On first trimester Down syndrome screening

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Enlarged nuchal translucency and low serum protein concentrations as possible markers for Zellweger syndrome

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We present a case of a fetus in which at 12 weeks' gestation an enlarged nuchal translucency was detected. The karyotype was normal. Subsequent ultrasound examination showed no obvious fetal abnormalities apart from a mild pericardial effusion. Serum screening revealed very low concentrations of estriol and human chorionic gonadotrophin. After birth the diagnosis of Zellweger syndrome was made. Nuchal translucency screening, estriol level identification and detailed ultrasound scan may help identify fetuses affected by this syndrome.

Introduction

Zellweger syndrome or Cerebro-hepato-renal syndrome was first described in 1964 by Bowen et al. (1964) as combination of clinical and pathological-anatomical abnormalities. Shortly thereafter, Smith et al. (1965) described more children with this syndrome, characterised by neonatal hypotonia, facial dysmorphism, hepatomegaly, renal cysts, severe psychomotor retardation and failure to thrive. When in 1973 Goldfischer et al. (1973) reported that peroxisomes, subcellular organelles that play a role in lipid metabolism, were absent in the liver and kidneys of these children, it was concluded that this syndrome was a metabolic (peroxisomal) disorder rather than a syndrome of multiple developmental defects.

Children suffering from this autosomal recessive single gene disorder usually die within 2 weeks to 2 years of life. Clinical recognition can be difficult because of the aspecific and varying phenotypic presentation (Theil et al., 1992). However recognition of this disorder is important as it will enable prenatal diagnosis in future pregnancies.

Children affected by this syndrome tend to have a large forehead with shallow supraorbital ridges, large fontanels, flat facies, mild micrognathia, hepatomegaly, cystic kidney syndrome and contractures of the extremities. These are aspecific features that can be detected at ultrasound examination. Recently it has been suggested that an increased nuchal translucency between 10-14 weeks of gestation, besides being associated with chromosomal anomalies, may also be a marker for genetic syndromes (Bilardo et al., 1998).

This report describes the prenatal findings and the post-natal diagnosis of a child affected by Zellweger syndrome.

Case report

A healthy 24 year old woman in her second pregnancy was referred to our prenatal diagnostic centre for amniocentesis because of an enlarged nuchal translucency of 6 mm detected at booking scan at 12 weeks’ gestation. The parents were not consanguineous and had no family history of genetic disorders. The first pregnancy resulted in a spontaneous abortion before 10 weeks of gestation.

The ultrasound scan showed a viable singleton pregnancy consistent with 15 weeks of gestation as calculated from the last menstrual period. A nuchal translucency of 5 mm (figure 1) was measured, indicating an increased risk for fetal aneuploidy.
Before amniocentesis was performed maternal blood was taken for serum screening as part from a research protocol. Cytogenetic analysis revealed a normal female karyotype. Although the nuchal translucency disappeared at subsequent scans an increased nuchal oedema persisted throughout pregnancy. The maximum thickness of the nuchal oedema was 9 mm at 24 weeks of gestation. Because of the enlarged nuchal translucency a detailed ultrasound examination was performed at 20 weeks of gestation. No clear fetal anomalies were detected, besides of a mild pericardial effusion (figure 2) and a strawberry shaped head. The structures of the heart could not be visualised optimally because of the fetal position. At repeat scan at 24 weeks of gestation a normal 4-chamber view and normal vascular connections of the great arteries were obtained. The pericardial effusion was still present but resolved completely by 28 weeks. Fetal growth remained stable on the 10th centile.
The serum concentrations of alpha-foeto-protein (AFP), estriol (uE3) and human chorionic gonadotrophin (hCG) were 30 kIU/L (1.21 MoM), 0.6 nmol/L (0.23 MoM) and 7 kIU/L (0.19 MoM) respectively. The concentrations for uE3 and hCG were very low.

Nine days after the expected date of delivery a caesarian section was performed because of breech presentation. A female infant was born weighing 2510 g (P3). Apgar-scores were 1 and 4 after 1 and 5 minutes respectively. The infant was very hypotonic and cyanotic. There was no spontaneous respiration. After intubation she was transported to a neonatal high care unit.

