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Two successive cases of fetal harlequin ichthyosis: A case report

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Abstract. Harlequin ichthyosis (HI) is a genetic skin disorder characterized by thickening and splitting of the skin. In fetuses presenting with the disorder, the mortality rate is markedly high. A number of fetal HI cases have been documented. The present study reports a case of a pregnant woman who underwent two successive pregnancies at the ages of 35 and 36, respectively, with both fetuses presenting with HI. The first fetus was delivered alive though succumbed shortly after birth, while the second fetus was stillborn and birthed by induced labor. The fetuses exhibited typical features of fetal HI, including thick, platelike scaling and fissuring, which act as a nidus for infection. The present study is the first to report two cases of fetal HI from successive pregnancies in the same woman. Improved understanding of the genetic basis of HI indicates that genetic screening for candidate gene mutations related to HI, particularly mutations in the adenosine triphosphate binding-cassette transporter ABCA12, may prove beneficial in prenatal diagnosis. Establishing methods for early diagnosis of fetal HI may reduce the physical and mental distress to parents and relatives.

Introduction

Harlequin ichthyosis (HI) is a rare and severe genetic skin disorder that occurs within the developing fetus, the underlying mechanisms of which are not well understood (1). Infants born with HI typically exhibit large, thick, plate-like scales covering the whole body associated with severe ectropion, eclabium and flattened ears, that later develop into a severe scaling erythroderma (2). The incidence of HI is relatively low, occurring in ~1 in 200,000 births (3), however there is a lack of effective treatment for the condition. The pathogenesis of HI was unknown until a recent report by Akiyama *et al* (1), in which HI was found to be a lipid metabolism disorder, caused by mutation in the adenosine triphosphate (ATP)-binding cassette (ABC) transporter, ABCA12. Historically, there has been a high early mortality rate in infants with HI; however, improved neonatal management and the early introduction of systemic retinoids may contribute to improved prognosis. Mortality in these patients is most commonly caused by sepsis, respiratory failure, or electrolyte imbalances (4). Early retinoid therapy and the administration of antibiotics may improve the prognosis of HI. Intrinsic factors may also be associated with the prognosis (5). Homozygous mutations in ABCA12 resulting in truncation of the ABCA12 protein were previously demonstrated to cause a severe HI phenotype, whereas heterozygous ABCA12 missense mutations resulted in a less severe phenotype (6). The current study suggests that a multidisciplinary approach involving surgeons, ophthalmologists, dermatologists, pediatricians, dieticians and psychologists is required for improving treatment in the future. Although fetal HI cases have been previously reported (3,4,7-9), two fetuses presenting with HI from successive pregnancies in a single woman are rare and have not previously been documented. The present study reports a case of a woman who delivered two fetuses with HI from two successive gestations at the ages of 35-36.

Case report

The present case is of a thirty-five year old woman who became pregnant for the first time at the age of 35. The patient had a regular period prior to the pregnancy. She was admitted in Obstetrics Department of He Xian Memorial Hospital (Guangdong, China) on 29th, July, 2007.

Treatment, including Progesterone 20 mg Q.D, human chorionic gonadotropin (HCG) 2000 u Q.O.D, was offered during the early stages of pregnancy (8 weeks) due to signs of threatened miscarriage, such as vaginal bleeding and abdominal pain. A virus test panel and toxoplasmosis test were conducted with negative results, and no signs of hyperglycemia or hypertension were observed during the pregnancy. The patient denied having a consanguineous marriage or a history of contact with insecticide and radioactive materials. As the disease is genetic, the sister-in-law and mother of the patient were evaluated and had unconfirmed ichthyotic-like lesions on their feet.

Sonography at twelve weeks of gestation found no abnormalities in fetal development, though ultrasound performed

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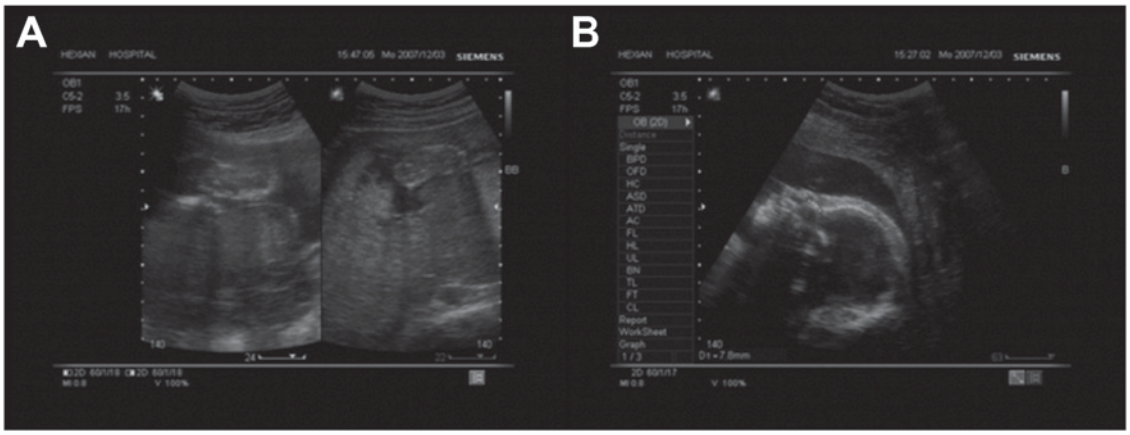

