CASE REPORT

Prenatal Diagnosis of Milroy's Syndrome

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Abstract

Aim: The aim of our case report is to display modern possibilities of prenatal diagnosis of different types of congenital lymphedemas compared to postnatal diagnostic options.

Background: Milroy´s syndrome (MS) or primary congenital lymphedema as the most common form of the group of hereditary primary lymphedemas. It is a rare condition and until these days FTL4 encoding vascular endothelial growth factor receptor 3 (VEGFR 3) is the only gene detected to be associated with MS.

Case description: We present a case of prenatally diagnosed MS with its typical clinical manifestation and postnatally confirmed genetic background. What makes our case interesting is the curiosity behind the combination of proven features of lymphedema type 1A and by DNA analysis detected chromosomal aberrance as a fragile site at chromosome 16q22 which responds to another types of congenital lymphedema.

Conclusion: MS has proven causality with hereditary defects in the gene encoding VEGFR 3 on 5q35.3. However, to date, no case of MS has been reported in which DNA analysis demonstrates the overlap of traits and features responded of other types of lymphedemas.

Clinical significance: The reported case provides an opportunity for further investigation and understanding of the genetic background and pathophysiology of this rare condition.

Keywords: DNA analysis, Lymphedema, Milroy´s syndrome, Prenatal ultrasound, Vascular tissue, VEGF.

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Introduction

Milroy´s syndrome or primary congenital lymphedema[1,2] is the most common form of the group of hereditary primary lymphedemas. It is named after William Milroy, the first one who in 19th century studied and described almost one hundred members of a single family, of whom almost one third had leg edema.[3] Lower-limb lymphedema is the most significant finding in MS. It is a rare condition with an incidence of 1 in 33 000 deliveries with the male/female ratio of 1: 2.3.[4] The inheritance is autosomal dominant[1,3] with different penetrance (80–100%) (4). Until these days FTL4 encoding VEGFR 3 is the only gene detected to be associated with MS.[3,5,6] We report a case of prenatally diagnosed MS which is interesting from the point of view of genetics, as there is no evidence in the literature of an association between hereditary lymphedema type I (MS) and fragile site at the 16q22. Postnatal DNA analysis confirmed the proposed diagnosis.

Case Description

A 31-year-old woman, gravida 2, para 1 (Cesarean section), was referred to the ultrasound unit of our department at 20 weeks' gestation for the second trimester morphological ultrasound screening.

