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Blackfan–Diamond anemia and dyserythropoietic anemia presenting with increased nuchal translucency at 12 weeks of gestation

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ABSTRACT

Blackfan–Diamond anemia is a congenital hypoplastic anemia with a birth prevalence of about 1 in 200 000, usually presenting in the first few months of life and commonly associated with cardiac, urogenital and digital anomalies. Congenital dyserythropoietic anemias are a group of rare congenital anemias characterized by ineffective erythropoiesis. We report on two cases of congenital fetal anemia, one with Blackfan–Diamond anemia and one with dyserythropoietic anemia, presenting with increased nuchal translucency at 12 weeks of gestation.

INTRODUCTION

Increased nuchal translucency at 11–14 weeks of gestation has been associated with chromosomal abnormalities, heart defects, structural abnormalities and genetic syndromes[1–5]. This paper reports on two cases of congenital anemia, Blackfan–Diamond anemia and dyserythropoietic anemia, presenting with increased nuchal translucency at 12 weeks.

CASE REPORTS

Case 1

A 30-year-old Asian woman was referred to our unit because of increased fetal nuchal translucency at the routine first trimester scan at her local hospital. She had had two previous pregnancies resulting in healthy livebirths at term, one first trimester miscarriage and one intrauterine death of unknown cause at 17 weeks. At 12 weeks the fetal crown–rump length and nuchal translucency were 62 mm and 4.8 mm, respectively. The estimated risk for Down syndrome, calculated by a combination of maternal age and fetal nuchal translucency thickness[2], was one in 12. Chorionic villus sampling was carried out and cytogenetic analysis demonstrated a normal male karyotype. Another ultrasound examination at 15 weeks showed resolution of the nuchal translucency and no obvious structural abnormalities. Specialist fetal echocardiography at 20 weeks demonstrated persistent left-sided superior vena cava draining to the coronary sinus and mild narrowing of the aorta raising the possibility of coarctation. At 28 weeks the discrepancy in the diameter of the great arteries was more marked. At 35 weeks the mother presented at her local hospital complaining of reduced fetal movements and fetal heart rate monitoring demonstrated a nonreactive decelerative trace. A male infant, weighing 2268 g was delivered by Cesarean section. The baby was severely anemic (Hb 6.5 g/dL) and required repeated transfusions in the first few days of life. The baby had a cleft soft palate but no hand abnormalities. Echocardiography did not confirm the suspicion of coarctation of the aorta. The anemia persisted and was treated with transfusions every 4 weeks. Bone marrow aspiration at the age of 6 months was diagnostic for Blackfan–Diamond anemia. The child is now 8 months old and is being treated with steroids and blood transfusions. It is of interest that although the parents were not related one paternal cousin and one maternal cousin have bifid thumbs.

Case 2

A 36-year-old Caucasian woman in her first pregnancy was referred to out unit because of increased fetal nuchal translucency at the routine first trimester scan at her local hospital. At 12 weeks the fetal crown–rump length and nuchal translucency were 59 mm and 4.2 mm, respectively. The estimated risk for Down syndrome, calculated by a combination of maternal age and fetal nuchal translucency thickness[2], was one in four. Chorionic villus sampling was carried out and cytogenetic analysis demonstrated a normal male karyotype. An ultrasound scan at 16 weeks of gestation showed mild pericardial effusion and persistence of nuchal edema. At

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18 weeks there was fetal hydrops with dilated heart, pericardial effusion, ascites, generalized edema and placentomegaly. There were no cardiac or other structural abnormalities. Fetal blood sampling demonstrated severe anemia (Hb 1.2 g/dL) and a blood transfusion was given to a post-transfusion hemoglobin of 12.1 g/dL. The mother was negative for TORCH infections and parvovirus B19. The parents and the fetus were Rhesus negative and the fetal Coomb's test was negative. Both parents had normal electrophoresis studies. Red cell enzyme studies in both parents were normal but purine/pyrimidine metabolic studies showed an increased level of ADA (108 nmol/μg Hb/h, normal range 40–100) in the father and this finding raised the suspicion of congenital anemia and in particular Blackfan–Diamond anemia. Fetal blood transfusions were given at 23, 24, 26, 29 and 32 weeks. The fetal hydrops resolved by 21 weeks and serial scans demonstrated normal growth but there was persistence of cardiomegaly. The baby was delivered by elective Cesarean section at 36 weeks. Despite vigorous attempts at resuscitation he died a few hours after birth because of heart failure. Bone marrow aspiration established the diagnosis of dyserythropoietic anemia.

