

# The swollen leg and primary lymphoedema

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## Abstract

**Children who present with unilateral or bilateral swelling of the legs are often suspected of having a deep venous thrombosis. The incidence of deep venous thrombosis in children is low and lymphoedema may be a more appropriate diagnosis. Lymphoedema can be primary or secondary. In childhood, primary lymphoedema is more common and may be seen associated with other congenital abnormalities, such as cardiac anomalies or gonadal dysgenesis. Primary hypoplastic lymphoedema is the most often encountered type. It is more common in girls, especially around puberty, and is typically painless. Atypical presentations produce diagnostic confusion and may require imaging to confirm the presence, extent, and precise anatomical nature of the lymphatic dysplasia. This article describes four patients presenting with limb pain and reviews the clinical features and imaging options in children with suspected lymphoedema.**

(*Arch Dis Child* 1994; 71: 44-49)

A child with a swollen leg may present a difficult diagnostic problem. The initial clinical diagnosis is usually a deep venous thrombosis, although these are uncommon in children. If pelvic and vascular ultrasound, including colour flow and Doppler imaging, does not show venous thrombus or its cause, then a large number of other disorders need to be considered. These include lymphoedema, lipoedema, hemihypertrophy, neurofibromatosis, macrodystrophia lipomatosa, reflex sympathetic dystrophy, multiple enchondromatosis, and the mixed vascular deformities (for example, Klippel-Trenaunay syndrome, congenital arteriovenous fistulas, and diffuse haemolymphangiomas). Although most of these uncommon disorders are clinically distinguishable, there will be a small proportion of patients in whom the diagnosis remains obscure. Such a group includes those children with primary lymphoedema. This paper discusses the clinical and radiological features of primary lymphoedema and presents four case reports.

## Case reports

### CASE 1

A 13 year old previously healthy girl presented to an orthopaedic clinic with an 11 month history of intermittent swelling of her ankles. She recalled a trivial injury to the back of her right calf before the onset of symptoms. She had also noticed mild intermittent swelling

of her right hand, but this was normal at presentation. The swelling of her ankles was associated with pain and limitation of movement. Menarche occurred at 11 years of age. On clinical examination she had bilateral pitting oedema of the legs, more marked on the right, and confined to below both knees. Haemoglobin, white cell count, platelet count, erythrocyte sedimentation rate, blood biochemistry, rheumatoid factor, and thyroid function tests were all normal. Plain radiography and an isotope bone scan gave normal results. The child was referred for rheumatological and dermatological opinions. A firm diagnosis was not made and advice was sought from a paediatrician. Further investigation was discussed with the radiology department and a lymphangiogram was suggested. A bilateral lymphangiogram showed a solitary, mildly ectatic lymphatic vessel on the left leg with normal inguinal, pelvic, and lumbar lymph nodes (fig 1). On the right there was aplasia of the lymphatic vessels with dermal backflow on injection of Patent Blue dye.

### CASE 2

A 14 year old previously healthy girl presented with a 12 month history of intermittent bilateral leg pain. The pain was initially localised around the knees but later affected the thighs and hips. It was occasionally severe enough to



Figure 1 Lymphangiogram showing a solitary, mildly ectatic lymphatic vessel in the thigh.

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Accepted 23 March 1994



*Figure 2 Bilateral lymphangiogram showing morphological hypoplasia and a paucity of valves in the lymphatic vessels of the calf.*

wake her at night. Shortly after the onset of symptoms, swelling of the legs developed. Clinical examination showed bilateral swelling of the legs with pitting oedema of both ankles and the presence of striae over the thighs and buttocks. She was normotensive. A number of clinical diagnoses were considered, including Cushing's disease and intra-abdominal pathology. Routine blood tests were normal, as were cortisol concentrations. A lateral skull radiograph and estimation of bone age were normal. Pelvic ultrasound and abdominal computed tomography were normal. A bilateral lymphangiogram showed morphological hypoplasia



*Figure 3 Lymphangiogram showing a solitary iliac lymphatic vessel and mildly hypoplastic lymph nodes. The thigh lymphatic vessels are normal in size but the valves are abnormal.*

with a paucity of valves, but normal nodal morphology (fig 2). Features were consistent with a primary lymphatic dysplasia.

