Prenatal diagnosis of congenital harlequin ichthyosis with 2D, 3D, and 4D ultrasonography

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Summary

Harlequin fetus is a rare and mostly fatal form of congenital ichthyosis that can be diagnosed by fetal skin biopsy in patients with a family history of the disease. More recently DNA analysis of amniocentesis and chorion villus sampling materials have also been utilized. We report a case of prenatally diagnosed congenital ichthyosis with no previous family history. Diagnosis was mainly achieved by 3D and 4D ultrasonography findings such as diffuse scaling of the skin, digital contractures, flattened rudimentary external ear, nasal hypoplasia, everted eyelids, typical fish mouth appearance, macroglossia, and persistently open fetal mouth.

Key words: 3D ultrasound; Harlequin ichthyosis; Prenatal diagnosis.

Introduction

Harlequin ichthyosis (HI) is an autosomal recessively inherited severe form of congenital ichthyosis (Mendelian Inheritance in Man 242500) with an incidence of about one in 300,000 births [1]. Various causative mutations have been identified recently [2]. One of the most significant mutations responsible for HI is the ABCA12 gene.

Harlequin ichthyosis phenotype begins to manifest itself prenatally inbetween the 14th and 17th gestational weeks when hair canal keratinization starts. Electron microscope of the hair follicles recently allowed identification at 17 weeks [2]. Skin keratinization occurs at 20 weeks. Prenatal diagnosis is possible by fetal skin biopsy using a light microscope after 20 gestational weeks. Under light microscope hyperkeratosis and hypertrophy of the horny layer can be observed. Other common phenotypic features are ectropion (eyelid eversion), eclabium (lip eversion), flattened ears and flexion deformities. Most neonates are lost just after birth due to respiratory failure, water loss, and infections [3].

Before the identification of ABCA12 mutations, prenatal diagnosis of the disease had been performed by fetal skin biopsy in patients with a family history of the disease at the 19th-23rd gestational weeks [4, 5]. DNA analysis via amniocentesis or chorion villus sampling allowed detection in earlier stages of pregnancy [6].

There are only few cases for which the diagnosis is suspected by ultrasound (US), where as pathologic US features are mostly detectable in the late second or third trimester of pregnancy. Here we describe a case of congenital ichthyosis without any family history. The diagnosis was firstly suspected in the third trimester by two-dimensional (2D) US. Afterwards 3D, and 4D US findings such as diffuse scaling of the skin, ear and nasal hypoplasia, persistently open fetal mouth, digital contractures, polyhydramnios and amniotic debris allowed the final diagnosis.

Case Report

The patient was a 28-year-old woman, gravida 1, para 0, who was referred to our institution for a persistently open fetal mouth observed on conventional 2D US at 32 weeks of pregnancy. She had an uncomplicated antepartum course and her US at 22 weeks of pregnancy and Doppler findings were reported to be normal. There was also no parental consanguinity and no family history of ichthyosis.

The 2D image showed a persistently open fetal mouth which did not change on serial scans, a flattened nose, flat face profile and protuberances over the orbits indicating ectropion (Figure 1). To further investigate the fetus when 3D ultrasound is used, the eclabium, eversion of the eyelids hanging over the eyes, and the flattened nose are visualized better. 3D also shows digital contractures, and a persistently open mouth (Figure 1). Fetal magnetic resonance imaging (MRI) further supported our findings detecting fetal ear canal, fetal ear, and nasal hypoplasia (Figure 1). As the family did not want karyotyping, the invasive procedure was not performed. The pregnancy was terminated at 34 weeks after counselling about the prognosis of the fetus. The postmortem findings of the fetus and autopsy results confirmed the diagnosis.

Discussion

During the course of the disease, the keratinization defect leads to the formation of a thick white membrane separated by erythematous fissures. It hinders the movement of the limbs of the fetus, so the hands and the feet are seen in a semi-flexed position which also restricts the growth of the feet. Digital and joint contractures appear [7]. Intrauterine growth restriction takes place. The thick cover on the face results in nasal hypoplasia and absence of the ears forming a flattened appearance of the face. The