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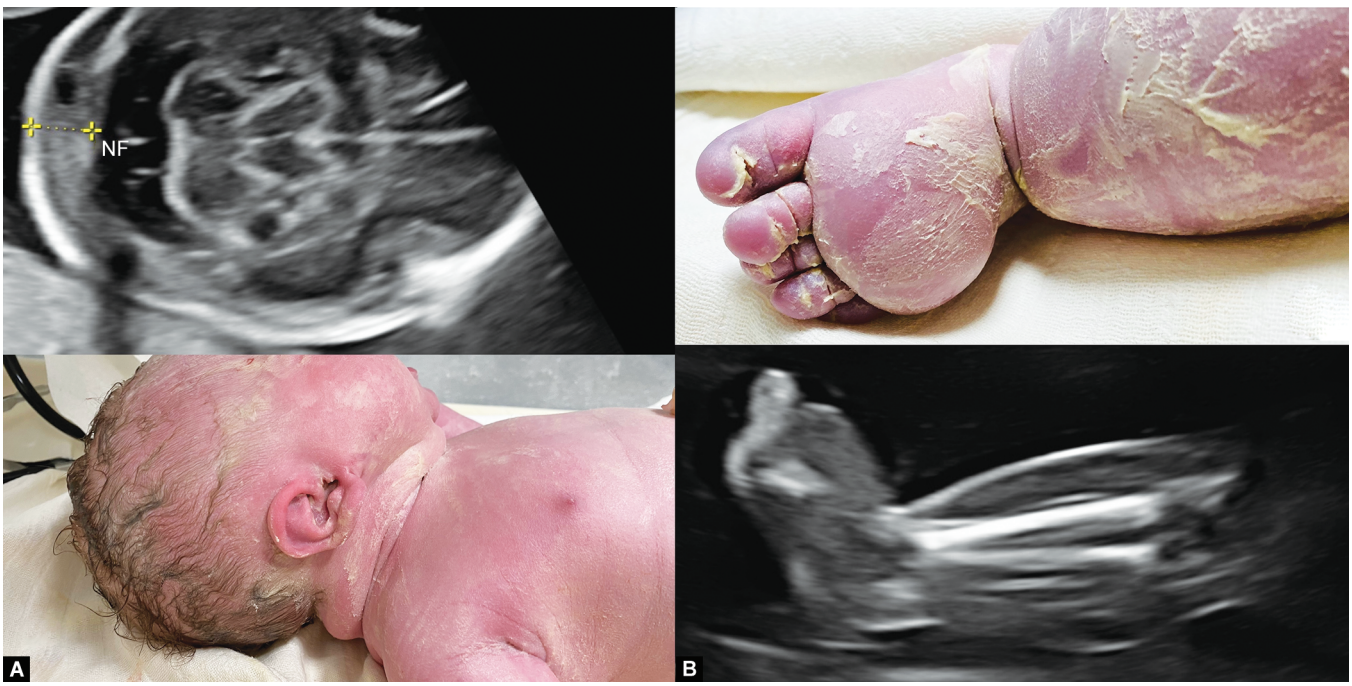
The mother's family history was insignificant. She did not take any drugs during the first 3 months of pregnancy, exposure to other teratogens was negative. Serological tests for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, HIV, hepatitis B surface antigen, and treponema pallidum hemagglutination were negative. First-trimester aneuploidy screening was not performed, but the ultrasound examination in the 14th week was reported to be normal. The triple test (AFP, hCG, estriol) performed at 16 weeks was negative for trisomy 21 and neural tube defects.

A 20th week ultrasound scan revealed a living male singleton fetus with a composite sonographic age of 20 weeks, 2 days, enlarged nuchal fold (NF) of 6,3 mm, hygroma colli cysticum, significant edema of the lower limbs, and a normal amount of hyperechoic amniotic fluid (Fig. 1). Based on this typical ultrasound findings, we assumed MS. Fetal morphology ultrasound follow-up examination in 2 weeks was recommended with the laboratory test for STORCH and indirect Combs testing. The mother was counselled on the risk of a chromosomal abnormality, and amniocentesis was performed. Array comparative genomic hybridization showed normal male karyotype. Molecular analysis of the gene PTPN11 for Noonan's syndrome was negative.

Morphology ultrasound scan of the fetus performed 2 weeks later at 22 weeks of gestational age showed persistent hygroma colli cysticum, NF 8,4 mm and subcutaneous edema with double skin contour of both lower limbs was present (Fig. 1). Amniotic fluid was hyperechoic. Fetal ultrasound screening at 32 weeks was normal, but there was still fetal lymphedema of the upper and lower limbs. It led us to think our primary diagnose of MS has been correct. The finding of asymmetrical edema predominantly on lower limbs was crucial for us to remain in your convictions.

Woman was indicated for termination of the pregnancy by the Cesarean section at 39 weeks of gestational age. Upon the patient's admission at 39 weeks, the ratio of soluble fms-like tyrosine kinase 1 and placenta growth factor (SFLT-1 and PLGF) was taken with the results 60,3 which is classified in the gray zone significant for abnormal placental infiltration and as a predicational factor of preeclampsia. The Cesarean section was performed at 38 weeks and 6 days of gestational age and a male neonate of 4320 g and 49 cm with Apgar score of 8/9/10 was delivered. Placenta, umbilical cord, and amniotic sac was sent to the histopathological examination with the final findings of chorioamnionitis stage 1 grade 1 according to Amsterdam consensus criteria 2016 of amnionitis sac. The neonatal examination revealed typical signs of idiopathic lymphedema of the lower limbs. Infant blood was sent to genetics examination. DNA analysis identified a known pathogenic variant c. 33,323_3325delTCT, p (Phe1108del) in a heterozygous state in the FLT4 gene, confirming the proposed diagnosis- hereditary lymphedema type 1A–Milroy disease. In the karyotype examination, 25 mitoses were evaluated, of which three mitoses were artificially hypodiploid, the other mitoses had a chromosome count of 46 and a normal karyotype of 46, XY. In one mitosis fragile site at 16q22 was confirmed. The variant originated de novo or was inherited from one of the parents, therefore genetic consultation and examination of the child's parents is recommended.