#### CASE 3

A 13 year old previously healthy girl presented with a three day history of unilateral calf swelling and itching around the ankle and foot. Clinical examination confirmed the presence of mildly tender pitting oedema from the knee to the ankle. Otherwise, the clinical examination was normal. A tentative diagnosis of deep venous thrombosis was made. Her haemoglobin, white cell count and differential, platelet, erythrocyte sedimentation rate, blood biochemistry, urine analysis, and clotting profile were all normal. Vascular Doppler ultrasound was performed and was normal. The swelling resolved within 72 hours with elevation and, although pain and tenderness persisted, the child was allowed home while receiving a short course of ibuprofen (200 mg four times a day). Approximately three weeks later she returned with recurrent symptoms. Her foot was also noted to be cooler, but peripheral pulses were normal. Plain radiography of the leg and ultrasound of the pelvis were normal. Further investigation was discussed with the radiology department. Ultrasound of the affected leg confirmed generalised thickening of the subcutaneous tissues distally. A lymphangiogram was performed on the affected leg. This showed fine calf lymphatic vessels and a solitary iliac lymphatic vessel. The lymph nodes appeared hypoplastic. The diagnosis of primary hypoplasia of the lymphatic system was made (fig 3).

#### CASE 4

A 16 year old previously healthy girl presented with an acutely swollen right hand and arm. A venous thrombosis was suspected and venography was performed on the arm. This was normal. Plain radiography showed no abnormality. Computed tomography showed an increase in the thickness of the subcutaneous layers of the arm, but no obvious cause for the swelling. Lymphoedema was suspected and lymphatic obstruction confirmed by lymphoscintigraphy, no obvious lymphatic vessels being identified. The arm swelling resolved spontaneously, but, a few months later, moderately painful leg swelling occurred. Atypical lymphoedema was suspected and a lymphangiogram was performed. This confirmed a lymphatic dysplasia of the legs.

#### Discussion

Lymphoedema has been described as 'a swelling of some part of the body due to a fault in the lymphatic system'.<sup>1</sup> The pathological characteristics include excess tissue protein and oedema, which are initially reversible, but eventually chronic inflammation and fibrosis occur.<sup>2</sup> This is reflected clinically by swelling which pits on pressure, but with time

*Genetic syndromes associated with lymphoedema*

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Turner's syndrome<sup>10</sup>  
 Noonan's syndrome<sup>11</sup>  
 Pes cavus<sup>12</sup>  
 Distichiasis (double row eyelashes)<sup>13 14</sup>  
 Yellow nail syndrome<sup>15 16</sup>  
 Ptosis<sup>17</sup>  
 Hypoparathyroidism<sup>18</sup>  
 Microcephaly<sup>19-21</sup>  
 Arteriovenous malformations<sup>22</sup>  
 Neuronal migration defects<sup>23</sup>  
 Facial anomalies<sup>24 25</sup>  
 Cholestasis<sup>26</sup>

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becomes thickened and unyielding. Super-vening inflammation accelerates the process and hyperkeratosis, verrucas, and condylomata formation may occur. Ulceration is rare. Further complications of chronicity include elephantiasis, lymphocutaneous fistulas, and rarely the development of angiosarcoma.<sup>3-7</sup>

CLASSIFICATION

Lymphoedema can be a primary or, more commonly, a secondary disorder. Primary lymphoedema is more often seen in children than in adults. The secondary causes are clearly defined by aetiology. They include those seen in generalised oedema (for example, cardiac, renal, and hepatic failure, and hypo-proteinaemia) and those due to local causes such as trauma (including surgery), malignancy, infection (for example, filarial), inflammation (for example, chronic eczema), and radiation.

