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Newborn With Puffy Feet: A Case Report

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Abstract

Hereditary congenital lymphedema, also known as Milroy disease, is an uncommon autosomal dominant disorder characterized by impaired lymphatic vessel development, resulting in bilateral lower limb edema at or shortly after birth. The condition exhibits incomplete penetrance. We report a case of a full-term female infant presenting with significant lower limb edema at birth, involving the dorsum of both feet and ankles, which was nonpitting in nature. The infant was admitted to the neonatal unit for respiratory support and discharged in good condition. There was a strong family history of Milroy disease, with four generations affected, but the parents declined confirmatory genetic testing and lymphoscintigraphy. This case adds to the body of research on this rare disease, illustrating that the diagnosis can be made clinically.

Categories: Genetics, Medical Education, Pediatrics
Keywords: disease genetics, lymphedema, milroy disease, puffy feet, term neonate

Introduction

Milroy disease, also known as hereditary congenital lymphedema, is a rare condition caused by impaired development of lymphatic vessels [1], resulting in bilateral lower limb edema at or shortly after birth, which is nonprogressive. Other symptoms and signs include cellulitis, large-caliber leg veins, upslanting toenails, papillomatosis, hydrocele in males, and, rarely, malignant transformation to lymphangiosarcoma.

The inheritance pattern of Milroy disease is autosomal dominant, with incomplete penetrance of 80-90% [2]. The locus for the disease is found at chromosome 5q35.3, in the FLT4 or VEGFR-3 gene in most families [3,4]. This gene codes for VEGFR-3, a tyrosine kinase receptor that is activated by VEGF-C and VEGF-D and is required for embryological development of the lymphatic system. Most mutations are missense mutations; however, a deletion mutation has also been reported [3].

Differential diagnoses for congenital lymphedema include Noonan syndrome, Turner syndrome, congenital hypothyroidism, and microcephaly-chorioretinopathy-lymphedema syndrome [2]. Genetic testing can be lengthy or, as in this case, declined. Therefore, a clinical diagnosis based on consideration of family history and exclusion of more serious differential diagnoses is important and can help guide management.

In Milroy disease, conservative management, such as compression garments, exercises, and manual lymphatic drainage, is generally successful. Surgical options include microsurgical transfer of lymph node tissue to improve drainage and removal of excess lymphedematous tissue. Education on skin care and diet to reduce the risk of cellulitis and lymphangitis is essential [5].

Case Presentation

A full-term female infant was noted to have significant lower limb swelling at birth, involving the dorsum of both feet and ankles (Figure *1*). The swelling was nonpitting in nature, with a positive Stemmer's sign (inability to pinch the skin over the dorsum of the proximal phalanx of the toes), indicating peripheral lymphedema at birth. There were no dysmorphic features suggestive of a syndromic diagnosis, no neck webbing, and no cardiac murmurs. There were no prominent veins in the lower limbs or toenail abnormalities. She was delivered by cesarean section due to fetal distress. Her birth weight was 3,475 g (50th percentile), and her head circumference was also at the 50th percentile.



FIGURE 1: Neonate with congenital lymphedema.

There was a maternal history of obsessive-compulsive disorder, post-traumatic stress disorder, bipolar disorder, asthma, and smoking, including cannabis use. The mother was taking duloxetine. Her antenatal scans showed polyhydramnios from 32 weeks of gestation, but no other abnormalities were detected.

The baby required brief resuscitation with ventilation breaths for one minute and was then managed with facial continuous positive airway pressure (CPAP), requiring 30% oxygen. She was admitted to the neonatal unit for respiratory distress requiring CPAP support for eight hours. Duloxetine is a serotonin-norepinephrine reuptake inhibitor, and one of the potential side effects of its use during pregnancy is poor neonatal adaptation in the newborn. The respiratory distress was thought to be due to poor neonatal adaptation related to maternal duloxetine use, resulting in the need for short-term respiratory support with CPAP. The baby recovered well. She received intravenous antibiotics, which were discontinued following negative blood cultures at 36 hours of age. C-reactive protein levels were low, and the full blood count was unremarkable. A chest X-ray was normal. Other than the lower limb swelling, there were no significant examination findings.

The baby remained well and was discharged two days later. Medical photography was performed, and the mother was offered genetic testing and lymphoscintigraphy; however, she declined. There was a significant family history of hereditary lymphedema. The baby's mother (Figure *2*), maternal grandfather, and maternal great-grandmother had lymphedema and had been diagnosed with Milroy disease. Due to the absence of clinical features suggestive of other causes of lymphedema and the strong family history spanning four generations, Milroy disease was diagnosed clinically in the baby.



FIGURE 2: Mother with congenital lymphedema.

Discussion

Primary lymphedema is the term used when there is a presumed genetic developmental problem affecting the structure or function of the lymphatic drainage system [6]. The incidence of Milroy disease is unknown [7]; some studies suggest that one in 33,000 deliveries are affected [8], while others suggest one in 6,000 births [9]. Milroy disease is the most common cause of primary congenital lymphedema. An autosomal dominant mutation in the FLT4 gene causes disruption of the tyrosine kinase domain of VEGFR-3, thereby disrupting the development of the lymphatic system. The typical phenotype is symmetrical bilateral lower limb edema, with prominent veins and occasionally upslanting toenails [10].