Figs 1A and B: (A) Fetal ultrasound at 22 weeks gestation showing increased nuchal fold compared to the postnatal appearance of the neonatal neck; (B) Leg lymphedema in comparison with postnatal appearance of the neonatal leg

Discussion

Primary lymphedema is caused by an intrinsic defect of the lymphatic vessels.[1,2] The condition is due to dysgenesis of lymphatic vessels with varying degrees of involvement. Prenatal ultrasound diagnosis is based on the presence of symmetrical swelling of both legs, mainly the dorsum of the feet.[3,6,7] Lev-Saige et al. also described that chylothorax, chylous ascites, and chylopericardium may rarely accompany the edema of the lower extremities as a variant termed atypical Nonne-Milroy syndrome.[8] This thoracic complication could be associated with an anomalous lymphatic system that results in lymph accumulation.[6]

Although MS is known since the 19th century, the 1998 was a turning point in the research and identification of the gene that carries the mutation for the disease. It was detected on chromosome 5q35.3.[9,10] FLT4 gene encoding vascular growth factor receptor (VEGFR 3), and its variants were identified as responsible genes[3,4] that lead to dysgenesis of lymphatic vessels.[8] Recent studies have shown that variants in VEGF-C, important for lymph vessel development, the gene coding for one of the VEGFR-3 ligands, can lead to an MS-like phenotype.[11,12] A list of other characteristics which are associated with MS includes hydrocele, prominent veins, slanting toenails, papillomatosis and urethral abnormalities in males.[3,13] The list of differential diagnoses includes microcephaly with or without chorioretinopathy, lymphedema or mental retardation, VEGFC-related lymphoedema, Turner syndrome, Noonan syndrome, Hypotrichosis-lymphedema-telangiectasia syndrome, Lymphedema-distichiasis syndrome, Meige disease and lymphedema with yellow nails.[3] Furthermore, there have been observed associations between chronic lymphedema and neoplasms, especially angiosarcoma (Stewart-Treves syndrome) as one of the most common tumors which arise in MS.[14,15]

In our case, it was a fetus with isolated lymphedema of the limbs and nuchal area since 20 weeks of gestation. No associated head, chest, or abdomen anomalies were diagnosed prenatally. For the first three months of life, the child was clinically perfectly fine. Swelling of the limbs was rehabilitated by decongestive regimen therapy. Postnatal genetic analysis revealed the fragile chromosome site at 16q22. This chromosomal defect has been described in the literature in some malignancies such as leukemia, but the relationship of heritable fragile sites to malignant processes remains speculative. Glasser et al. described the occurrence of hereditary benign neutropenia in a mother and daughter who had a fragile site on chromosome 16 and sought to determine whether there is the possibility of development of malignity because these chromosomal abnormalities have been observed in myelodysplastic syndrome and acute myeloid leukemia. Until these days the pathologic significance of the fragile site on chromosome 16 in leukemogenesis has not been resolved. But it needs to point out that an association could be inferred if the breakpoint of the fragile site occurs at or near the breakpoint of nonrandom chromosomal abnormalities in leukemia.[16]

