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SHORT COMMUNICATION

Congenital lymphedema presenting with increased nuchal translucency at 13 weeks of gestation

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Congenital lymphedema is an autosomal dominant condition characterized by chronic tissue swelling caused by deficient lymphatic drainage due to hypoplastic/aplastic lymphatic vessels and usually affecting the lower limbs. The locus of the gene has been identified in the long arm of chromosome 15. We report one case of congenital lymphedema presenting with increased nuchal translucency at 13 weeks of gestation.

KEY WORDS: congenital lymphedema; nuchal translucency

INTRODUCTION

Increased nuchal translucency (accumulation of fluid on the back of the fetal neck) in the first trimester and in particular between 11 and 14 weeks of gestation has been associated with chromosomal abnormalities, heart defects, structural abnormalities and genetic syndromes (Snidjers *et al*., 1998; Souka *et al*., 1998; Hyett *et al*., 1999). This paper reports on a case of congenital lymphedema of the lower limb presenting with increased nuchal translucency at 13 weeks of gestation.

CASE REPORT

A 36-year-old Caucasian woman was referred to the Harris Birthright Centre of Fetal Medicine because of increased nuchal translucency at her first trimester scan at her local hospital. She had one healthy child.

The crown–rump–length and nuchal translucency were 79 mm and 4.3 mm, respectively (Figure 1). The estimated risk for Down's syndrome, calculated by a combination of maternal age and fetal nuchal translucency thickness, was 1 in 6 and the parents opted for chorionic villus sampling; cytogenetic analysis demonstrated a normal female karyotype. Ultrasound scans at 15 and 20 weeks showed resolution of the nuchal fluid and no obvious structural abnormalities. Fetal echocardiography showed a normally connected heart.

An apparently healthy female infant was born at term. In the first few weeks after birth the parents noticed swelling of the left foot, below the ankle, and investigations confirmed congenital lymphedema. It is of interest that the father has congenital lymphedema affecting both lower limbs below the knees since childhood.

DISCUSSION

Lymphedema is a chronic tissue swelling caused by deficient lymphatic drainage due to hypoplastic/aplastic lymphatic vessels, usually affecting the lower limbs. There are three clinical subtypes, congenital (Milroy disease, present at birth), praecox (pubertal onset) and tarda (midlife onset), with congenital lymphedema being the rarest and most severe of the three (Child *et al*., 1999). Lymphedema can be part of a syndrome such as Noonan syndrome, Turner syndrome and yellow nail syndrome. The oedema causes disfigurement and serious psychological problems but also recurrent cellulitis, papillomatosis and

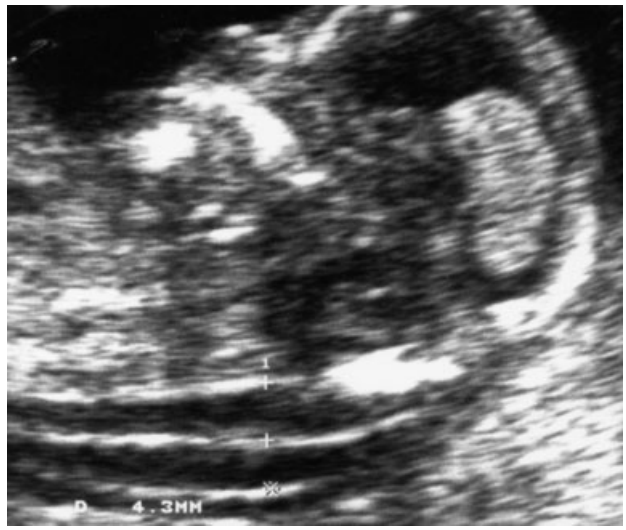

Figure 1—Increased nuchal translucency in the 13-week fetus

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rarely cancer. The treatment consists of compression, manual massage and antibiotics.

The pattern of inheritance is autosomal dominant with variable penetrance and expressivity. The first chromosomal locus of the gene has been recently identified in the long arm of chromosome 5 (5q34-5q35) (Evans *et al*., 1999; Irrthum *et al*., 2000; Karkkainen *et al*., 2000). The vascular endothelial growth factor receptor-3 gene (VEGFR3, FLT4) is located in this region and codes a receptor tyrosine kinase specific for lymphatic vessels (Irrthum *et al*., 2000). The gene is expressed in all vessels during embryogenesis, and subsequently its expression is limited to developing lymphatic vessels (Kaipainen *et al*., 1995). Irrthum *et al*. (2000) and Karkkainen *et al*. (2000) showed that a mutation in this gene alters the protein receptor and causes deficient VEGFR3 signalling.

Increased nuchal translucency has been reported in fetuses with lymphatic hypoplasia due to Turner syndrome (von Kaisenberg *et al*., 1999). The possible mechanism is a deficiency in the tyrosine kinase BMX, whose gene is located in chromosome X. This enzyme is thought to play an important role in mediating the effects of vascular endothelial growth factors in the embryogenesis of blood and lymphatic vessels.

The most likely pathophysiological mechanism for the increased nuchal translucency in the present case of congenital lymphedema is lymphatic hypoplasia leading to accumulation of the lymph in the nuchal area due to the predominantly supine position of the fetus.

REFERENCES

Child AH, Beninson J, Sarfarazi M. 1999. Cause of primary congenital lymphedema. *Angiology* **50**: 325–326.

Evans AL, Brice G, Sotirova V, *et al*. 1999. Mapping of primary congenital lymphedema to the 5q35.3 region. *Am J Hum Genet* **64**: 547–555.

Hyett J, Perdu M, Sharland G, Snidjers R, Nicolaides K. 1999. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestation: population based cohort study. *Br Med J* **318**: 81–85.

Irrthum A, Karkkainen M, Devriendt K, Alitalo K, Vikkula M. 2000. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. *Am J Hum Genet* **67**: 295–301.

Kaipainen A, Korhonen J, Mustonen T, *et al*. 1995. Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development. *Proc Natl Acad Sci U S A* **92**: 3566–3570.

Karkkainen MJ, Ferrell RE, Lawrence EC, *et al*. 2000. Missence mutations interfere with VEGFR-3 signalling in primary lymphedema. *Nat Genet* **25**: 153–159.

Snidjers RJM, Noble P, Sebire N, Souka A, Nicolaides KH, for the Fetal Medicine Foundation First Trimester Screening Group. 1998. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Lancet* **352**: 343–346.

Souka AP, Snidjers RJM, Novakov A, Soares W, Nicolaides KH. 1998. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* **11**: 391–400.

von Kaisenberg CS, Nicolaides KH, Brand-Saberi B. 1999. Lymphatic vessel hypoplasia in fetuses with Turner syndrome. *Hum Reprod* **14**: 823–826.