Figure 1. Sonography of the first fetus at thirty weeks of gestation. Representative images of (A) fixed flexion deformity of the extremities and (B) a flattened nose with thickened skin in the head region are presented.

at the same time showed that the bipedal length of the fetus was shorter than expected, compared with infants of the same age and that the fetus had a relatively flattened nose. At thirty weeks of gestation, sonography identified thickened skin covering the body of the fetus without obvious signs of edema (Fig. 1). In the thirty-first week of gestation (16th January 2008), a live female infant was delivered due to premature rupture of membranes. No abnormalities in the amniotic fluid or placenta were observed during ultrasound assessment. The neonate breathed in a normal and regular rhythm (<60 breaths per minute) and had a normal heart rate of 145 bpm. Scores of an Apgar test, performed as previously described (10) (used to evaluate the health status of neonates) were completed as follows: 9 at 1 min and 9 at 5 min, and the infant failed to suckle or bottle feed. The infant had a body weight of 2.0 kg, a body length of 42 cm and a head circumference of 31 cm, as a premature infant these measurements are smaller than a normal full-term infant. The skin covering the body exhibited hyperkeratosis and cracks that penetrated to epidermis level were observed between thickened regions on the head, neck, subaxillary, lower back rump areas and extremities. Bilateral congenital upper eyelid eversion that appeared red in colour was also observed. In addition, there was contraction and deformation of the skin of the perioral area and lip eversion, causing the mouth to be fixed in an O-shape. As a result, dentium caverna was exposed. The infant had a flattened nose with no obvious nasal bridge and the external ears appeared continuous with the skin of the head. The infant also had external auditory canal atresia with an accumulation of thick yellow substance. No hair had grown and the middle and marginal head regions exhibited keratosis and thickened skin with deep cracks. Furthermore, the infant had a fixed flexion deformity of the extremities with a normal number of fingers and toes. However, the fingers and toes were stubbed and webbed with constriction of the skin. The infant had a normal vulvo and anus. The infant succumbed two days after birth. The final pathological diagnosis was severe fetus harlequin ichthyosis.

At the age of 36, the woman had a second pregnancy. Similar to the first gestation, signs of threatened miscarriage were observed during the early pregnancy stages, including vaginal bleeding and abdominal pain. Furthermore, a urine culture performed at week 10, was positive for *E. coli*. As a result, cystitis was diagnosed and cefuroxime 3.5 g was administrated twice a day for 5 days as an anti-bacterial treatment. The husband denied a history of medication, sickness or contact with toxic substances in the 3 months prior to the pregnancy. The woman underwent genetic tests at sixteen weeks gestation for Down's syndrome, neural tube defect and trisomy 18 syndrome, the results of which were all negative. A karyotype analysis of the amniotic fluid at twenty weeks of gestation exhibited no chromosomal abnormalities. However, a three-dimensional sonography construction at twenty-four weeks of gestation revealed bilaterally thickened soft tissue resonance in the anterior region of the eyeballs, with the thickest region measuring 3.6 mm. This is unusual, as the soft tissue resonance is not identified in the anterior region of the eyeballs (11). The fetus also had fixed flexion deformity of the extremities and thickened soft tissue in the lower back region with deep cracks, which was measured by palpitation (Fig. 2A). On the sagittal section, the curve of the frontal bone and nasal tip appeared flattened and dissipated. Two nostrils were observed, with a nasal wing width of 14 mm. The mouth was unable to fully close, leaving a gap of 30 mm between the upper and lower lips, and the lips were markedly thickened and everted (Fig. 2B). At 24 weeks, labor was induced and a stillborn infant was delivered. In accordance with the sonography, the infant exhibited typical characteristics of HI.

All subjects discussed in the present study provided informed consent for the use of their data in the present report.

