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Hypophosphatasia associated with increased nuchal translucency: a report of two affected pregnancies

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ABSTRACT

Perinatal hypophosphatasia is a lethal autosomal recessive skeletal abnormality with a birth prevalence of about 1 per 100 000. It is characterized by deficiency of the tissue-nonspecific isoenzyme of alkaline phosphatase causing abnormal bone mineralization. In the two affected fetuses from the same family ultrasound examination at 14 and 12 weeks, respectively, demonstrated increased nuchal translucency thickness, hypomineralization of the skull and spine, narrowing of the chest and shortening of the limbs.

INTRODUCTION

Subcutaneous accumulation of fluid at the back of the fetal neck at 10–14 weeks' gestation, visualized by ultrasound examination as increased nuchal translucency thickness, is associated with chromosomal defects, structural abnormalities and a wide range of genetic syndromes, including many skeletal dysplasias[1–4].

Hypophosphatasia is a rare autosomal recessive condition characterized by abnormal bone mineralization and low or absent activity of tissue nonspecific alkaline phosphatase[5]. In this paper we report on three consecutive pregnancies of a nonconsanguineous couple at risk of the perinatal form of the disease.

CASE REPORT

A 27-year-old Caucasian woman was referred to the Harris Birthright Centre of Fetal Medicine at 14 weeks of gestation in her first pregnancy because, at routine ultrasound examination at her local hospital, the fetus was found to have fixed flexed upper and lower limbs and increased nuchal translucency thickness. The crown–rump length (CRL) was 93 mm and the nuchal translucency was 4.1 mm. There was marked hypomineralization of the skull and spine, narrowing of the chest with short ribs, shortening of all the long bones and bilateral talipes. The findings were suggestive of a lethal skeletal dysplasia and the parents chose to have termination of the pregnancy, which was performed by induction of labor with prostaglandin. Pathological examination, including radiological studies, of the fetus led to the diagnosis of hypophosphatasia. Analysis of DNA from the fetus confirmed the radiological findings and showed the fetus to be a compound heterozygote for known disease causing mutations in the ALPL gene. These were at I195F and E337D on either allele.

In their second pregnancy the parents had an ultrasound examination in our center at 12 weeks of gestation. The fetus had a CRL of 53 mm and appeared normal with appropriate mineralization of the skull and the long bones. The nuchal translucency thickness was 1.4 mm. Follow-up ultrasound examinations at 16 and 20 weeks confirmed normal skeletal development. A healthy female infant was born at 41 weeks of gestation weighing 3912 g.

In the third pregnancy, ultrasound examination in our center at 12 weeks of gestation demonstrated hypomineralization of the skull (Figure 1b) and spine, narrowing of the chest and shortening and bowing of the limbs. The CRL was 63 mm and the nuchal translucency was increased (2.5 mm). The parents opted for termination of the pregnancy and a recurrence of hypophosphatasia in the fetus was confirmed from DNA extracted from the placenta.

DISCUSSION

The disease hypophosphatasia is clinically classified according to the age of onset of symptoms and subdivides into perinatal, infantile, childhood and adult forms[5–7]. The most severe type is perinatal hypophosphatasia, which has an autosomal recessive mode of inheritance and occurs in about

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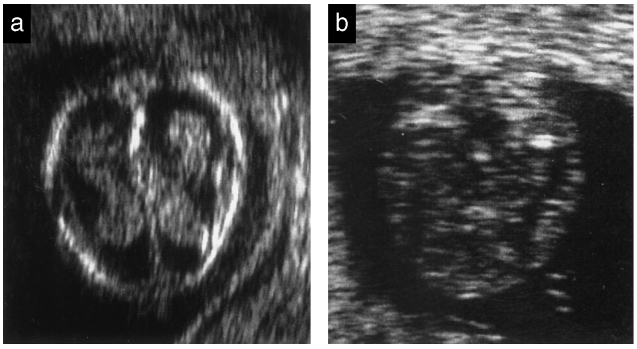

Figure 1 Transverse section of the fetal head at 12 weeks of gestation in (a) a normal fetus and (b) one affected by hypophosphatasia.

1 per 100 000 births[5]. The later onset forms of the condition have a more varied inheritance pattern and etiology.

The severe autosomal recessive form is due to abnormalities in the tissue-nonspecific isoenzyme of alkaline phosphatase (TNS-ALP). This causes severe skeletal abnormalities due to abnormal bone mineralization[5,6]. The most likely mechanism responsible for the defect is inhibition of mineralization because of the phosphocompounds that accumulate due to the inactive enzyme[8]. Typically, the placental and bowel isoenzymes are of normal activity[6].

Mutations in the TNS-ALP gene at 1p36 have been identified as causing severe hypophosphatasia and thus where mutations can be identified in an affected family member accurate molecular prenatal testing can now be offered in a subsequent pregnancy[9–11]. In new cases or in cases when the mutation has not been isolated, prenatal diagnosis of hypophosphatasia relies on ultrasound examination and enzyme activity studies in chorionic villi, amniotic fluid, fibroblasts and fetal serum[10,11].

The diagnosis of severe perinatal hypophosphatasia by ultrasound examination has been reported from as early as 14 weeks of gestation and is characterized by poor ossification of all bones, most pronounced in the calvarium, shortening and bowing of the long bones and narrow chest[12–15]. As onset of ossification of the skull occurs at 11 weeks of gestation it would be desirable to detect signs of severe hypomineralization as early as possible during a pregnancy known to be at high risk of being affected[16]. Our case illustrates that it is indeed possible to detect a recurrence of this skeletal dysplasia as early as 12 weeks' gestation. The combination of the hypomineralization and the increased nuchal translucency probably secondary to mediastinal compression by the narrow thoracic cage led to the clinical diagnosis of the recurrent dysplasia which was confirmed molecularly at termination[17].

This case report illustrates that in families at high risk of hypophosphatasia, detailed first-trimester ultrasound examination could offer an alternative to invasive testing for a subsequent affected fetus.

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