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CASE REPORT

PRENATAL DIAGNOSIS OF CONGENITAL BILATERAL LOWER LIMB LYMPHEDEMA MILROY TYPE: CASE REPORT

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ABSTRACT

Congenital lymphedema is a rare inherited genetic disorder of the lymphatic system. It is usually diagnosed in childhood and occasionally in the prenatal stage. This article aims to present a case with a prenatal diagnosis of congenital bilateral lower limb lymphedema Milroy type. This is a 21-year-old pregnant woman, with a gestational age of 24 weeks. Ultrasounds of chromosomopathies and morphological markers in the first and second trimesters of pregnancy did not report structural alterations. At 24 weeks, a two-dimensional ultrasound was performed that confirmed bilateral lymphedema of the lower limbs. When performing genealogy of four generations, no personal or family history of circulatory disorders or other health problems is reported. Genetic counseling was offered and the surrogate requested voluntary termination of the pregnancy. The pathological analysis confirmed the ultrasound findings with a diagnosis of congenital bilateral lymphedema of the lower limbs Milroy type.

Key words: Congenital lymphedema, Milroy disease, Prenatal diagnosis, Genetic counseling (Source: MeSH NLM)

INTRODUCTION

Lymphedema is defined as an excessive accumulation of lymphatic fluid in the subcutaneous tissue, due to the inability of the lymphatic system to maintain normal homeostasis. It can be classified as either primary or secondary. Primary lymphedema results from a congenital abnormality or dysfunction of the lymphatic vessels, while secondary lymphedema can develop as a result of the destruction or obstruction of the lymphatic channels by other pathological conditions such as infection, trauma, or cancer. (1)

Primary lymphedema is an inherited genetic disorder of the lymphatic system. These genetic disorders can lead to malformations or dysfunctions of the lymphatic system, leading to an accumulation of interstitial fluid and thus the formation of edema. It is more common at the peripheral level of the lower limbs, but systemic manifestations such as intestinal lymphangiectasia, ascites, chylothorax or hydrops fetalis may also occur. (2,3)

Primary lymphedema affects approximately 1/100,000 predominantly female persons under the age of 20. The clinical presentation and degree of involvement vary depending on the causative gene and the specific genetic alteration. It is divided into five categories: (1) disorders with somatic mosaicism and segmental growth abnormality, (2a) syndromic disorders, (2b) disorders with systemic involvement, (2c) congenital lymphedema, and (2d) disorders that occur after the first year of life (late-onset lymphedema). (4-6)

Only a few cases diagnosed before birth have been reported in the international literature, none of them in Cuba. (7,8) The objective of this article is to present a case with a prenatal diagnosis of bilateral congenital lymphedema of the lower limbs of the Milroy type.

CASE DESCRIPTION

A 21-year-old pregnant woman with a corrected gestational age of 24 weeks was first born with an initial assessment of increased genetic risk due to exposure to teratogens (alcoholic beverages in the fifth week). Denies a personal and family history of circulatory disorders or other health problems. Non-consanguinity. Ultrasounds of chromosomal and morphological markers were performed in the first and second trimesters of pregnancy (13, 18 and 21 weeks) that had not reported structural alterations. Normal fetal echocardiogram, which indicates that there is an increase in the distal volume of the lower limbs.

At 24 weeks, confirmatory ultrasound was performed with two-dimensional Mindray DC7 equipment at the Provincial Center for Medical Genetics of Mayabeque, which reported normal bone configuration, biometries of long bones of symmetrical lower limbs between the 5th and 50th percentile. At the level of both legs and feet, an increase in volume is described at the expense of the subcutaneous cellular tissue, more marked in the distal portion that does not map color Doppler flow, compatible with bilateral congenital lymphedema of the lower limbs (**Figure 1**). A cytogenetic prenatal diagnosis was performed due to cordocentesis, which was normal (46, XX).

