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Case Report of Mild Harlequin Ichthyosis

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Abstract

Harlequin ichthyosis is a severe autosomal recessive skin disorder. Most deaths occur within the first few days after birth, and the survivors still have severe chronic skin disease throughout their lives. Almost all cases were associated with a pathogenic variant of adenosine triphosphate binding cassette transporter, subfamily a, member 12 (ABCA12) gene. We described a case of HI diagnosed by ultrasound examination during pregnancy, moderate phenotype of Harlequin ichthyosis. The ultrasound features have been described well and the diagnosis can be made with a fair degree of confidence, death occur within the first few days after birth for respiratory infection.

Keywords: Prenatal diagnosis; Harlequin ichthyosis; Ultrasound; Gene; Adenosine triphosphate binding cassette transporter; Subfamily A; Member 12 (ABCA12)

Introduction

Harlequin ichthyosis (HI) or ichthyosis fetalis (IF), severe hereditary skin condition, are inherited via the autosomal recessive gene [1,2]. It is an uncommon sickness because of its peculiar clinical appearance and exceedingly high perinatal mortality. In about 1 in 300,000 new-borns, the problem manifests. As of 2003 138 instances of HI had been documented [3]. As of 2014 (the most recent data), about 200 cases of HI have been reported throughout the world [2]. The first occurrence of a prenatal sonographic diagnoqsis of HI [4]. Hart published the first account of congenital ichthyosis in 1750 [5]. The first report of an HI prenatal diagnosis was reported in 1983. It was based on a skin sample taken from a patient undergoing a fetoscopy who had already given birth to two affected children [6].

The causative gene, ABCA12 (Adenosine Triphosphate Binding Cassette A12), was discovered in 2005. It was found that the ABC transporter ABCA12 mutation causes HI, a lipid metabolic disorder. Normally, the skin creates a barrier of protection between the body and its environment. Harlequin ichthyosis-related skin defects compromise this barrier, making it challenging for affected new-borns to balance water loss, maintain a stable body temperature, and fight infections. In the first few weeks of life, infants with harlequin ichthyosis

frequently undergo excessive fluid loss (dehydration) and acquire infections that can be fatal. Instructions for creating a protein that is necessary for the typical growth of skin cells are provided by the ABCA12 gene. This protein is essential for the transportation of lipids and enzymes in the epidermis.

Certain ABCA12 gene variations stop cells from producing any ABCA12 protein. Other variations result in the synthesis of an unusually tiny protein that is incapable of properly transporting lipids. The epidermis fails to grow normally before and after birth when functional ABCA12 protein is lost, leading to severe skin defects that are indicative of harlequin ichthyosis.

Deep cracks separate the huge, diamond-shaped plates that the skin develops (fissures). These skin flaws restrict arm and leg movement in addition to changing the appearance of the eyelids, nose, mouth, and ears. Babies with harlequin ichthyosis who also experience feeding issues may experience breathing difficulties and respiratory failure due to restricted chest movement. Sepsis, respiratory failure, or electrolyte imbalances are the most typical causes of mortality in these patients [7,8].

Prenatal diagnosis is now possible thanks to improvements in ultrasound resolution and our understanding of the illness. However, a definitive diagnosis is only made following invasive prenatal testing or following the fetus's delivery. Fetal MRI in conjunction with genetic testing is a more productive diagnostic strategy [9].

Here, we present a case of HI that was identified during pregnancy using ultrasound testing. Lesions are not more noticeable, and the patient rejects further testing following a diagnosis.

Case Report

A pregnant 23-year-old syrian woman, para 0 At 10 weeks, she had one abortion. The pair had a consanguineous marriage, family history of inherited skin conditions.

At 22 weeks, the fetus had atypical facial traits in the current pregnancy, including eversion of the eyelids, normal nasal morphology, a large open mouth, and normal ear morphology. The examination was performed using a Samsung real-time ultrasound system and a 3.5 Mhz convex probe. The fetus also had thick skin, hypo plastic fingers and toes, incurved toes, a clubfoot, and a clenched hand as well as limb deformities. The infant may have HI, according to the ultrasound findings. After being notified, the parents declined to conduct any research.