Discussion

HI, otherwise known as *keratosis diffusa fetalis*, is a distinct form of congenital ichthyosis, which occurs due to mutation in the ABC transporters ABCA12, a cell membrane transporter associated with lipid transportation (1,12). Fetuses carrying this mutation have defective lipid secretion within epidermal keratinocytes, leading to a loss of the skin lipid barrier and development of harlequin-type ichthyosis (1). HI is a rare autosomal-recessive disease with a high mortality rate for affected fetuses, although there is limited epidemiological data

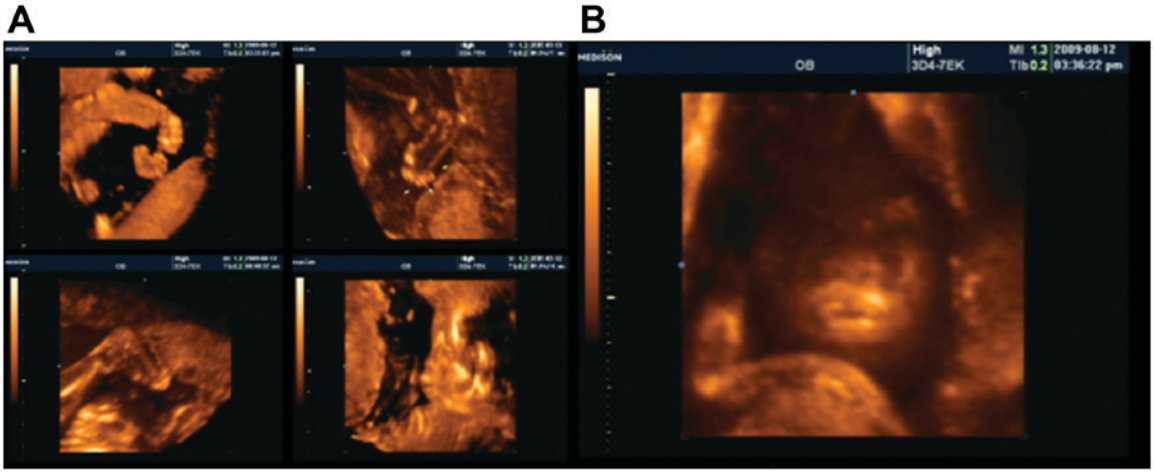

Figure 2. Three-dimensional sonography construction at twenty-four weeks of gestation exhibited typical characteristics of HI in the fetus, including (A) fixed flexion deformity of the extremities and (B) thickened lips and open mouth.

currently (3). In the majority of cases, the fetus succumbs during pregnancy, preventing the possibility of a lvive birth (13). In a number of cases, fetuses with HI have been born alive, though with severe respiratory defects or feeding difficulties. Thus, the probability of mortality for infants with HI is high, due to respiratory failure, loss of fluid or skin infection (14). As such, prenatal diagnosis of fetal HI is critical for appropriate perinatal and postnatal management and to prepare parents for future pregnancies.

In the present study, two cases of successive fetal HI were reported, a phenomenon that has not previously been documented. In particular, the prenatal sonography images of each HI fetus was analyzed, in which a discontinuity of the ultrasound signal indicated a thickening of the skin across the body. Furthermore, the fetuses exhibited thickened and convex lips. Fixed flexion of the extremities, short digits and an open mouth were also observed by two-dimensional sonography. Such characteristics are typical of fetal HI (15).

Sonography is an important method of diagnosing of HI, although it is unable to conclusively differentiate fetal HI from other fetal diseases, including fetal macroglossia and congenital tumor-like fetus angeioma (15). The development of the latter conditions is detected by sonography as a marked enlargement of the tongue, with extension of the tongue from the mouth, causing opening of the mouth itself. Such features appear similar to those of fetal HI; however, macroglossia is invariably associated with genetic disorders, including trisomy 21 syndrome (Down's syndrome) and Beckwith-Wiedemann syndrome. Therefore, genetic testing is a critical method to differentiate HI from other macroglossia genetic diseases (16). Another disease requiring a differentiating diagnostic method is congenital hemangioma. The thickened tongue in fetuses with congenital hemangioma typically exhibits blood flow, as observed by color Doppler imaging (17), therefore differentiation is less challenging. However, HI also has distinct sonographic characteristics that aid in its diagnosis, as the discontinuous reflecting signal, indicating thickened skin, and fixed flexion deformity of the extremities observed in sonography of HI are absent in congenital hemangioma and fetal macroglossia (17).

As HI is a severe congenital abnormality, fetuses commonly experience respiratory defects and/or severe clinical complications, including skin infections and sepsis (12). This leads to a high probability of mortality for the few cases of live born infants. Therefore, prenatal diagnosis of HI principally via sonographic techniques is critical in managing the condition. Due to the recent establishment of a genetic basis for HI, genetic screening for candidate gene mutations associated with HI, such as ABCA12, may aid in prenatal diagnosis. In turn, early diagnosis by genetic screening may reduce the physical and mental impacts of fetal HI for parents and relatives.

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