Primary lymphoedema is classified by age at presentation: congenita, praecox (age 1 to 35 years old), and tarda (over 35 years). Some confusion may arise in that lymphoedema praecox and tarda, though presenting in later life, are due to an underlying congenital anomaly. The suffix merely describes the age at presentation. An alternative classification uses radiological appearances: aplasia, hypoplasia, and hyperplasia. There is a large, but comparatively rare, heterogeneous group of primary lymphoedemas which are hereditary (Milroy's and Meige's disease<sup>8 9</sup>) or associated with genetic syndromes. The table above summarises the latter; most show features which should not cause diagnostic problems. An increased incidence of lymphoedema is also seen in congenital heart disease<sup>27</sup> and the mixed vascular deformities.<sup>28 29</sup> Primary lymphoedema has also been considered as one end of a spectrum of disorders of the lymphatic system encompassing lymphangiectasia, lymphangiomas, and chylous effusions.<sup>30</sup> The incidence of other congenital malformations seen in children with primary lymphoedema is reported by some workers to be high,<sup>1 31 32</sup> although this is contentious.<sup>33</sup>

CLINICAL ASPECTS OF PRIMARY LYMPHOEDEMA

Classical primary lymphoedema is a mild, painless swelling of the distal extremity which progresses relentlessly to a huge, swollen limb. The diagnosis of primary lymphoedema is made by taking a careful history and performing a thorough examination. There may be obvious features, such as those of Turner's

syndrome, which help in confirming the diagnosis. The clinical diagnosis in the four cases presented here was made difficult by the presence of a painful limb, which undoubtedly caused some confusion.

Lymphoedema praecox is the most common type of primary lymphoedema and both the congenita and the praecox types are more common in females (2:1 and 4:1 respectively). The sex difference is especially notable in the second decade, possibly due to the onset of puberty with consequent alterations in pelvic lymph flow and the effects of hormonal changes. This theory is supported by children with Turner's syndrome who develop lymphoedema of the congenita type which often spontaneously resolves, only to recur once menarche is induced.<sup>10</sup> Oestrogen has been specifically implicated and subcutaneous tissue pressure is also thought to play a part, it being slightly higher in boys than girls.<sup>33</sup> Features often arise spontaneously or are related to a minor insult such as in case 1.

Some distinct clinicoradiological groups of patients with primary lymphoedema have been described.<sup>1</sup> These include patients with primary hypoplastic lymphoedema, unilateral megalymphatics, and bilateral hyperplasia of the lymphatics.

*Primary hypoplastic lymphoedema*

This group forms about 80% of patients with primary lymphoedema of the legs. It is also the group of patients causing the greatest diagnostic confusion. The comments made about lymphoedema praecox refer mainly to this group. There is a spectrum of disease with two extremes defined by lymphographic, genetic, and histopathological features. At one end of the spectrum are patients with hypoplasia of the proximal lymphatics and distal distension. There is usually a more acute history of unilateral severe swelling, an equal sex distribution, and extensive lymph node fibrosis. At the opposite end is distal lymphatic hypoplasia, which is more common in females, milder in nature, symmetrical, and confined to below the knee. There may be a family history and the lymph nodes are normal.<sup>34 35</sup> Many patients have features between these two extremes, as do all four cases presented here.

*Unilateral megalymphatics*

In this group, patients almost always have a capillary angioma on the affected limb or trunk. Bilateral features are rare, there is no family history, and there is an even sex distribution.

*Bilateral hyperplasia*

This predominantly male group of patients shows bilateral symmetrical lymphoedema mainly affecting the legs below the knees. Some also have symmetrical angiomata around their feet. A family history is common and a number of other deformities may be present, the most common being distichiasis<sup>36</sup>

and cardiac anomalies.<sup>27</sup> The thoracic duct is often absent or abnormal, reflecting the intimate relation between cardiac and lymphatic development.

