A Diagnostic Challenge: Prenatal Ultrasound Findings in Severe Epidermolysis Bullosa

Eine diagnostische Herausforderung: schwere Verlaufsform der Epidermolysis Bullosa im pränatalen Ultraschall

Introduction

Epidermolysis bullosa is a rare condition with clinical and genetic heterogeneity. This report describes the prenatal clinical manifestations in a case with a severe form of junctional epidermolysis bullosa with pyloric stenosis. We discuss the diagnostic challenge but also the ultrasound signs emerging to be reminiscent of this condition.

Case description

A 31 year-old, gravida III, para I, patient of Turkish descent, presented for routine second trimester anomaly scan after first trimester screening at low risk for the frequent trisomies. The pregnancy was complicated by insulin-dependent gestational diabetes. The patient received antiepileptic treatment (Levetiracetam 1500 mg/d) for an epilepsy diagnosed in childhood. Family history was uneventful, there was suspected distant consanguinity. Detailed anomaly scan at 22 weeks gestational age revealed edematous swelling of the right dorsal foot; the left foot and lower leg were slim and appeared hypotrophic, the tibia shorter, in comparison to the right lower limb (▶ Fig. 1, 2a, b). There were no additional anomalies. Based on the clinical findings parents were counselled about an uncertain diagnosis ranging from a possible isolated localized finding of non-genetic etiology to a sign of a systemic or syndromic condition with unknown outcome at this point of pregnancy. The patient opted for amniocentesis for chromosomal microarray analysis revealing a normal molecular karyotype [arr(1–22)x2,(XY)x1]. Stretches of loss of heterozygosity (chromosomes 3, 5, 7, 12, 13 and 17) indicated consanguinity and an increased risk for recessive conditions. Amniotic fluid alpha-fetoprotein was excessively increased (AFAFP: 112’705 IU/ml = 136’373ug/l), and subsequent measurement of acetylcholinesterase (ACHE) was weak positive. In the absence of ultrasound findings of neural tube defects and fetal structural anomalies known to cause fetal leakage such as e.g. abdominal wall defects the patient and her husband were counselled for an increased risk for a rare systemic disease in the child and opted to continue the pregnancy.

Ultrasound follow-up of the pregnancy detected additional anomalies such as progressive polyhydramnios and hydronephrosis starting at 27 weeks of the right kidney and a dilated stomach without depictable obstruction at 33 weeks (▶ Fig. 3).

The boy was delivered prematurely at 34 weeks of gestation and presented with extensive skin areas of aplasia cutis (head, face, thorax, back, limbs, genitals), a dystrophic external left ear, esophageal atresia type I and pyloric atresia, bilateral pyelectasia with a right ureterocele and a hypoplastic lower left leg (▶ Fig. 4). The newborn deceased on day 5 after birth.

The clinical diagnosis of junctional epidermolysis bullosa (EB) with pyloric atresia (EB-PA) was confirmed by a loss of integrin alpha6/beta4 in a skin biopsy using immunofluorescence staining. Genetic testing of the ITGA6 and ITGB4 genes identified a novel homozygous mutation c.1761 + 3A > C in the ITGB4 gene, not previously described, but in association with the clinical diagnosis and skin biopsy results likely causal for the EB-PA in the child. Other mutations in the ITGB4 gene are known to cause autosomal recessive EB with and without pyloric atresia.

Discussion

Junctional epidermolysis bullosa with pyloric atresia (EB-PA) is a usually severe and often lethal condition in the neonatal period. It is characterized by fragility of the skin and mucous membranes manifesting with blistering with little or no trauma, and congenital localized aplasia cutis affecting predominantly limbs and the head. Atresia in the gastrointestinal tract, ureteral and renal anomalies, contractures, nail dystrophy, scarring alopecia, hypotrichosis and dilated cardiomyopathy are variably present. Most affected children succumb as neonates. Non-lethal milder variants exist [1]. It is debated...
whether the variably associated esophageal, pyloric, duodenal and intestinal atresia are primary malformations or occur as secondary stenoses or constrictions as a result of mucous membrane lesions.

In the absence of a previous family history the prenatal diagnosis of EB and EB-PA is notoriously difficult. We illustrate this challenge since the postnatal recognizable clinical sign of aplasia cutis cannot be appreciated by ultrasound, and other indirect signs such as dilated stomach and polyhydramnios as a consequence of oesophageal atresia may only manifest later in pregnancy, if present at all. Unilateral oedematous tissue and lower leg deformations were the first, but subtle and unspecific findings without an elevated maternal serum alpha-fetoprotein level in a fetus with epidermolysis bullosa simplex. Br Med J 1979; 1: 307

Conflict of Interest

The authors declare that they have no conflict of interest.

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