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Case Report

Prenatal diagnose of a fetus with Harlequin ichthyosis in a Chinese family

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ABSTRACT

Objective: Harlequin ichthyosis (HI) was the most severe form of ichthyoses, which leaded to neonatal death in 50% of cases. It was the result of mutations in *ABCA12* gene. With the development of ultrasound skills and genetic analysis, HI could be prenatal diagnosed.
Case report: Here, we reported a case of HI, which was prenatal diagnosed by ultrasound examination and genetic analysis. The fetus was found that severe ectropion, eclabium, flattened nose, and rudimentary ears by ultrasound at 20 weeks gestation. A molecular genetic analysis was performed and revealed two mutations in the *ABCA12* gene. One of two mutations were not reported in the past. The fetus was terminated.
Conclusion: HI was associated with the poor prognosis of HI neonates. Prenatal ultrasound and genetic analysis were important for prenatal diagnosis of HI and were helpful to give sufficient prenatal counsels for the family with HI baby.

Introduction

Harlequin ichthyosis (HI) was the most severe form of ichthyoses, which was an autosomal recessive congenital ichthyosis associated with mutations in *ABCA 12* [1]. The clinical features of HI not only included a stiffened skin surface at birth, which struggled to control water loss and to regulate temperature, and were more susceptible to infection, but also included respiratory distress, feeding problems and dehydration and so on. The clinical features of HI were thought to be associated with the poor prognosis of HI neonates. The prenatal ultrasound and genetic analysis were helpful for diagnosis of HI.

Here, we reported a case of HI, which was prenatal diagnosed by ultrasound examination. By genetic analysis, we found a novel mutation in *ABCA12* gene on chromosome 2.

Case report

A 27-year-old Chinese woman, gravid 2, para 1, came to genetic counsel for abnormal fetal ultrasonography result on gestational 27 weeks. She had delivered a healthful male baby at term in her first pregnancy. Routine two-dimensional (2D) sonography screening found that the fetus had abnormal facial features in the present pregnancy, which included eversion of eyelids (Fig. 1A), absence of typical nasal morphology, large open mouth (Fig. 1B) and absence of normal ear morphology. Additionally, the fetal was thick skin, limb anomalies with hypoplastic fingers and toes, incurved toes, clubfoot and clenched fist. Antenatal three-dimensional (3D) ultrasound also showed clearly the fetal with abnormal facial features (Fig. 1C). The diagnosis of ultrasound suggested the baby with HI.

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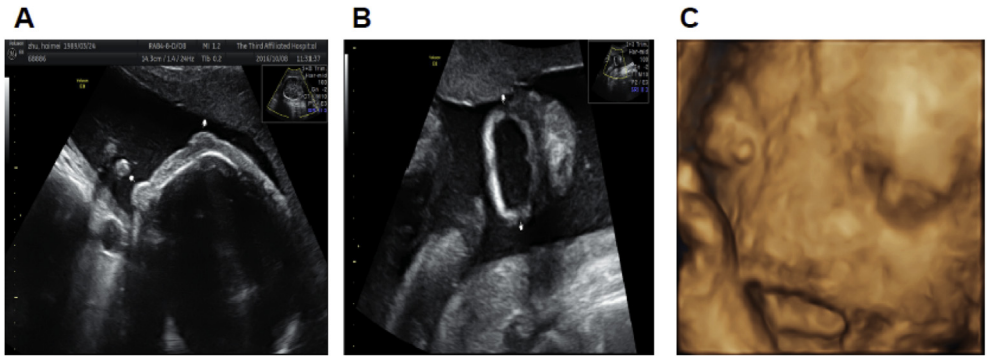

Fig. 1. The ultrasound image of HI. (A) The fetus was with eversion of eyelids; (B) The fetus was with a large open mouth; (C) 3D ultrasound showed fetal with abnormal facial features.

The family did not have history of relative disorder or any genetic diseases. A multi-disciplinary term discussion was performed. Although the family did not have history, the features of ultrasound were in accordance with HI diagnosis. HI would bring a poor neonatal outcome. The family opted to terminate the pregnancy. The baby was induced vaginal delivery at gestational 28 weeks. The appearance feature of the baby indicated HI (Fig. 2). Skin biopsy was sent for histopathological examination. Under microscopy, there was an extraordinarily thick stratum corneum in the baby skin of any region, including the body, the face, arms and legs, which indicated hyperkeratosis (Fig. 3A). A small number of Skeletal muscle cells were observed in dermis and subcutaneous fat tissue (Fig. 3B).

