Case Report

Prenatal diagnosis of harlequin ichthyosis by ultrasonography: a case report

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Abstract: Autosomal recessive congenital ichthyosis is a genetically and phenotypically heterogeneous group of skin disorders, including harlequin ichthyosis (HI), lamellar ichthyosis, and bullous congenital ichthyosiform erythroderma. HI is the most phenotypically severe autosomal recessive congenital ichthyosis associated with the mutation of the adenosine triphosphate—binding cassette subfamily A member 12 (*ABCA12*) gene. The clinical manifestations include generalized hyperkeratotic plaques and deep fissures, ectropion, eclabium, and contractures. However, the severe HI may easily be misdiagnosed as epidermolysis bullosa or syndromic ichthyosis. Meanwhile, no consensus exists about the best used in clinical trials or clinical practice when more elaborate scoring systems have been proposed to evaluate skin xerosis, palmoplantar keratoderma, and disease extension an accurate prenatal diagnosis is necessary. Until the ABCA12 gene was identified as the pathogenic gene, prenatal diagnosis of HI had been performed by the invasive techniques of fetal skin biopsy. Now, advances in ultrasound technology and fetal DNA-based analysis have replaced it. The mortality rate is markedly high and prompt; prenatal diagnosis of neonate HI is critical for appropriate perinatal and postnatal management. It is also essential to prepare parents for future pregnancies and reduce the family's physical and mental distress and financial burden. This report presents a rare case of harlequin ichthyosis diagnosed by the ultrasound and discusses the significance of prenatal ultrasound diagnosis and molecular diagnosis in the prenatal diagnosis of HI.

Keywords: Harlequin ichthyosis; molecular diagnosis; prenatal ultrasound; prenatal diagnosis; case report

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Introduction

Inherited ichthyoses comprise of ichthyosis syndrome and non-syndromic ichthyosis. Ichthyosis syndromes are disorders that can be observed in combination with other organ involvements. Non-syndromic ichthyoses are disorders that can be observed only in the skin (1). These two syndromes are genetic skin disorders and exhibit typical features that include hyperkeratosis, scaling, and generalized dry skin, mainly because of mutations on one or over 30 different alleles involved in skin barrier formation (2). Autosomal recessive congenital ichthyosis (ARCI) is a genetically and phenotypically heterogeneous group of skin disorders, which is one form of non-syndromic ichthyosis, including harlequin ichthyosis (HI), lamellar ichthyosis, and bullous congenital ichthyosiform erythroderma (2). HI is the most phenotypically severe ARCI associated with the mutation of the adenosine triphosphate (ATP)—binding cassette subfamily A member 12 (ABCA12) gene (3-6). The clinical manifestations include generalized hyperkeratotic plaques and deep fissures, ectropion, eclabium, and contractures and affect 1 in 300,000 live births (3)—onset at birth, often preterm babies. The risk of death is extremely high during the neonatal period (2).

This report presents a case of a pregnant woman who underwent three adverse pregnancies at the ages of 21, 24, and 25, respectively, with the recent pregnancy presenting with HI, revealed by ultrasound, and to discuss the