Two other distinct groups were described by Kinmonth,<sup>1</sup> Milroy's disease and lymphoedema associated with gonadal dysgenesis or pes cavus. In the two groups the lymphatics show hypoplasia or aplasia. Nodal fibrosis similar to that seen in primary hypoplastic lymphoedema is seen in Milroy's disease.

#### IMAGING

The investigation of a child with a swollen leg must include the initial exclusion of systemic and vascular causes. The latter is relatively easy and should include vascular Doppler ultrasound in the first instance. The exclusion of systemic causes and secondary lymphoedema may involve a wide range of investigations, and, from the imaging aspect, pelvic ultrasound is probably the simplest, non-invasive next step, and can be combined with the vascular study. Subsequently, imaging should be guided by the clinical course and the results of other investigations. Once primary lymphoedema is suspected, imaging should aim to confirm the diagnosis, define its extent and severity, and detect any possible complications. Consideration must be given to the necessity of further investigation. It is of limited value in confirming the presence of a lymphatic problem in a child with a disease known to be associated with lymphatic abnormality, such as Turner's syndrome, and we would confine further investigation to those patients in whom there is diagnostic confusion. Therefore, most of our remarks refer to primary hypoplastic lymphoedema, usually presenting as lymphoedema praecox.

Plain radiographs are primarily performed to exclude underlying soft tissue or bony pathology. Radiographs may show a general increase in the depth of the fat planes, but unless particularly marked, these may only be identified in retrospect and are of little discriminatory value.

Ultrasound examination is mandatory and should be performed to exclude an underlying vascular abnormality. It may also detect the increased thickness of the subcutaneous and subfascial compartments, especially when the disorder is unilateral, and has been used for volumetric assessment.<sup>37</sup>

#### *Lymphography*

There are two types of radiographic lymphography: intralymphatic and interstitial.

Intralymphatic lymphography is the traditional method and involves the cannulation of a lymphatic vessel. It is technically demanding and is described in detail by Kinmonth.<sup>1</sup> The lymphatic vessels are initially visualised after a dermal injection of Patent Blue dye into an interdigital webspace. Lymphatic obstruction may be suspected at this stage if the

dye forms a large, but finely reticulated, network on the skin (dermal backflow). Several lymphographic patterns have been described. In primary hypoplastic lymphoedema, the two extremes of the disease spectrum show distinctive appearances. In the distal hypoplasia group there is a reduction in the number and calibre of the lymphatic vessels. In proximal hypoplasia, the trunk lymphatics are abnormal and hypoplastic, with a distended lymphatic tree distally. In unilateral megalymphatics, the affected limb has large and valveless lymphatic vessels, and the lymph nodes are small, multiple, and scattered. The thoracic duct is large and incompetent. In bilateral hyperplasia, there is both numerical and morphological hyperplasia of the vessels and lymph nodes with an absent or partially atretic thoracic duct.

Interstitial lymphangiography is a relatively new technique which allows the visualisation of the peripheral lymphatic vessels.<sup>38-39</sup> The technique is easier to perform than intralymphatic lymphography and it has been advocated as the study of choice for assessing lymphatic vascular morphology.<sup>40</sup> It does not show nodal morphology adequately, however, and this may be important in assessing prognosis.

#### *Other imaging modalities*

Radioisotopes (lymphoscintigraphy) can be used to evaluate lymphatic morphology and function.<sup>41-47</sup> Several agents have been used, including technetium-99m labelled antimony sulphide colloid, dextran, and human serum albumin. The radiolabelled isotope is injected into the subcutaneous interdigital space and images obtained using a gamma camera. Static and dynamic images can be obtained. Lymph vessels and nodes, collateral circulation, dermal backflow, and vessel dilatation can be recognised by lymphoscintigraphy, but it lacks precise anatomical definition. Quantitative (dynamic) assessment allows the detection and grading of lymphoedema, and is a sensitive method of assessing mild and/or incipient lymphoedema.<sup>41</sup>