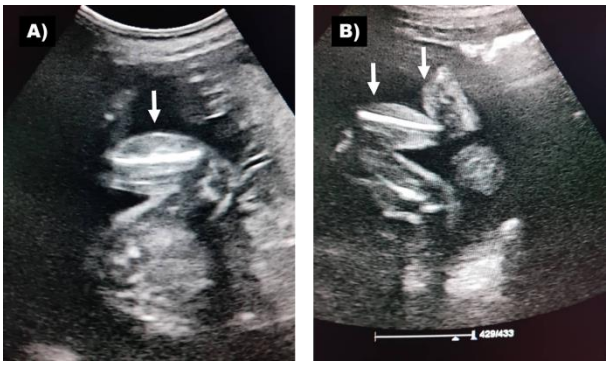
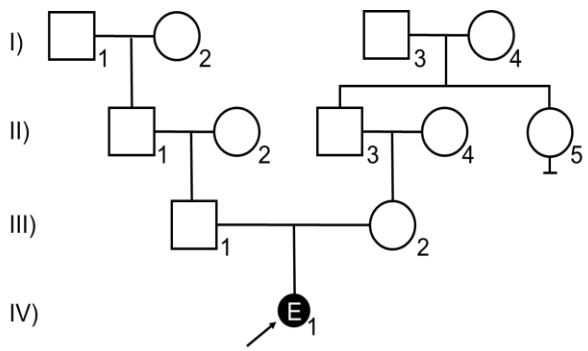


Figure 1. Two-dimensional ultrasound of the fetus with bilateral lymphedema of the lower limbs. An increase in volume is noted at the expense of the subcutaneous cellular tissue, which is more marked in the distal portion. A) At the level of the left leg. B) At the level of the right

Genealogy of three generations was performed (**Figure 2**) and genetic counseling was offered, and information was provided on the defect described, the prognosis, and possible complications. The pregnant woman requested voluntary termination of the pregnancy. Interruption was induced with intravaginal prostaglandins, resulting in a female fetus weighing 600 grams. The pathological analysis confirmed the diagnosis made by ultrasound (**Figure 3**).



Purpose: A 24-week-old female fetus diagnosed with congenital lower limb lymphedema Milroy.

Figure 2. Four-Generation Genealogy

Informed consent (written and verbal) was obtained from the couple to publish the case. The principles of the World Medical Association's Code of Ethics (Declaration of Helsinki) for human experiments were adhered to.

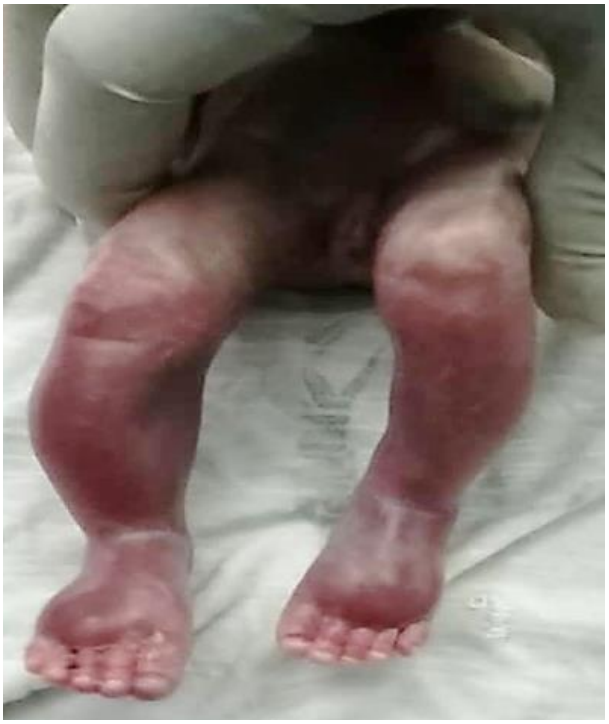


Figure 3. Macroscopic study of the lower limbs with evident bilateral edema at the level of the legs and feet