At 39 weeks, the fetus was sonographically examined to determine whether active labour was present. A single fetus with a frank breech presentation was discovered during the examination. The biparietal diameter, head circumference, belly circumference, and femur length all indicated a gestational age of 39 weeks. Amniotic fluid was present in a usual amount. Although the embryonic abdominal wall thickened, there was no other sign of fetal hydrops. Upon examination, bilaterally symmetric cystic masses anterior to each orbit were visible on the fetal face. The scalp of the fetus thickened. The fetal limbs were morphologically healthy and had free gross mobility. Other organ systems' congenital anomalies were not discovered. The new born displayed signs of harlequin ichthyosis upon birth (Figure 1).

The skin had become thicker and cracked. Both eclabium and ectropion were observed following consideration of the illness and outlook, the parents decided to just provide supportive care. One week after the baby's birth, the infant passed away from a respiratory infection.

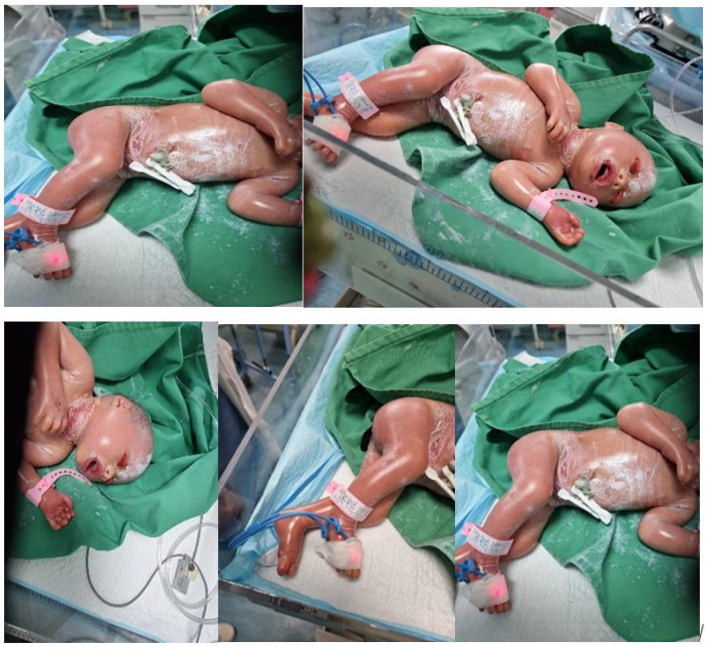

Figure 1: *Mild Harlequin Ichthyosis.*

Discussion

The clinical hallmark of HI is diffuse hyperkeratosis skin and loss of the barrier that serves as the skin's defense mechanism. HI is a dangerous, uncommon, and occasionally fatal skin condition with a wide range of consequences. Normal skin cornification starts between 14 and 16 weeks of pregnancy. The skin lesions can be detected as early as the second trimester of pregnancy, opening the door to a 2D ultrasound-based prenatal diagnosis of HI. Normal fetal facial lesions can now be seen in ultrasound exams, particularly three-dimensional ultrasonography, which is more intuitive and vivid than before [10-14]. Infants with HI have a high mortality rate, a dismal prognosis, and the majority pass away very soon after birth from infection, heat loss, dehydration, electrolyte imbalances, or respiratory distress. Prenatal diagnosis is crucial since there is a 25% chance that a pregnancy will return [7].

Fetoscopy with skin biopsy and ultrastructural analysis of the cells in the amniotic fluid and hair canal may be beneficial in

patients with family histories [12]. Many cases are overlooked by people without a family history. By combining this case with earlier literature reports the ultrasonic characteristics of HI were examined in this study [15-19]. They include the following: (1 the presence of ectropion; (2) the presence of an abnormal double auricle; (3) the presence of thickened skin that appears to be armor;(4) the presence of double lips thickened valgus, a sustained state of an open mouth that resembles a fish's mouth; (5) the presence of limb contracture.