Both computed tomography and magnetic resonance imaging (MRI) are better known for their ability to show lymphatic nodal morphology. They can also differentiate lymphoedema from lipoedema and phleboedema.<sup>48-50</sup> Lymphoedema shows a typical honeycomb pattern in both modalities between the muscle and subcutis. A pronounced increase in signal intensity is seen on T2 weighted images using MRI. Failure to demonstrate the honeycomb pattern does not exclude lymphoedema, however. Angiosarcomatous change can also be detected.<sup>51</sup>

#### PROGNOSIS AND MANAGEMENT

The prognosis of primary hypoplastic lymphoedema of the legs is variable. Relentless progression of the lymphoedema may not occur and about 60% of patients reach a plateau of clinical severity after several

years.<sup>33 52</sup> It is therefore essential that a sufficiently long period of conservative management is undertaken to allow the disorder to stabilise before contemplating an operation. There are some clinical features which may be helpful in predicting outcome. The prognosis is better for females, even if there is bilateral disease. The outcome is generally worse with an acute onset of oedema and if swelling begins in the thigh. Males with unilateral oedema tend to progress to severe change. The extent and degree of lymphatic abnormality in the vessels and nodes seen on lymphography will help to predict the outcome. Quantitative lymphoscintigraphy can also be helpful in grading disease severity and assessing treatment success.<sup>41</sup>

The conservative management of lymphoedema includes exercise, self massage, elevation, compression (such as elasticated stockings or pneumatic machine), and scrupulous attention to skin care. Medical treatment with diuretics has shown disappointing results,<sup>33</sup> and they are not recommended for long term treatment.<sup>2</sup> Treatment with benzopyrones has been shown to reduce excess protein in the tissues with some beneficial effects.<sup>53</sup> It is also important not to underestimate the psychological effects of the disorder, especially in adolescence.

An operation should be a last resort when all conservative measures have failed. Moreover, an operation early in the disease is inadvisable because of its varied nature. There are numerous potential surgical procedures, such as excisional operations, buried dermal flaps, and attempts at creating lymphaticovenous anastomoses, but complications are common and there is generally only a 30% success rate.<sup>33</sup>

Dr N B Wright, research fellow in paediatric radiology, is partly funded by a grant from E Merck Limited and I G E Medical Systems Limited.

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### Carbamazepine, phenytoin, and the fetus

The fetal hydantoin syndrome was first described in 1975.<sup>1</sup> It has been estimated to occur in between 6 and 30% of at risk babies. Reports of adverse effects from carbamazepine in pregnancy have been less common. A report from Toronto (Dennis Scolnik and colleagues, *Journal of the American Medical Association* 1994; **271**: 767-70) compares children born after exposure during pregnancy to either phenytoin or carbamazepine used as single drugs. In a prospective study the children of 34 mothers who took phenytoin in pregnancy were compared with those of 36 who took carbamazepine and 70 paired mothers matched for age, parity, gravidity, and social class, who took only non-teratogens. The children were assessed between 18 and 36 months of age using Bayley or McCarthy scales of development and Reynell language scales.

Mean IQ was 103.1 in the phenytoin-exposed children and 113.4 in their paired controls. In children who had been exposed as fetuses to carbamazepine the mean IQ was 111.5 and in their paired controls it was 114.9. The difference was significant only for the phenytoin group ( $p < 0.05$ ). Seven of the phenytoin children had features of the fetal hydantoin syndrome. An IQ of 84 or less was found in seven of the 34 children in the phenytoin group and one of their controls ( $p < 0.01$ ). (Of the seven children with fetal hydantoin syndrome two had  $IQ \leq 84$ .) Such an IQ was found in three of the 36 carbamazepine-exposed children and one of their controls. The phenytoin-exposed children also performed poorly on tests of verbal comprehension and expressive language. There was no significant difference between trial mothers and controls as regards IQ or social class.

The authors suggest that carbamazepine should be preferred to phenytoin in pregnancy. Most paediatricians prefer carbamazepine anyway.

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<sup>1</sup> Hanson JW, Smith DW. The fetal hydantoin syndrome. *J Pediatr* 1975; **87**: 285-90.