Fetal blood was collected for analysis of relative ichthyosis diseases' genes. Targeted DNA-HiSeq technology was performed and designed an array-based gene chip to capture 23 genes of ichthyosis diseases. A compound heterozygote for the mutations c.1552G > T (p. Glu518Ter) and c.859C > T (p. Arg287Ter) were found in *ABCA12* gene, which respectively located chromosome 2:215884165 and chromosome 2:215910584. The Sanger test were performed on the fetus, the patient and her husband. From Fig. 4A, her husband was heterozygous carrier for the mutation c.1552G > T on *ABCA12* gene, which was never reported in the past. We found the patient with heterozygous mutation c. 859C > T on *ABCA12* gene (Fig. 4B). Two mutations were all nonsense mutations.

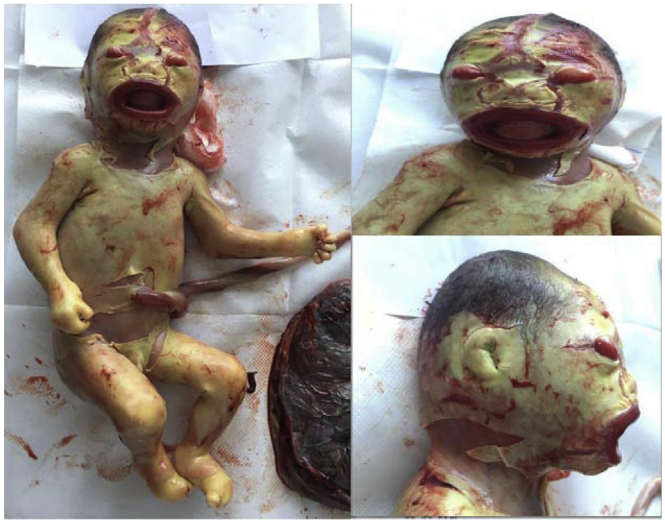

Fig. 2. The appearance of the baby with HI.

Discussion

HI was an autosomal recessive disease. It was one of the most severe genodermatosis. The overall incidence was 1 in 300,000 births [2]. The rate of recurrence was 25% in subsequent pregnancies. Due to severe characteristic clinical features, HI was easily diagnosed at birth. But with development of prenatal diagnostic techniques, some cases of HI with family history had been prenatal diagnosed and the families received sufficient counseling before the baby births [3,4]. We reported the case without HI family history. However, prenatal routine ultrasound screening indicated the baby with the feature of HI. By ultrasound, features of HI, included that ectropion and eclabium, dysplastic ears, fixed position of the hands, absent nose, edematous thighs and feet, fetal growth restriction, polyhydramnios and the skin with "snowflake sign" [2], could be observed. For the families with de novo mutations and without family history, the clinical features of HI were identified by routine ultrasound screening in the prenatal period. Usually, the ultrasonographic diagnosis could be made in the second trimester.

For DNA based diagnosis, many literatures were performed to identify *ABCA12* mutations in patients with HI [5]. ABCA12 is a member of a superfamily of ATP-binding cassette transporters that bind and hydrolyze ATP to various molecules across limiting membranes or into vesicles [6]. And ABCA12 protein located in the lamellar granules of keratinocytes, where it played a major role in the regulation of lipid trafficking [7]. In our case, nonsense mutations were found in *ABCA12* gene, which were thought to lead to disruption of important nucleotide-binding fold domains, resulting in sever functional deficiency in the ABCA12 protein. Recently, with the development of gene diagnostic technology, more new mutations were found. But for judgment of whether the new detected mutation be a pathogenic de novo mutation, it was based on the clinical phenotype. Combined with the fetal clinical phenotype, we thought the new mutation in *ABCA12* was a de novo pathogenic mutation.

The fetal with HI usually had a fatal outcome in the perinatal period, or quality of life was seriously affected in long-term. Neonatal death was common in HI. In our case, the family opted terminated the pregnancy after counseling. The skin biopsy and gene assay confirmed that prenatal ultrasound diagnosis of HI. From this case, we had learned that routine ultrasound screening was an important screening tool for HI with/without family history. Through DNA sequencing technology, we found a de novo mutation, which would be helpful to diagnosed HI in the future.