Physical examination showed craniofacial dysmorphism, with a triangular shape of the skull, flat facies with shallow supra-orbital ridges, widely split sutures and large fontanels. Moreover a low implant of the ears, hypertelorism and a broad nasal bridge were observed. There was redundant skin in the neck and nuchal area. Severe hypotonia remained and deep tendon reflexes could not be elicited.

Routine laboratory test results were within normal values. A cranial ultrasound examination showed no macroscopic abnormalities. At abdominal CAT-scan normal kidneys were seen. Because of clinical suspicion of Zellweger syndrome radiological examination of the long bones and fatty acid analysis were done. Radiological examination of the long bones showed irregular calcifications of the patellae. Fatty acid analysis revealed significantly increased levels of very-long-chain fatty acids (VLCFA), with an increased C26/C22 ratio. The cholic acids di-hydroxy cholestane acid (DHCA) and C29 were also increased. This is characteristic of Zellweger syndrome. Peroxisomes could not be detected in a liver biopt.

The clinical course was dramatic. The infant had to be fed by a stomach tube. Seizures were initially controlled by Luminal, but their frequency increased and the overall condition continued to deteriorate. She died from respiratory arrest at the age of five and a half months. The parents did not consent to post-mortem examination.

Discussion

This is the first report on the association between an increased nuchal translucency, detected at 12 weeks’ gestation, and Zellweger syndrome. Ultrasound measurement of nuchal translucency thickness has proven to be an effective first trimester screening method for fetal aneuploidy. An enlarged nuchal translucency measurement, which is gestational age-dependent, is associated with an increased risk
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of chromosomal anomalies (Pandya et al., 1995). Fetuses with a normal karyotype and enlarged nuchal translucency have been reported to have an increased incidence of cardiac defects, structural anomalies and rare genetic syndromes (Bilardo et al., 1998). Thus far an increased nuchal translucency has incidentally been described in fetuses affected by Noonan syndrome, Smith-Lemli-Opitz syndrome, EEC-syndrome, Stickler syndrome, Fryns syndrome, arthrogryposis, Jarco-Levin syndrome, Joubert syndrome (Trauffer et al., 1994; Hyett et al., 1997; Hösli et al., 1997; Souka et al., 1998), and this list is still growing. An increased nuchal translucency is a transient feature which tends to resolve at subsequent observation in both chromosomally normal and abnormal fetuses (Pandya et al., 1995b; Pajkrt et al., 1995). In some trisomy 21 fetuses an increased nuchal translucency has been described to evolve into an enlarged nuchal oedema. In this case of Zellweger syndrome the increased nuchal thickness converted into an enlarged nuchal oedema which persisted throughout pregnancy.

Prenatal diagnosis of Zellweger syndrome by culture of chorionic villi can be offered to parents with a previously affected child. Carriers in affected families can be identified with certainty.

Among the frequent structural anomalies that could be easily detected at ultrasound investigation there are cystic kidneys and excessive skin on the neck and nuchal area.

In a previous report of a case of Smit-Lemli-Opitz syndrome, a possible association of increased nuchal translucency and low maternal serum estriol concentration has been suggested (Hyett et al., 1995). Our case-report confirms this association. A low serum estriol level has also been associated with other chromosomal anomalies and an increased incidence of intrauterine death (Goodburn et al., 1994). Determination of estriol level concentration may be introduced as a part of a standard protocol in case of increased nuchal translucency and normal karyotype to help identify rare genetic syndromes.

In fetuses with an enlarged nuchal translucency and normal karyotype the finding of even mild dysmorphic features at ultrasound should alert the clinician about the presence of a rare genetic syndrome. In this case, apart from the increased nuchal thickness, the only dysmorphic features were the strange shape of the head and the transient presence of pericardial effusion. However, a more stringent search at ultrasound examination for facial dysmorphism like the hypertelorism and the flattened profile may have reinforced the suspicion of a genetic syndrome.

This study suggests that the combination of nuchal translucency screening, estriol concentration measurement and detailed ultrasound scan may help identify fetuses affected by rare genetic syndromes, such as Zellweger syndrome.
Chapter 7

References


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