DISCUSSION

Blackfan–Diamond anemia is a rare congenital hypoplastic anemia with a birth prevalence of 1 : 200 000. Most of the cases are diagnosed in the first 6 months of life and usually present with pallor, failure to thrive and persistent diarrhea. Low birth weight is common[6]. Congenital anomalies are present in about 40% of the cases and include thumb malformations (supernumerary, bifid or triphalangeal), facial anomalies (cleft or high arched palate, hypertelorism, strabismus, cataracts) and cardiac and urogenital anomalies. The risk of hematological malignancies, mainly acute leukemia, is increased. Both autosomal dominant and recessive modes of inheritance have been reported and in some families X-linked inheritance has been suspected[6]. The bone marrow shows a selective deficiency of red cell precursors beyond the level of proerythroblasts. The pathogenesis remains obscure but recent studies have identified mutations in the ribosomal protein RPS19 in 25% of sporadic and familial cases, a second gene in chromosome 8p and evidence of an additional locus[7]. About 60% of patients respond to steroids and some may be in remission for years without treatment, while others become steroid-dependent. The mainstay of treatment for the non-responders is red blood cell transfusions, usually every 3–6 weeks and the main complications are iron overload and blood-borne infections. The only curative treatment is bone marrow transplantation and the results from such treatment have been encouraging[6].

McLennan *et al.*[8] reported a case of Blackfan–Diamond anemia in a fetus presenting with hydrops in the third trimester. The mother was known to have Blackfan–Diamond anemia and was treated with steroids and blood transfusions. At 22 weeks of gestation the fetus was found to have cardiomegaly and mild pericardial effusion but by 33 weeks there was marked enlargement of the heart and ascites. Cordocentesis confirmed severe anemia (Hb 1.6 g/dL) and the fetus was transfused. A female infant was delivered at 34 weeks; the child became anemic in the first few weeks of life and Blackfan–Diamond anemia was confirmed at the age of 3 months by bone marrow aspiration.

Congenital dyserythropoietic anemias (CDAs) are a group of rare inherited anemias characterized by ineffective erythropoiesis, morphologic abnormalities of the mature red cells and morphologic and functional abnormalities of the erythroblasts, resulting in an increased rate of phagocytosis of the abnormal erythroblasts in the bone marrow[9,10]. The anemia is usually mild to moderate and severe, transfusion-dependent cases are not common. The life-span of the red cells is shortened leading to fluctuating jaundice and gall stones. Iron overload can cause damage in the liver, heart, pancreas and other organs even in patients that are not transfused regularly because of increased absorption of iron. The diagnosis is usually made in childhood by exclusion of other causes of congenital dyserythropoiesis. Heimpel and Wendt[11], classified CDAs into three types on the basis of the pattern of the dysplastic changes in the erythroblasts and the acidified serum lysis test (Ham test). Several other types have been described since and new forms continue to be reported[12]. CDA type I is an autosomal recessive condition occasionally associated with dysmorphic features (patches of brown skin pigmentation, short stature, abnormalities of the fingers and toes). In the bone marrow about 10% erythroblasts are binucleated and a small number of erythroblasts shows internuclear chromatin bridges[9]. Dyserythropoiesis is usually limited to more mature red cell precursors. Tamary *et al.*[13] reported the linkage of the gene in chromosome 15. Type II is the commonest of the CDAs and is inherited as an autosomal recessive trait. The characteristic feature is the finding that sera from ABO-compatible individuals cause hemolysis of erythrocytes in the acidified lysis test and this process is mediated by IgM antibodies[9]. The localization of the gene is unknown. The rarest of the three forms is CDA III which is inherited as an autosomal dominant condition with occasional sporadic cases, probably representing new mutations. The most distinctive feature is the presence of giant erythroblasts with up to 12 nuclei in the bone marrow. Lind *et al.*[14] have shown that the gene resides in the long arm of chromosome 15.

There are several previous case reports on dyserythropoietic anemia causing hydrops fetalis, and intrauterine or neonatal death[15–17]. Jijina *et al.*[18] published the case of a woman affected by CDA III and treated with regular transfusions; her four pregnancies resulted in intrauterine deaths at 25–30 weeks. There are also reports of severely anemic neonates that survived but became transfusion dependent[19,20]. There is one previous report of intrauterine therapy. Cantu-Rajnoldi *et al.*[21] presented the case of a transfusion-dependent female child affected by a CDA variant who needed intrauterine transfusions at 20 and 25 weeks. The mother had a previous pregnancy resulting in intrauterine death of a hydropic fetus at 23 weeks.

These cases demonstrate that fetal anemia can present with increased nuchal translucency and this association has also been reported in cases of homozygous alpha-thalassemia and parvovirus B19 infection[22–25]. In fetuses with CDA it is also likely that the anemia is present in the first trimester and is responsible for the increased nuchal translucency. However,

in fetuses with Blackfan–Diamond anemia the pathophysiological mechanism of the transient increased nuchal fluid is unclear, because anemia is unlikely to be present at this early stage. In our case of Blackfan–Diamond anemia it is possible that the the increased nuchal translucency is a consequence of the narrowing of the aorta, which was detected by fetal echocardiography. Such a transient narrowing of the aorta has also been reported in association with trisomy 21[26].

We suggest that fetal anemia should be considered as one of the causes of increased nuchal translucency in fetuses with normal karyotype and appropriate investigations with Doppler studies will be helpful to establish the diagnosis and institute treatment.

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