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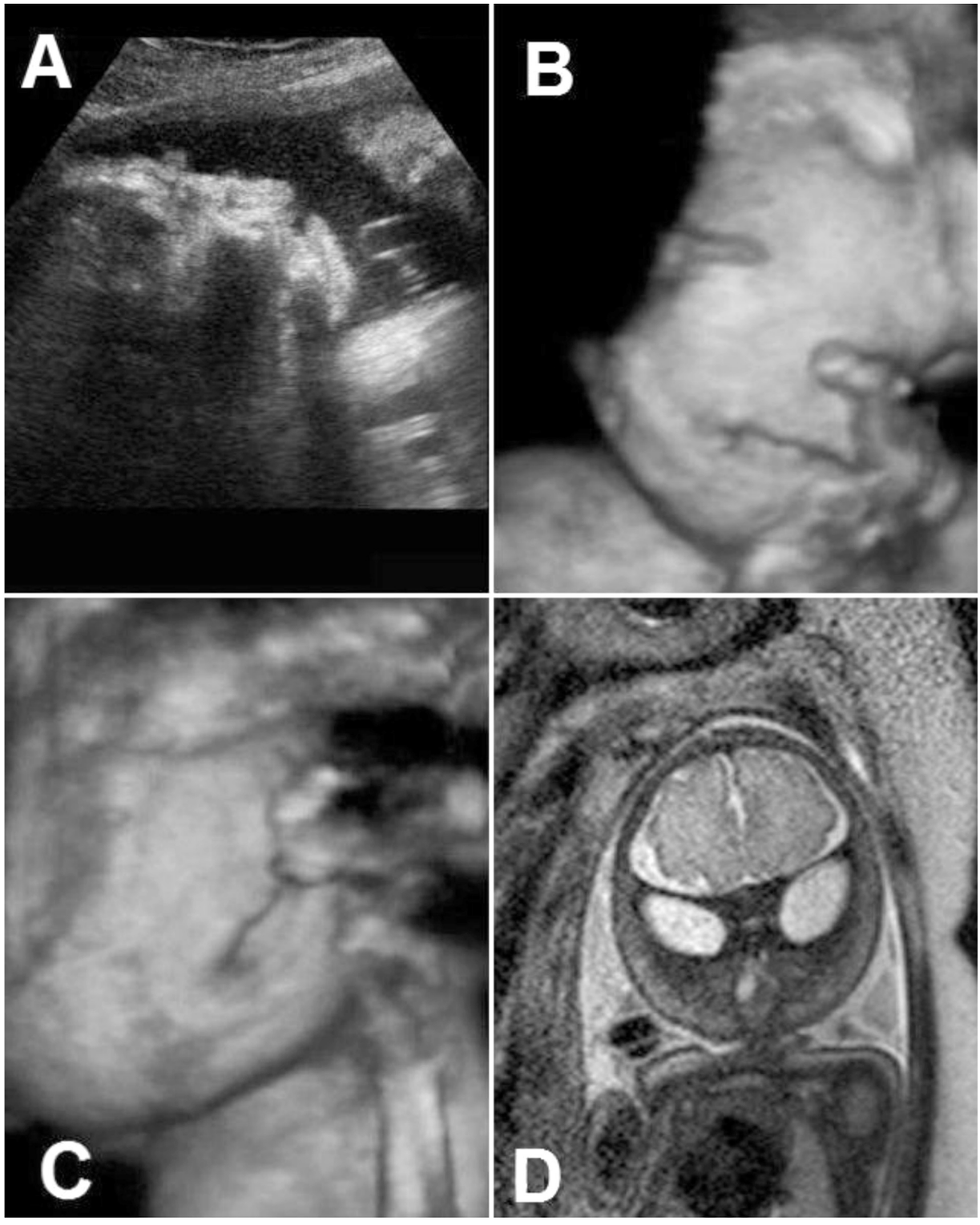

Figure 1. — Intrauterine US and MRI findings of harlequin fetus.
(A) 2D image shows a persistantly open fetal mouth and the skin tag hanging over the eyes. (B) 3D image shows a persistantly open fetal mouth and eversion of the eyelids. (C) 3D image shows a persistantly open fetal mouth and digital contractures. (D) Fetal MRI shows the fetal ear and ear canal hypoplasia.

edema underneath the skin produces eversion of the lips (eclabium), which causes the mouth to remain in a fixed open position [8]. The edematous tongue protrudes through the large gaping mouth. Also, eversion of the eyelids (ectropion) occurs leading to complete closure of the eyes [9]. Desquamation of the epidermis is seen as an echogenic amniotic fluid [10].

In our case, the most remarkable sonographic features that led to the diagnosis were the fixed open immobile mouth, large protruding mouth with thick lips (eclabium), everted eyelids (ectropion), flattened ears and nose, a flat facial profile, digital and joint contractures and the echogenic amniotic fluid. We did not visualize micrognathia, macroglossia and polyhydramnios that have been noted in previous articles [7, 9, 11].

HI should be differentiated from aplasia cutis congenita, arthrogryposis and Neu-Laxova syndrome (NLS). Overlapping features of HI and NLS are fatality, ectropion, micrognathia and joint contractures. Eclabium is unique to HI. MRI does not contribute to the diagnosis or differential diagnosis of HI, but it can be important to know the presence of ear canal hypoplasia when deciding whether to terminate.

As congenital ichthyosis is a lethal devastating condition, the antenatal diagnosis of the disease allows the parents and healthcare providers to prepare for the upcoming shocking appearance of the anomalous newborn. In patients with family history, fetal skin biopsy or today amniocentesis might allow early recognition and termination of pregnancy. With the availability of very recent genetic implementations, DNA-based prenatal diagnosis has been reported in patients with a family history of HI [6].

We have presented a case of congenital ichthyosis where prenatal diagnosis of congenital ichthyosis was done primarily by US [12] instead of fetal biopsy or amniocentesis. As our case was already at 32 weeks' gestation it was too late at the time the disorder was suspected, and 3D and 4D US showed a nearly immobile fetus with characteristic fish mouth. It takes three to four weeks to detect the gene responsible for the disease either by amniocentesis or fetal biopsy. Firstly, with 2D US persistently open fetal mouth is observed and then 3D and 4D US can be used to confirm further findings.

In patients with no such previous encounter in the family history, the diagnosis is delayed until the sonographic findings appear after mid-gestation. The sonographic characteristics should be suspected at US as described above, and the patient should be referred to specialized centers.

In conclusion, congenital ichthyosis is a rare, lethal condition and a devastating disorder where the appearance of the neonate can be shocking to parents. With the help of 3D US images, suspicion of HI and even confirmation of a HI diagnosis is possible. Additionally, better delineation of the features of HI can help in counselling the parents about the prognosis, preparing the parents for the appearance of the newborn at birth, and can also help in the decision about the termination or continuation of the pregnancy by transferring to a tertiary center.

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