for pregnancy-associated plasma protein A in prenatal screening for Down syndrome.

Nicholas Wald, Charles Rodeck, Alicja Rudnicka and Allan Hackshaw
On behalf of the SURUSS Research Group
DOI: 10.1002/pd.840

REFERENCES

First-trimester increased nuchal translucency as a prenatal sign of Zellweger syndrome

Measurement of fetal nuchal translucency (NT) between 10 and 14 weeks of gestation has proven to be an effective screening method for fetal aneuploidy (Bilardo et al., 1998; Souka et al., 1998; Van Vugt et al., 1998). Increased fetal NT thickness is a common phenotypic sign of trisomy 21 and other chromosomal defects. Moreover, an enlarged NT can be found in structural defects of the fetus such as cardiac, renal, abdominal wall, and diaphragmatic malformations or skeletal dysplasias. Increased NT is also known to be associated with a variety of genetic syndromes (Bilardo et al., 1998; Souka et al., 1998; Hyett, 2002). Souka et al. (1998) reported a series of 4116 chromosomally normal fetuses with increased NT. The study demonstrated the association between increased NT and a wide range of fetal abnormalities at 10 to 14 weeks of gestation. Bilardo et al. (1998) diagnosed genetic syndromes and single-gene disorders in 12.7% of fetuses with enlarged NT and normal karyotype.

CASE REPORT

A healthy 30-year-old, gravida 7, para 6 and her healthy 36-year-old husband of Iraqi origin were referred for genetic counselling because one of their six children had died of Zellweger syndrome. There was consanguinity (first cousins) but the family history was otherwise unremarkable. The affected boy had marked hypotonia, seizures, nystagmus, craniofacial anomalies (large fontanelles, high forehead, mild downslanting palpebral fissures, dysplastic ears), dilated cerebral ventricles, hepatomegaly, and renal cortical cysts. Neonatal reflexes were absent. He was diagnosed to have cerebrohepatorenal (Zellweger) syndrome. Fatty acid analysis revealed significantly elevated levels of very-long-chain fatty acids (VLCFAs) in plasma. The pregnancy was terminated. The most common mutations of the PEX1 gene [c.2097insT in exon 13 and c.2528G→A (p.gly843asp) in exon 15] were excluded by molecular analysis of DNA isolated from chorionic villus cells.

Case I

Chorionic villus sampling (CVS) was done at 12 weeks and 1 day. At that time, a crown-rump length (CRL) of 56.3 mm was measured. Transabdominal ultrasonography (Figure 1) showed an increased nuchal translucency of 5.3 mm, and hydrops was present. The fetal chromosome analysis revealed a normal male karyotype 46,XY. Biochemical analysis of the villi indicated Zellweger syndrome. Metabolic studies showed significantly elevated concentrations of VLCFAs. The pregnancy was terminated. The most common mutations of the PEX1 gene [c.2097insT in exon 13 and c.2528G→A (p.gly843asp) in exon 15] were excluded by molecular analysis of DNA isolated from chorionic villus cells.

Case II

In the next pregnancy—7 months later—the patient was first seen at 10 weeks and 3 days. At that time, a CRL

Figure 1—Increased nuchal translucency in a fetus with Zellweger syndrome

Copyright © 2004 John Wiley & Sons, Ltd.
of 37.5 mm was measured. Transabdominal ultrasonography showed a normal nuchal translucency of 1.0 mm. CVS was performed at 11 weeks and 4 days. At that time, CRL was 50.3 mm and the nuchal translucency of 1.5 mm (Figure 2) was again normal. Prenatal biochemical analyses were performed. VLCFAs measured in cultured chorionic villus cells showed low levels and the ratios C24 : 0/C22 : 0 and C26 : 0/C22 : 0 were in the normal range. Moreover, peroxisomal plasmalogen biosynthesis was shown to be normal. The existence of normal peroxisomes was pointed out because of normal sedimentation of catalase. Ultrasonography at 19 weeks and 4 days showed no fetal abnormalities and that the pregnancy was continuing. The list of genetic syndromes that have been reported as being associated with increased NT is long, but causality has only been identified in a few cases. Most genetic syndromes are rare, and therefore the number of described cases are still too small to secure the association of enlarged NT and specific inherited genetic syndromes. Further reports may be useful in assessing the importance of nuchal anomalies. Zellweger syndrome or cerebrohepatorenal syndrome is an autosomal recessive disorder of peroxisome biogenesis. It is characterised by the absence or marked decrease of the number of peroxisomes. Children with Zellweger syndrome show muscular hypotonia, facial dysmorphism, renal cysts, hepatomegaly, contractures of the extremities, severe psychomotor retardation and failure to thrive. They often die within the first two years of life. Prenatal diagnosis of Zellweger syndrome can be offered to parents with a previously affected child. Specific prenatal biochemical diagnosis of the disorder is possible, both in chorionic villi and in amniotic fluid (Roscher et al., 1985; Wanders et al., 1991, 1995; Steinberg et al., 1999; Weller and Gartner, 2002). Prenatal molecular diagnosis can be offered in cases where the molecular defect has been identified in the index patient. Peroxisome biogenesis disorders result from mutations in any of at least 12 PEX genes (Brosius et al., 2002), which limits the applicability of DNA diagnosis.

The association between increased NT and Zellweger syndrome was described first by Bilardo et al. (1998) and de Graaf et al. (1999). In these reports, the diagnosis was made postnatally. Cases of prenatally detected Zellweger syndrome associated with increased NT have been described by Christiaens et al. (2000) and Johnson et al. (2001). Christiaens et al. reported on two families at risk for Zellweger syndrome. An increased NT, measured between 11 and 13 weeks of gestation, was found in four fetuses. Specific biochemical analyses indicated that these fetuses were affected by Zellweger syndrome. Johnson et al. (2001) reported on a case of prenatal detection of increased NT and decreased fetal movements at 11 weeks of gestation in a fetus at risk for Zellweger syndrome. The diagnosis of Zellweger syndrome was confirmed by biochemical examinations.Christiaens et al. (2000) and Johnson et al. (2001) suggested that in families at risk for Zellweger syndrome, the specific ultrasound finding of increased NT may be helpful in predicting an affected fetus. Our findings support the association between Zellweger syndrome and an increased NT in the first trimester. NT screening may help in identifying fetuses affected in families at risk for Zellweger syndrome earlier.

S. Strenge1, U. G. Froster1, R. J. A. Wanders2, J. Gartner3, E. M. Maier4, A. C. Muntau4 and R. Faber5
1Institute of Human Genetics, University of Leipzig, Germany
2Departments of Clinical Chemistry and Pediatrics, Emma Children’s Hospital, Academic Medical Center, University of Amsterdam, The Netherlands
3Department of Pediatrics, Georg August University Göttingen, Germany
4Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany
5Department of Obstetrics and Gynecology, University of Leipzig, Germany
DOI: 10.1002/pd.805

REFERENCES


