

Research Letter

Prenatal diagnosis of Milroy's primary congenital lymphedema

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Primary lymphedema, which is caused by an intrinsic defect of the lymphatic vessels, can be genetic in origin (aplasia, hypoplasia, hyperplasia, and tortuosities). The most common form of hereditary primary lymphedema is Milroy disease, also known as primary congenital lymphedema. It is a relatively rare disorder, characterized by a firm edema of the lower extremities that can be generalized to the whole leg or limited to the feet or toes [1].

Its inheritance is autosomal dominant, and it is estimated to occur with an incidence rate of approximately 1 in 6000. The only known molecular cause of Milroy disease is mutation in the vascular endothelial growth factor receptor 3 (*VEGFR3*) gene. The gene locus of this malformation has been mapped to 5q35.3 [2]. In some families, the disorder is completely penetrant, while in others penetrance is incomplete (80–84%), with a male/female ratio of 1:2.3 [3].

Lymphoscintigraphy can be performed, and a lymphedema therapist may utilize fitted stockings and massage to improve the cosmetic appearance or decrease the size of the limb and reduce the risk of complications [2].

We present a case of Milroy's primary congenital lymphedema (PCL) that presented prenatally with bilateral leg edema and edema of the dorsal aspects of both feet with cyst of umbilical cord at 19 weeks' gestation.

A 34-year-old pregnant woman with gravida 2, parite 1 was referred to our hospital because of a prenatal ultrasound detection of isolated bilateral lower extremity edema and cyst of umbilical cord at 19 weeks of gestation. The scan showed a normal amount of amniotic fluid and a singleton normally developed fetus with edema on the dorsum of the feet and with a suspected edema on the legs (Fig. 1). In addition to that, we confirmed a 35 × 25 mm cyst in the proximal part of the umbilical cord (Fig. 2). The main fetal measurements were all within normal limits. All internal organs were apparently normal and no other major malformations were noted. The

patient refused amniocentesis. Maternal evaluation for other causes of lymphedema including parvovirus, cytomegalovirus, toxoplasma, and rubella serology was negative. She was followed up closely during the course of her pregnancy. According to the patient's family history, there was no relationship between the parents. The husband's family history was positive for hereditary lymphedema found in three generations. The affected family members, including the husband himself, the husband's father, and the husband's nephew, had isolated leg lymphedema of variable degrees of severity at their birth. They healed without any sequelae.

Cesarean section was performed at 39 weeks of gestation. The patient gave birth to a girl with the following birth measurements: weight 3300 g, length 49.5 cm, head circumference 33.7 cm. Clinical examination showed firm edema of the lower limbs, particularly evident at the back of the feet, and a 3 × 4 cm cyst at the proximal part of the umbilical cord (Fig. 3). The rest of the clinical examination yielded normal results.

The baby's chromosomal analysis showed a normal female karyotype (46, XX). In our hospital, the calculated blood biochemical and complete blood count values, and findings of the lower extremity arterial and venous Doppler ultrasound for the etiology of edema were normal. Lymphoscintigraphy was done, after injection of contrast material, and no lymphatic clearance was noticed in the proximal region of the lower extremity. Thus, a diagnosis of Milroy disease was made.

Milroy disease is characterized by lower-limb lymphedema, present at birth as pedal edema or developing soon after. The severity of edema shows both inter- and intrafamilial variability. Swelling is usually bilateral but can be asymmetric. The degree of edema can progress, but in some instances improvement can occur, particularly in the early years [2]. In our case, the family members healed without any sequelae.

PCL is rare, and its incidence rate has not been determined. The male/female ratio is 1:2.3. Lymphedema in PCL is painless and non-pitting, with no tendency to ulceration and no associated varicosities. The pathogenesis of PCL is based on a congenital dysgenesis of lymphatic microvessels [4]. Milroy disease is inherited in an autosomal dominant manner [2].

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Fig. 1. Milroy's primary congenital lymphedema: firm edema of the lower limbs by a fetal ultrasonographic examination.

Primary congenital lymphedema results from a mutation in the *VEGFR-3* gene located on chromosome 5q35.3 [5]. In this case, the husband's family history was positive for hereditary lymphedema found in three generations, and the sex of all patients was male; only this baby was female.

PCL is to be differentiated from nonlymphatic edema, Turner syndrome, Noonan syndrome, microcephaly-lymphedema, lymphedema–distichiasis syndrome, lymphedema and ptosis syndrome, hereditary lymphedema type II (Meige lymphedema, late-onset lymphedema, lymphedema praecox), and congenital recessive-type lymphedema. Noonan syndrome was excluded in



Fig. 2. A 3 × 4 cm cyst at the proximal part of the umbilical cord by ultrasonographic examination.



Fig. 3. Postnatal photograph showing lymphedema of the foot and the leg, and cyst of umbilical cord.

the absence of other fetal malformations. Turner syndrome was ruled out by fetal chromosomal analysis. Distichiasis lymphedema was ruled out in the absence of two rows of eyelashes and by early-onset lymphedema in the patient's family. The normal cranial size ruled out microcephaly–lymphedema. Type II lymphedema develops around puberty or later, and can involve the upper limbs, lower limbs, face, larynx, and pleural cavity, while the congenital recessive type may be associated with abnormalities of the external genitalia, intestinal lymphedema, and chemosis [4]. In our case, the main fetal measurements were all within normal limits. All internal organs were apparently normal and there were no other major malformations.

Milroy disease is diagnosed by clinical findings and confirmed by molecular genetic testing. Lymphoscintigraphy can be performed; the characteristic finding is a lack of uptake of radioactive colloid in the ilioinguinal lymph nodes caused by a paucity of lymphatic vessels or abnormal function of the vessels in the lower limbs. Molecular genetic testing for *FLT4* (*VEGFR3*), the only gene known to be associated with Milroy disease, is available on a clinical basis [2]. In this case, where lymphatic clearance was not monitored in the proximal region of the lower extremity after lymphoscintigraphy injection, a diagnosis of Milroy disease was made.

PCL is rarely associated with significant complications. Nonetheless, there are case reports of intestinal lymphangiectasia, bacterial infections of the dorsal aspects of feet and toes, recurrent septic arthritis, angiosarcoma, and lymphangiosarcoma [4].

A lymphedema therapist may utilize fitted stockings and massage to improve the cosmetic appearance or decrease the size of the limb and reduce the risk of complications. Frequency of cellulites can be reduced through good skin hygiene, prompt treatment of infections with antibiotics, and prophylactic antibiotics for recurrent episodes [2]. Affected individuals may benefit from avoiding prolonged standing and

using mechanical means of lymphatic drainage such as elastic stockings or bandages. Careful attention to foot hygiene may decrease the risk for, and aid early recognition of, fungal or bacterial infections [5].

Knowledge of the clinical presentation, genetic basis, pathogenesis, life time course, and complications of PCL by perinatologists, sonologists, pediatricians, plastic and orthopedic surgeons, general practitioners, and other health professionals, will contribute to the provision of better counseling for parents of an affected fetus [4].

In conclusion, when isolated lower extremities lymphedema is noticed during routine ultrasonographic examination, family history should be inquired and Milroy disease should be kept in mind.

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