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SHORT COMMUNICATION

Congenital nephrotic syndrome presenting with increased nuchal translucency in the first trimester

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Congenital nephrotic syndrome of the Finnish type (CNF) and diffuse mesangial sclerosis (DMS) are rare causes of renal failure in infants. We report two cases, one of each condition, presenting with increased nuchal translucency at the 11–14-week scan, and review the literature. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS: congenital nephrotic syndrome; nuchal translucency

INTRODUCTION

Increased nuchal translucency thickness at 10–14 weeks of gestation has been associated with chromosomal abnormalities, heart defects, structural abnormalities and genetic syndromes (Snijders *et al.*, 1998; Souka *et al.*, 1998; Hyett *et al.*, 1999). This paper reports on two cases of congenital nephrotic syndrome of the Finnish type (CNF) and diffuse mesangial sclerosis (DMS), respectively, presenting with increased nuchal translucency at the 10–14-week scan.

CASE 1

A 23-year-old Caucasian woman was referred to the Harris Birthright Research Centre for Fetal Medicine at 12 weeks of gestation because of increased nuchal translucency observed at the routine 11–14-week scan at her local hospital. She had one normal child and one first trimester miscarriage and neither of the parents had Finnish ancestry.

The crown–rump length was 73 mm and the nuchal translucency was 5.6 mm. The estimated risk for Down syndrome, calculated by a combination of maternal age and fetal nuchal translucency thickness, was 1 in 12 and the parents opted for chorionic villus sampling (CVS); cytogenetic analysis demonstrated a normal female karyotype. Repeat ultrasound scan at 14 weeks showed persistence of the nuchal translucency and mild right-sided pleural effusion. There were no obvious structural abnormalities and TORCH screen was negative. At 19 weeks of gestation marked nuchal oedema (11 mm) was still present and there were mild bilateral pleural effusions. Fetal echocardiography showed a normally connected heart. The parents were counselled about the increased risk of rare genetic syndromes and opted to continue the pregnancy. By 21 weeks of gestation the nuchal oedema started to resolve (8.3 mm) and the pleural effusions were completely resolved. Further scans at 23 and 27 weeks showed gradual resolution of the nuchal oedema and normal amniotic fluid volume and fetal growth (50th centile). The kidneys appeared normal in all the scans. An apparently normal female baby weighing 2.8 kg was born vaginally at 38 weeks. The placental weight was not recorded.

At 56 days of age the baby was admitted to the local hospital because of oedema of the lower limbs. On admission the baby weighed 3.6 kg and was normotensive and apyrexial. There was severe proteinuria (3+++), mildly raised serum creatinine (100 μm/l), normal urea (8.9 mmol/l) and potassium (5.0 mmol/l), mild hypoproteinaemia (46 g/l) and marked hypoalbuminaemia (19 g/l). She was treated with albumin infusions and furosemide. An open renal biopsy showed swollen epithelial cells surrounding the glomeruli, about one-third of which had a shrunken primitive appearance. Multisegmental sclerosis was present in some glomeruli. The tubules were dilated and many were filled with eosinophilic protein casts. Immunostaining was negative for immunoglobulins and complement. In electron microscopy the basement membrane showed wrinkling and crenation over the mesangium and the foot processes of the visceral epithelial cells were effaced. These changes were considered to be consistent with congenital nephrotic syndrome of the Finnish type. In the subsequent weeks her condition deteriorated and she died at the age of 3 months.

CASE 2

A 30-year-old Caucasian woman was referred to the Harris Birthright Research Centre of Fetal Medicine at 12 weeks of gestation because of increased nuchal

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translucency observed at the routine 11–14-week scan at her local hospital. She had one normal child.

The crown-rump length was 65 mm and the nuchal translucency was 4.1 mm. The estimated risk for Down syndrome, calculated by a combination of maternal age and fetal nuchal translucency thickness, was 1 in 9 and the parents opted for CVS; cytogenetic analysis demonstrated a normal female karyotype. Detailed ultrasound scans at 15 and 20 weeks, including fetal echocardiography, showed gradual resolution of the nuchal fluid and no obvious structural abnormalities. The growth and amniotic fluid volume were normal and TORCH screen was negative. At 29 weeks the mother presented at her local hospital with a history of ruptured membranes and an ultrasound scan showed oligohydramnios. She was again referred to the Harris Birthright Centre where oligohydramnios was confirmed; the kidneys were noted to be large and hyperechogenic (Figure 1), the heart was dilated with a mild pericardial effusion and the lungs were small. It was felt that the most likely diagnosis was infantile polycystic kidneys. At 30 weeks a female infant weighing 1400 g (50th centile for gestation) was born vaginally and survived for only 1 h.

Postmortem examination showed dysmorphic features including small mouth, receding mandible, deep nasal bridge, minor hypotelorism, low-set ears with poor development of the helices and fixed flexion deformity of the left elbow. The chest was small and the lungs hypoplastic. In the periventricular region of the brain there was marked gliosis, calcifications and small cystic spaces, thought to represent periventricular leucomalacia. The kidneys were markedly enlarged, to about double the normal size for gestation, and in the cortex there was a reduction in the number of proximal tubules and numerous tubular and ductal cysts, some of which contained hyaline casts. Immunostaining revealed no deposition of IgM or C3 in the glomeruli. Although the appearances were not typical, this was thought to be an early stage of diffuse mesangial sclerosis and the lack of positive immunostaining was attributed to prematurity. There was marked placentomegaly (621 g), the size and weight of the placenta corresponding to a term rather than a 30-week pregnancy.