Milroy disease can be diagnosed clinically by identifying lower limb edema before the age of one year, which commonly has a symmetrical distribution on the dorsal aspect of the feet, and either identifying an FLT4 gene variant through molecular genetic testing or detecting reduced uptake of radioactive material in the ilioinguinal lymph nodes on lymphoscintigraphy [2,7].

Congenital lymphedema can be suspected antenatally, with visible lymphedema noted on scans, and can be confirmed via amniocentesis [8]. In some severe cases of Milroy disease, pleural effusion, hydrothorax, and hydrops fetalis have been described. In the case presented here, there was no suspicion based on antenatal scans. While the severity of symptoms can vary within the same family [2], in our case, the mother felt that the presentation was sufficiently similar to her family's history and was satisfied with the likely diagnosis; therefore, she did not consent to genetic confirmation.

Primary lymphatic anomalies are highly diverse and have historically been difficult to classify. The updated St George's classification algorithm categorizes primary lymphatic anomalies into five distinct, color-coded groups based on the age of onset of swelling, the body areas affected, and associated systemic or syndromic features [6]. This classification of primary lymphatic disorders brings them into alignment with the International Society for the Study of Vascular Anomalies 2018 classification for vascular anomalies.

The framework classifies anomalies into five main groups: (1) vascular and lymphatic malformations (yellow), characterized by segmental, patchy swelling often accompanied by tissue overgrowth and typically caused by postzygotic (mosaic) mutations, such as PIK3CA; (2) syndromic lymphedema (blue), in which lymphedema presents as a secondary feature alongside broader anomalies (e.g., Noonan or Turner syndrome); (3) systemic/visceral involvement (pink), characterized by lymphedema paired with internal lymphatic dysfunction, such as fetal hydrops, intestinal lymphangiectasia, or chylous effusions (e.g., Hennekam syndrome); (4) congenital-onset primary lymphedema (green), in which swelling develops within the first year of life as the primary symptom, most notably in Milroy disease (VEGFR3/FLT4); and (5) late-onset primary lymphedema (purple), in which swelling develops after the first year of life (e.g., Meige

disease or lymphedema-distichiasis syndrome caused by FOXC2).

Features that would suggest a syndrome or a disease other than Milroy disease include dysmorphism (including facial features, webbed neck, unusual chest shape, or high palate), renal and cardiac abnormalities (including congenital heart disease, atrial septal defect, hydrops, or effusions), telangiectasia, and segmental tissue overgrowth. There were no phenotypic features of Turner syndrome or other dysmorphic features, placing our case in the green group, as described above. Lymphedema can also be an early symptom of other conditions, and neonates with congenital primary lymphedema may later present with systemic involvement, vascular malformations, or developmental delay. Genetic testing is therefore helpful in confirming the diagnosis and guiding further management.

In this case, the mother declined genetic testing and lymphoscintigraphy, which does not preclude the diagnosis in the child, as Milroy disease can be diagnosed based on a classical phenotype and positive family history [10]. However, this may increase the possibility that a diagnosis of another syndrome could be missed. It is worth noting that there are some variations and challenges in the diagnosis of Milroy disease: only 70% of patients with Milroy disease have mutations in FLT4, approximately 10% of mutation carriers do not have lymphedema, some mutations occur de novo and therefore are not associated with a positive family history, and lower limb edema may sometimes be unilateral. Hence, a molecular diagnosis in the neonatal period is very useful in the management of these patients [6].

Management of Milroy disease includes compression, massage, prevention of secondary complications such as cellulitis through proper hygiene, and routine follow-up in a clinic specializing in lymphedema. As the mother in this case was familiar with the disease and was already linked with a specialized lymphedema clinic, she preferred to contact the primary care provider and have the baby referred to a lymphedema clinic for long-term follow-up.

The main limitation of this case report is that it describes a single case, which limits generalizability. Furthermore, the family declined genetic testing, and hence, the diagnosis rests on the clinical phenotype and family history alone, without molecular or lymphoscintigraphic confirmation. Thus, a coexisting or syndromic cause cannot be entirely excluded on clinical grounds. Long-term follow-up data are not available to confirm the expected nonprogressive course.

Conclusions

In the presence of a strong family history spanning four generations affected by typical congenital lower limb edema and the absence of features suggestive of other causes of lymphedema, Milroy disease was diagnosed. Milroy disease can be strongly suspected based on clinical features and family history; some may argue that genetic confirmation (identifying a pathogenic variant in the FLT4 gene) is required for a definitive, precise diagnosis. Genetic testing adds value in cases with atypical presentations (later onset, unilateral edema, or additional systemic features), sporadic cases without a family history, or when providing genetic counseling about recurrence risk.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Lauren Foster, Geethanath R. Mohanram

Drafting of the manuscript: Lauren Foster, Geethanath R. Mohanram

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Disclosures

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