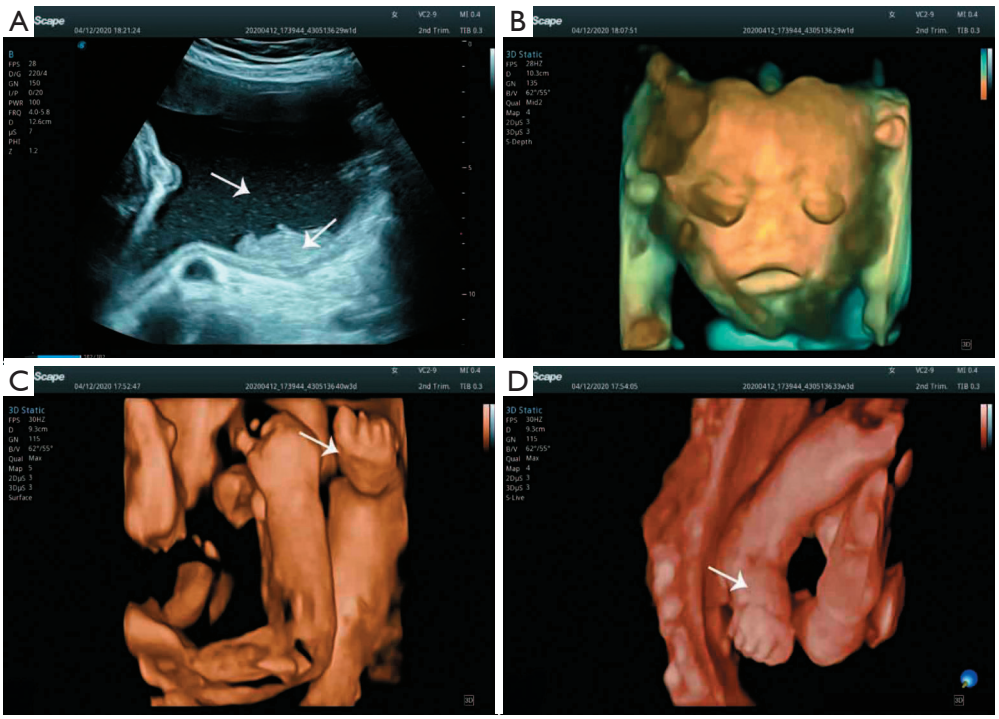

Figure 1 Three-dimensional ultrasound. (A) The dense floating particles in amniotic fluid (arrows); (B) the harlequin phenotype ("clown-like face"); (C) the contracted and edema hands (arrow); (D) the contracted and edema feet (arrow).

significance of prenatal ultrasound diagnosis and molecular diagnosis in prenatal diagnosis of HI.

We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-8223).

Case presentation

A 26-year-old multipara woman was referred to our hospital with a suspected fetal abnormality in the third trimester (28^{+5} weeks). On her admission, there were no symptoms or signs. Five years prior, she had undergone induced labor on week 20 of pregnancy due to fetal abnormalities. Three-year ago, she had a cesarean section at 32 weeks of pregnancy. Unfortunately, the infant was premature, had deformities (the whole skin was red, and the rest was unknown), and died five days later (no fetal tissue examination). The present case was genetically tested for Down's syndrome, neural tube defect, and trisomy 18 syndrome, and the results were all negative. Non-invasive DNA screening showed no chromosomal abnormalities. Meanwhile, there were no signs of hyperglycemia or hypertension during pregnancy, and the woman denied having a consanguineous marriage or contact with pesticides and radioactive substances. However, repeated on admission, three-dimensional sonography construction revealed dense floating particles in amniotic fluid ("snowflake sign"). The bilaterally soft tissue in the anterior region of the eyeballs was thickened. The upper and lower lips were markedly thickened and everted, causing the mouth to be fixed in an O-shape. No apparent nostrils and normal nasal shape were observed. The fetus also had a fixed flexion deformity of the extremities (*Figure 1*). Considering ichthyosis by ultrasound, it is suggested to form a further prenatal diagnosis. At 29^{+3} weeks, the labor was induced, and a dead female infant was delivered. The premature infant exhibited typical characteristics of HI following the sonography (thick, platelike scaling and deep fissures, extreme ectropion, and eclabium. The nose was not observed. The ears with the ear canal were small and without auricles. *Figure 2* shows the palmoplantar involvement, synechiae of fingers, and toes. With the patient and her family's signature, a genetic study was performed with the dead infant's lower extremities' gastrocnemius muscle tissue by whole-exome sequencing (WES). Data analysis found that: The paternal variant was a missense mutation (c.1300C>T; p.Arg434*) present at