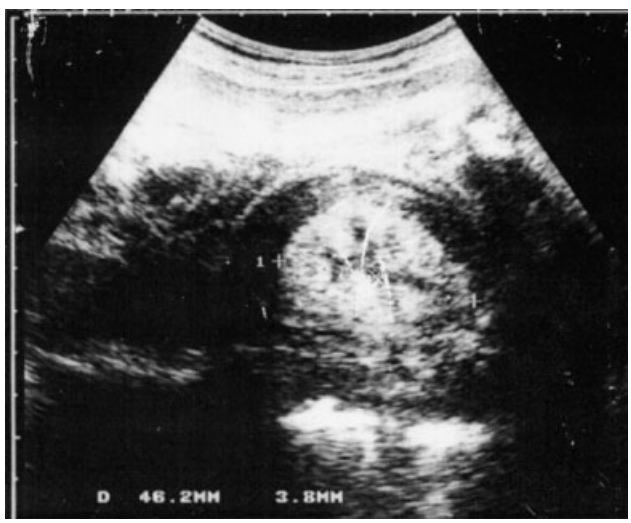

Figure 1—Ultrasound scan at 29 weeks' gestation showing enlarged and hyperechogenic kidneys (Case 2)

DISCUSSION

The causes of congenital nephrotic syndrome include infections such as syphilis; renal diseases such as lupus erythematosus, renal vein thrombosis, minimal change nephrotic syndrome, hemolytic uremic syndrome and diffuse mesangial sclerosis; and genetic syndromes such as Drash syndrome, nail-patela syndrome, Frasier syndrome and, most commonly, CNF. The latter is an autosomal recessive condition with a birth prevalence of about 1 in 8000 in Finland but it is very rare in non-Finnish couples. The genetic basis for CNF is a mutation in the NPHS1 gene, which is located in the long arm of chromosome 19. This gene codes for nephrin, a protein of the glomerular basement membrane, which is thought to play an essential role in the normal glomerular filtration barrier (Holmberg *et al.*, 1996; Salomon *et al.*, 2000).

Prenatal diagnosis and carrier screening of CNF are now possible by DNA analysis (Romppanen and Mononen, 2000). The condition is associated with fetal proteinuria leading to increased amniotic fluid and maternal serum AFP (Rapola and Romppanen, 1990). In a screening study involving about 10 000 women in Finland, amniocentesis was carried out in women with serum alpha-fetoprotein (AFP) ≥ 2.5 MoM (multiples of the median) in two consecutive samples (Ryynanen *et al.*, 1983). In this population there were six affected fetuses and they were all identified prenatally by increased amniotic fluid AFP, which was >10 SD. However, Morris *et al.* (1995) reported a false-negative result after amniocentesis in a high-risk woman at 16 weeks when AFP levels were normal. At 19 weeks a repeat amniocentesis, prompted by the ultrasound appearance of large and echogenic kidneys, showed increased AFP. In the present case maternal serum AFP levels are not available; it is our policy to offer an ultrasound scan at 11–14 weeks for basic anatomic examination of the fetus and nuchal translucency measurement as a screening test for Down syndrome. It is interesting that in the present case both amniotic fluid volume and renal morphology appeared normal until the last scan at 27 weeks. Enlarged and hyperechoic kidneys have been reported in affected fetuses from as early as 18 weeks but the finding is more common in the third trimester (Moore *et al.*, 1992; Suren *et al.*, 1993; Santolaya *et al.*, 1994).

Postnatally, CNF typically presents with severe proteinuria, hypoproteinemia, generalised oedema, ascites, hyperlipidemia, hypercoagulopathy and susceptibility to bacterial infections. Treatment includes albumin infusions for substitution of urinary loss of proteins in order to maintain normal growth and prevent edema, anticoagulants and antibiotics. Most

authors advocate bilateral nephrectomy at 1–4 years of age and peritoneal dialysis prior to transplantation (Holmberg *et al*., 1996).

Diffuse mesangial sclerosis can be idiopathic or syndromic with probable autosomal recessive inheritance. Associated abnormalities include microphthalmia and cataracts, facial cleft, microcephaly, Dandy-Walker malformation, gyral abnormalities, cardiac defects, diaphragmatic hernia, polydactyly and rocker-bottom feet (Mildenberger *et al*., 1998). An association with Wilms tumor and/or male pseudohermaphroditism has also been observed (Schumacher *et al*., 1998). DMS is characterised by an increase in the mesangial matrix, thickening of glomerular basement membranes, tubular atrophy and formation of tubular microcysts (Mildenberger *et al*., 1998). Immunostaining may reveal IgM and C3 depositions (Palomeque *et al*., 1979). Nearly all children progress to end-stage renal failure by the age of 4 years. Scott and Rochefort reported a case of an infant affected by DMS that died in the neonatal period; the second trimester ultrasound scan was normal but maternal serum AFP at 18 weeks was raised (3.5 MoM) (Scott and Rochefort, 1992). Spear *et al*. reported a case of DMS presenting at 18 weeks of gestation with increased maternal serum AFP (5.99 MoM), oligohydramnios, intrauterine growth restriction and non-visible bladder (Spear *et al*., 1991). The diagnosis of DMS was made at postmortem examination.

The findings of the present study suggest that congenital nephrotic syndrome can present in the first trimester of pregnancy with increased nuchal translucency thickness. The underlying mechanism for the increased translucency is presumably hypoproteinemia.

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