There is currently no evidence in the literature of an association between hereditary lymphedema type I (MS) and fragile site at the 16q22. Anomalies of chromosome 16 are associated with hereditary lymphedema type II (Meige disease), which does not manifest prenatally. Whatsmore, the fragile site at 16q22 was reported with an association of neuropsychiatric disorders such as mental retardation, Tourette´s syndrome, bipolar disorder, and autistic disorder.[17] The information is supported by a descriptive study about the frequency and distribution of chromosome fragile sites or lesions in males with mental retardation.[18] Furthermore, a distinctive syndrome involving aberrant orofacial development may be linked to the fragile site at 16q22.[19] Of interest is the family described by Bettex, with the autosomal dominant inheritance of U-shaped cleft palate, microstomia, micrognathia, and oligodontia where all affected members were shown to have the fragile site at 16q22 in a proportion of their cells. Another family was also reported, and all affected family members were demonstrated to have a fragile site on chromosome 16q22 but otherwise normal karyotypes.[19,20]

Because there is currently no gene therapy available for hereditary lymphedema, it is usually an incurable lifelong condition but does not affect life expectancy.[1,21] There is the possibility of some improvement with the use of compression or bandaging and well-fitting, supportive shoes. Good skin care is essential to reduce the risk of complications.[3] A hope in diagnostics and consequently a better prognosis provide available quite new findings from 2019 when Luo et al. investigated the effects of paternal mosaicism on their preimplantation embryos with the use of methods of assisted reproduction with preimplantation genetic testing (PGT). The results show that PGT is beneficial and highly recommended in a group of mosaic patients with structural abnormalities of autosomes, especially with the fragile site at 16q22 which is a relatively high risk of abnormal embryos.[22] In the absence of chromosomal defects, fetuses with increased NT have a greater occurrence of major cardiac defects, skeletal dysplasia, and rare genetic syndromes. Whole exome sequencing (WES) provides the potential to diagnose almost any single gene disorder.[6]

Conclusion

Milroy´s syndrome has proven causality with hereditary defects in the gene encoding VEGFR 3 on 5q35.3. However, to date, no case of MS has been reported in which DNA analysis demonstrates the overlap of traits and features responded of other types of lymphedemas. We are the first to describe such an interesting example of prenatally diagnosed MS in combination with the fragile site 16q22 in a male neonate with a normal karyotype of 46, XY. Whether it is an artificial

chromosomal break or we will encounter other cases in the future is a question of diagnosis and investigation of this rare disease, for example, the use of WES.