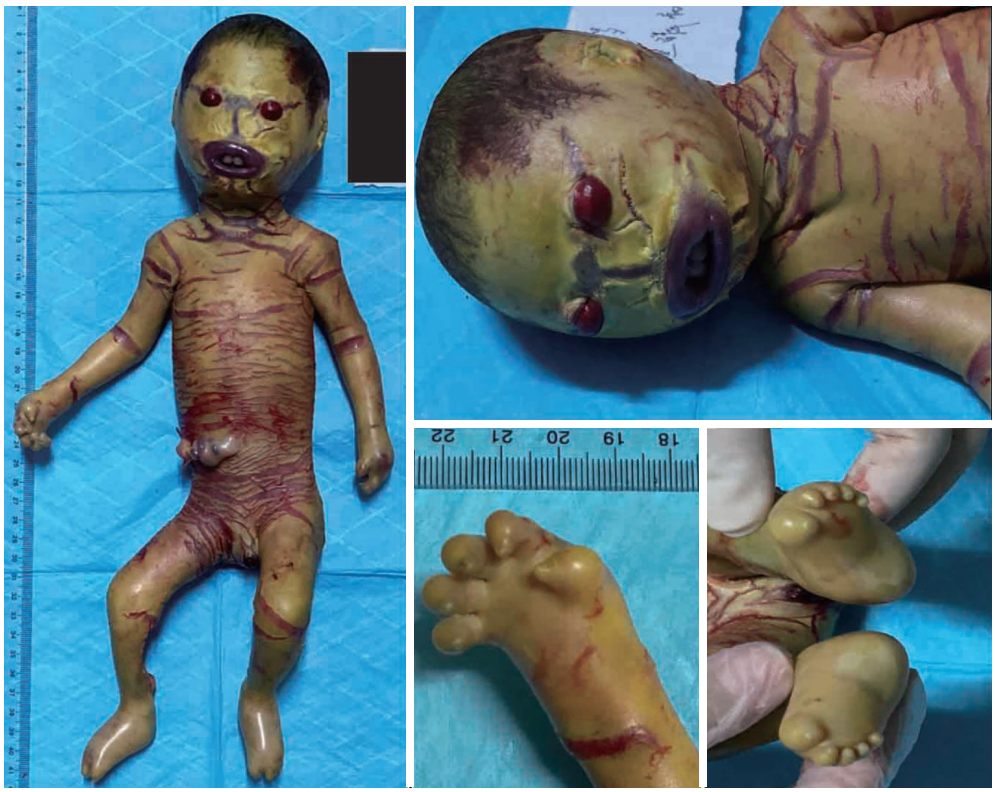

Figure 2 General view of harlequin ichthyosis fetal.

exon 12. According to the American Society of Medical Genetics and Genomics (ACMG) guidelines, the mutation was pathogenic. According to the public database query, the mutation may lead to autosomal recessive clown ichthyosis, and the phenotype of the disease is consistent with the disease. While the maternal variant was a deletion mutation (c.3179+3_3179+6delAAGT) present at the intron 22 and according to the ACMG guidelines, the variation was judged to be an unknown variable.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Second Hospital of Hebei Medical University (approval letter no. 2020-P019) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

HI is a rare and severe ARCI genetic skin disorder. Reverend Oliver Hart reported the first case in 1750 (3). Until 2005, the underlying mechanisms were not well understood. The mutation of the ABCA12 gene found in chromosome 2 (2q34) causes a change in the stratum corneum's lipid deposition, leading to skin barrier disruption and compensatory hyperkeratinization (4,7). In other words, HI is a lipid metabolism disorder (4). Skin development is changed in the uterus, and hair canal hyperkeratosis occurs in the second trimester (8). Historically, fetuses presenting with HI are born with a distinct clinical appearance and have increased perinatal mortality (2). Hence, prenatal diagnosis of neonate HI is significantly essential for proper perinatal and postnatal management, prepare parents for future pregnancies, and reduce the physical and mental distress and financial burden of the family.

