surgery in children and adolescents must be avoided because of the highly variable course of the illness. If surgery is considered, the patient should be forewarned that there is only a 30% success rate, and that complications, especially cosmetic, are frequent.

Complications

The most dreaded complication of chronic primary lymphedema, not found in our series, is lymphangiosarcoma. There have been less than 20 verified, reported cases of lymphangiosarcoma arising in patients with primary lymphedema. The association between this cancer and chronic lymphedema was first made by Stewart and Treves[143] in patients who had had a mastectomy. Schirger et al[19] reported

one case of primary lymphedema in which lymphangiosarcoma developed. Several other cases have been reported.[144-150] The incidence of this tumor arising in primary lymphedema is extremely low, but this complication should not be forgotten. The outcome in all of these cases of lymphangiosarcoma has been poor. The average survival time after diagnosis has been only 18 to 34 months.[145,147] Complete excision of the tumor (usually amputation) is the only accepted treatment. There appears to be a long delay between the onset of primary lymphedema and the appearance of the tumor. Mackenzie[145] reported an average of 24 years in lymphedema praecox and 43 years in congenital lymphedema. The tumor is heralded by a "nonhealing bruise"[10]—a blue-to-purple papule appearing on an extremity with ulceration and necrosis.[19] Ulceration is virtually never seen on a normal lymphedematous extremity.

A more common complication of congenital lymphedema and lymphedema praecox is repeated attacks of cellulitis and lymphangitis. A typical attack is characterized by chills and fever (39.4 to 40.6°C), prostration, nausea, vomiting, and headache. Red streaks on the extremity, tender nodes, and warm skin are also present. Hospitalization and intravenous administration of antibiotics are the recommended and effective treatment.

Cellulitis is a complication in about 30% of cases of primary lymphedema. This study found that 36% of the patients had at least one episode of cellulitis; Wolfe and Kinmonth[18] reported that 27% of their patients had had at least one episode of cellulitis by follow-up. Interestingly, in our study, infection was a complication in more than 50% of the patients with congenital lymphedema, conflicting with other reports stating this to be a rare occurrence.[5,19] Brunner and Knüsel[151] and Babb et al[152,153] both reported a high association between tinea pedis and cellulitis, possibly up to 35%. It is believed that the small fissures between the toes in tinea pedis allow infective organisms to enter the skin and proliferate in the lymphedematous tissue, a good culture medium for bacteria.[121]

Babb et al[152,153] and others[154] recommended a prophylactic antibiotic regimen in patients who had repeated attacks of cellulitis. Penicillin, given orally 1 week per month, was shown to decrease the infection rate markedly. However, these patients all had secondary lymphedema, and these results do not necessarily transfer.

IMPLICATIONS

Primary lymphedema has not been studied as extensively in children and adolescents as in adults. The etiologic factors in this age group necessitate some changes in the diagnosis and treatment of primary lymphedema. Because the incidence of malignancy complicating or causing the edema is extremely low in children and adolescents, only a complete history and physical examination should be performed in a patient with chronic swelling of an extremity. No other diagnostic measures should be done because none will alter the treatment. In children and adolescents, this should consist of conservative treatment in all patients except newborns and infants; careful observation is mandatory. A Jobst-type stocking, elevation, and foot care will achieve the best results. In 60% of these patients, swelling will be stable within a few years after onset. Surgical treatment should be delayed as long as possible because of its complications and disappointing results, and it should only be performed in patients who have severe disfigurement that interferes with daily activities and life-style, not because of cosmetic indications. The psychologic aspect of this disfiguring illness should be addressed, especially in adolescents, so that these patients can better cope with their illness.

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