We investigated the reasons and found that in the typical fetus, keratinization does not start until 22 to 24 weeks of gestation [16,17]. A chorionic villus or amniotic fluid sample may be used to confirm the diagnosis when the ABCA12 mutation has been identified (6), although the target gene is not commonly investigated in patients without a family history.

The majority of ultrasound's distinguishing characteristics won't be seen until much later in pregnancy; when the fetus's growth and movements are constrained by restricted skin development. A prenatal diagnosis is commonly missed during this gestational stage since it is challenging to do a systematic fetal examination due to the pregnant woman's conceptual difficulties and some fetuses are not examined during the third trimester although the morphological scan at 20 weeks of gestation was unremarkable, 19 observed an HI fetus. However, by 26 weeks 15, aberrant facial traits, incurved toes, clenched fists, and polyhydramnios were visible. In order to detect any HI symptoms or other structural abnormalities, it is required to perform a series of ultrasound scans for high-risk pregnant women in the middle and late stages of the pregnancy.

A single ultrasound test cannot entirely rule out HI as a possible diagnosis. Prenatal diagnosis in low-risk pregnancies is extremely challenging without any indication of HI, nevertheless. Most cases that have been recorded have a late-pregnancy diagnosis.

Unfortunately, due to the effects of gestational age, fetal position, and maternal obesity, fetal face, and limb morphologic abnormalities may not be totally exposed, which will cause low-risk cases to be ignored. For the prenatal diagnosis of HI, specific information regarding the family history and past affected children is crucial. In our instance, HI was detected at the end of the second trimester but was not more obvious in the first [4,5,6,11].

The ABCA12 gene pathogenic mutation causes hyperkeratosis and impaired barrier function. ARCI, encompassing HI, congenital ichthyosiform erythroderma, and lamellar ichthyosis, has been linked to mutations in ABCA12. The most severe phenotype is seen in HI. The ABCA12 mutations are connected to almost all HI cases Since nonsense and frameshift substitutions are likely to result in a shortened protein and a significant loss of ABCA12 function, the majority of pathogenic mutations connected to HI are homozygous or compound heterozygous, as was previously observed. However, there is debate concerning the genotype/phenotype relationship of HI with ABCA12 mutations [20].

In contrast to all deaths, which were linked to homozygous mutations [21,22]. Reported that 52% of HI survivors had compound heterozygous mutations in the ABCA12 gene. The most severe and lethal form of HI occurred in those who were homozygous for a harmful loss-of-function allele. Compound heterozygous individuals had less severe symptoms. The clinical prognosis of HI correlates only with the residual protein function, not with homozygosity or compound heterozygosity; and that a less severe ARCI is typically caused by the presence of a residual protein function. The severity of HI, on the other hand, is likewise linked to the ABCA12 mutant protein's differential expression.

A case of HI with variable expression of alternatively spliced mutant ABCA12 transcripts that had a good prognosis was described [21].

This couple must both complete karyotypes for our case. Preimplantation genetic diagnosis and in vitro fertilization are the greatest options for the upcoming pregnancy.

A systematic examination during the third trimester of pregnancy should be done in accordance with the clinical characteristics of the disease to avoid missing a diagnosis of HI, especially in cases without a family history.

In conclusion, HI can be easily detected by 2D ultrasound combined with 3D ultrasound. Most often, the fetus dies while the mother is pregnant, eliminating the chance of a live birth. Numerous HI-affected fetuses have been born alive, despite having significant respiratory problems or feeding issues. Therefore, there is a substantial likelihood that new-borns with HI may die from respiratory failure, fluid loss, or skin infection [14].

For proper perinatal and postnatal care as well as to prepare parents for future pregnancies, fetal HI must be diagnosed during pregnancy [23-25].

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