References

1. Gezginç K, Yazıcı F, Gök D. Prenatal diagnosis of Milroy's primary congenital lymphedema. Taiwan J Obstet Gynecol 2012;51(2):280–282. DOI: 10.1016/j.tjog.2011.01.041
2. Milroy WF. Chronic hereditary edema: Milroy's disease. JAMA 1928;91(16):1172–1175. DOI: 10.1001/jama.1928.02700160024005
3. Brice GW, Mansour S, Ostergaard P, et al. Milroy disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. [updated 2014 Sep 25]. Seattle (WA): University of Washington, Seattle; 2006. p. 1993–2020.
4. Franceschini P, Licata D, Rapello G, et al. Prenatal diagnosis of Nonne-Milroy lymphedema. Ultrasound Obstet Gynecol 2001;18(2):182–183. DOI: 10.1046/j.1469-0705.2001.00463.x
5. Brice G, Child AH, Evans A, et al. Milroy disease and the VEGFR-3 mutation phenotype. J Med Genet 2005;42(2):98–102. DOI: 10.1136/jmg.2004.024802
6. Drury S, Williams H, Trump N, et al. Exome sequencing for prenatal diagnosis of fetuses with sonographic abnormalities. Prenat Diagn 2015;35(10):1010–1017. DOI: 10.1002/pd.4675
7. Urbaneja Rodríguez E, Garrote Molpeceres R, Pino Vázquez MA, et al. Linfedema congénito, secundario a, enfermedad de Milroy [Primary lymphedema due to Milroy disease]. An Pediatr (Barc) 2017;86(3):169–170. DOI: 10.1016/j.anpedi.2015.12.007
8. Lev-Sagie A, Hamani Y, Raas-Rothschild A, et al. Prenatal ultrasonographic diagnosis of atypical Nonne-Milroy lymphedema. Ultrasound Obstet Gynecol 2003;21(1):72–74. DOI: 10.1002/uog.16
9. Gordon K, Spiden SL, Connell FC, et al. FLT4/VEGFR3 and Milroy disease: novel mutations, a review of published variants and database update. Hum Mutat 2013;34(1):23–31. DOI: 10.1002/humu.22223
10. Evans AL, Brice G, Sotirova V, et al. Mapping of primary congenital lymphedema to the 5q35.3 region. Am J Hum Genet 1999;64(2):547–555. DOI: 10.1086/302248
11. Mukenge S, Jha SK, Catena M, et al. Investigation on the role of biallelic variants in VEGF-C found in a patient affected by Milroy-like lymphedema. Mol Genet Genomic Med 2020;8(9):e1389. DOI: 10.1002/mgg3.1389
12. Nadarajah N, Schulte D, McConnell V, et al. A novel splice-site mutation in VEGFC is associated with congenital primary lymphoedema of Gordon. Int J Mol Sci 2018;19(8):2259. DOI: 10.3390/ijms19082259
13. Butler C, Osterberg C, Horvai A, et al. Milroy's disease and scrotal lymphoedema: pathological insight. BMJ Case Rep 2016;2016:bcr2016215396. DOI: 10.1136/bcr-2016-215396
14. Cheirif-Wolosky O, Ramírez-Hobak L, Toussaint-Caire S, et al. Milroy disease or primary congenital lymphedema associated with invasive squamous cell carcinoma. Actas Dermosifiliogr 2016;107(10):864–866. DOI: 10.1016/j.ad.2016.05.011
15. Veiga RR, Nascimento BA, Carvalho AH, et al. Stewart-Treves syndrome of the lower extremity. An Bras Dermatol 2015;90 (3 Suppl 1):232–234. DOI: 10.1590/abd1806-4841.20153926
16. Glasser L, Meloni-Ehrig A, Joseph P, et al. Benign chronic neutropenia with abnormalities involving 16q22, affecting mother and daughter. Am J Hematol 2006;81(4):262–270. DOI: 10.1002/ajh.20550
17. Kerbeshian J, Severud R, Burd L, et al. Peek-a-boo fragile site at 16d associated with Tourette syndrome, bipolar disorder, autistic disorder, and mental retardation. Am J Med Genet 2000;96(1):69–73. DOI: 10.1002/(sici)1096-8628(20000207)96:1<69::aid-ajmg14>3.0.co;2-5
18. Butler MG. Frequency and distribution of chromosome fragile sites or lesions in male with mental retardation: a descriptive study. J Tenn Acad Sci 1998;73(3-4):87–99. PMID: 28163338; PMCID: PMC5286990.
19. Janiszewska-Olszowska J, Gawrych E, Dydyk A, et al. Oro-palatal dysplasia Bettex-Graf–clinical findings, genetic background, treatment. J Craniomaxillofac Surg 2013;41(1):e29–e32. DOI: 10.1016/j.jcms.2012.06.002
20. McKenzie F, Turner A, Withers S, et al. Dominant inheritance of cleft palate, microstomia and micrognathia–possible linkage to the fragile site at 16q22(FRA16B). Clin Dysmorphol 2002;11(4):237–241. DOI: 10.1097/00019605-200210000-00002
21. Jones GE, Mansour S. An approach to familial lymphoedema. Clin Med (Lond) 2017;17(6):552–557. DOI: 10.7861/clinmedicine.17-6-552
22. Luo K, Lan Y, Xie P, et al. Next-generation sequencing analysis of embryos from mosaic patients undergoing in vitro fertilization and preimplantation genetic testing. Fertil Steril 2019;112(2):291–297.e3. DOI: 10.1016/j.fertnstert.2019.03.035