DISCUSSION

Primary lymphedema may be idiopathic or associated with a variety of genetic syndromes. The diagnosis is usually clinical, although imaging can be a useful complement, as this is the method available for its identification in the prenatal stage. (7)

Milroy disease is the most common inherited form of primary lymphedema. This syndrome is attributable to an autosomal dominant mutation of the FLT4 gene in the 5q35.3 gene encoding vascular endothelial growth factor receptor receptor 3 (VEGFR-3) protein. In humans, Milroy's disease is not associated with lymphatic aplasia, but rather with functional failure: a significant impairment of initial lymphatic absorption that is assumed to be attributable to impaired endothelial junction valves and lymphatic transport associated with vessel hypoplasia. (7-9)

Patients with Milroy disease present in the perinatal period with bilateral lymphedema in the lower extremities, often associated with "woody" skin covering the lower extremities, and prominent veins. Lymphedema is usually limited to the feet and ankles, with toenails bent in a "ski jump" shape due to nail bed disease. The diagnosis can be suspected as early as 12 weeks of gestation with ultrasound identification of edema at the level of the foot, although it is rare for the diagnosis to be made prenatally. (7,8)

The term "Milroy's disease" has been erroneously used as an umbrella phrase to encompass all cases that present with lymphedema present at birth or during the first year of life. The correct terminology refers to a familial form of primary lymphedema characterized by edema of the lower extremities at birth. Historically, patients required both a consistent phenotype and a positive family history to be diagnosed with Milroy; however, de novo mutations can occur in patients with no family history. Therefore, the diagnostic criteria for Milroy disease now include cases diagnosed with lower extremity lymphedema with a positive family history and/or documented FLT4 mutation. (8)

In this case, there was no family history of circulatory disorders. Molecular study to rule out the de novo mutation of the FLT4 gene was also not

available. Disease phenotypically compatible with Milroy disease but without a positive family history of FLT4 mutation is called "Milroy-type lymphedema." (8)

In relation to the differential diagnosis, when there is prenatal suspicion of congenital lymphedema in the lower limbs of the Milroy type in a female fetus, it is important to fundamentally rule out Turner syndrome and Noonan syndrome. The first was ruled out by cytogenetic study with normal results. The second was due to the ultrasound clinic and the anatomopathological analysis where the cardinal signs of this syndrome were not reported, such as increased nuchal translucency, pleural effusions, cystic hygroma and distended jugular lymphatic sac. There were also no facial dysmorphisms, congenital heart disease (pulmonary stenosis and cardiomyopathies) or fetal growth restriction that would lead to suspicion of this diagnosis. (10-13)

Lymphedema is a chronic condition that is often delayed, potentially disabling, and places a long-term burden on the lives of the patient and their families physically, socially, and emotionally. It has been reported that patients with lymphedema have an excess of psychological sequelae and low levels of psychosocial adaptation compared to the general population, so the option of voluntary termination of pregnancy determined by the couple was considered ethically accepted. (1,14)

In conclusion, to make the prenatal diagnosis of congenital lymphedema of the lower limbs Milroy type, fetal ultrasound phenotyping, analysis of family history and anatomopathological findings are the key to personalized genetic counseling that allows the couple to make the reproductive decision they consider most appropriate.

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Contributions:

Daniel Quintana Hernández (30%): Carried out the conception and design of the work, the bibliographic review, translation of articles, analysis and discussion of the information, writing of the manuscript, revision, correction and approval of its final version. **Yanisbell Fajardo Peña (30%):** Carried out the conception and design of the work, data collection, analysis and discussion of the information, correction and approval of its final version. **Dayami Ramírez Arias (20%):** Discussed the information, corrected and approved the final version. **Ainadys Herrera Luis (20%):** Carried out the data collection, correction and approval of its final version.