A correct diagnosis of HI is critical for genetic counseling and adequate patient information about prognosis and therapeutic options. Given the patients present with a harlequin phenotype precisely like the case, one may surmise that it is easy to make a correct diagnosis of HI. However, the severe HI may easily be misdiagnosed as epidermolysis bullosa or syndromic ichthyosis (9). Meanwhile, no consensus exists about the best used in clinical trials or clinical practice when more elaborate scoring systems have been proposed to evaluate skin xerosis,

palmoplantar keratoderma, and disease extension (10,11). An accurate prenatal diagnosis is necessary.

Until the ABCA12 gene was identified as the pathogenic gene, prenatal diagnosis of HI had been performed by the invasive techniques of fetal skin biopsy (8,12). Now, advances in ultrasound technology and fetal DNA-based analysis have replaced it (3). In the present case, the prenatal sonography analyzed the HI fetus images, and they were following the type of fetal HI, including eclabium, ectropion, contractures, and "snowflake sign" (dense floating particles in amniotic fluid) (13,14). Moreover, three-dimensional ultrasound significantly improves the facial morphology analysis and may be conducive to prenatal diagnosis (15). It is worth noting these unusual features are not detectable until the second trimester, except for early termination (3). Besides, fetal HI cannot differentiate from fetal macroglossia and congenital tumor-like fetus angioma (13). They both had their tongues extended from the mouth, causing the mouth to be fixed in an O-shape, like fetal HI. However, macroglossia is always associated with genetic disorders (Down's syndrome and Beckwith-Wiedemann syndrome), and genetic testing can differentiate it from HI (16). The thickened tongue in congenital hemangioma fetal typically exhibits blood flow by color Doppler imaging (17). Therefore, HI ultrasound diagnosis needs to be combined with disease characteristics and gene detection for differential diagnosis.

A deep understanding of the HI genetic basis shows that genetic screening for candidate gene mutations associated with HI may aid in prenatal diagnosis. The first DNA-based prenatal diagnosis of HI was performed by direct sequence analysis of the ABCA12 mutation from amniotic fluid cells, which showed the effectiveness of early DNA-based prenatal diagnosis (18). It is becoming a standard technique for the early and accurate diagnosis of HI (19). The next generation sequencing (NGS) technology has been developed and applied to large-scale gene diagnosis, analyzing the whole coding part of a genome or even the whole genome in a few days. If mutations cannot be identified, more genes will be analyzed, or whole-exome sequencing (WES) will be sequenced. Moreover, large-scale sequencing may lead to additional and coincidental findings. However, exome sequencing may produce sequence variants that cannot be interpreted as pathogenic or nonpathogenic.

In the present case, a genetic study was performed by WES and found the paternal variant was a missense mutation (c.1300C>T; p.Arg434*) present at exon 12, and the pathogenicity of this mutation had been reported (4). While the maternal variant (c.3179+3_3179+6delAAGT) present at the intron 22 was judged to be an unknown variable. No related cases have been reported. The mutation is close to the splicing site of "GT" and may affect mRNA's transcriptional process. This may be supported by collecting more cases of similar gene mutations or functional verification at the RNA level. However, it is still difficult to predict its pathogenic potential. For example, a negligible point mutation in TGM1 may change the TGm-1 3D structure only when the skin temperature is elevated (20). Hence, genetic screening also should combine with detailed anamnestic and clinical investigations.

In short, prenatal sonography and molecular diagnosis are increasingly feasible in patients with HI and are essential for giving correct genetic advice. Combined with the pre-implantation genetic diagnosis (PGD) to select and transfer an unaffected embryo will reduce the family's physical and mental distress and financial burden.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-8223

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-8223). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Second Hospital of Hebei Medical University (approval letter no. 2020-P019) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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