Full term delivery of a Harlequin ichthyosis baby: a case report

Ahmed M. Abbas,[1] Armia Michael,[2] Ayman A. Askar,[2] Shymaa S. Ali[1]

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Abstract

Harlequin ichthyosis (HI) is one of the most severe and rare autosomal recessive congenital ichthyosis (ARCI), characterized by severe hyperkeratosis, extensive fissuring and a variable degree of cutaneous malformations. Here we report a case of 22 years old female patient in her first pregnancy. The baby was born at 39 weeks of gestation from non-consanguineous parents. At birth the baby had thick skin with deep fissures. The baby was admitted to the neonatal intensive care unit and survived for 11 days.

[1]Department of Obstetrics and Gynecology, Faculty of Medicine; Assiut University, Assiut, Egypt
[2]Faculty of Medicine; Assiut University, Assiut, Egypt

Introduction

Harlequin ichthyosis (HI) is rare and the most severe form of autosomal recessive congenital ichthyosis (ARCI) which is often lethal in the neonatal period.[1] Patients may survive for several months or years in very rare cases.[2]

HI appears with severely thickened and scaly skin over the whole body. There are deep, erythematous fissures which separate large diamond-shaped, thick skin plates. The skin anomalies affect the shape of the eyes, ears, nose and mouth. HI also appears with bilateral ectropion and eclabium. The external parts of the nose and ears are not completely developed. Other manifestations include hypoplastic fingers, absence of nails and mobility limitation of the joints.[3]

Neonates with HI are at high risk for development of hypothermia, hyperthermia, dehydration, respiratory distress, hypoventilation, malnutrition, hypernatremia, seizure, and skin infections[4] HI is associated with preterm birth and often leads to death due to neonatal complications such as fluid loss and septicemia.[5] With improved neonatal care and probably the early introduction of oral retinoids, the number of survivors is increasing.[1]

The underlying genetic abnormality in HI

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Corresponding author: *Ahmed M. Abbas, MD, Department of Obstetrics and Gynecology, Faculty of Medicine; Assiut University, Assiut, Egypt; Woman's Health Hospital, 71511, Assiut, Egypt, Cellular: +20 10033851833; Tel: +20 88 2414616; email: bmr90@hotmail.com*

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has been identified as an alteration in the lipid-transporter gene adenosine triphosphate-binding cassette transporter A12 (ABCA12) on chromosome 2.[6] Histological examination of the skin reveals characteristic abnormalities in the structure of lamellar granules and in the expression of epidermal Keratin.[2]

Case presentation

On 12 February 2017, a 22-year-old pregnant woman was admitted to the reception unit of Women's Health Hospital, Assiut, Egypt in her first pregnancy with labor pains. The gestational age was approximately 39 weeks based on both the first day of the last menstrual period and ultrasound. Vaginal examination revealed 3 cm cervical dilatation, 50% effacement, and intact amniotic membrane. There were insufficient uterine contractions, so artificial rupture of membrane was done which revealed clear amniotic fluid then oxytocin infusion was used for further augmentation of labor. Progress of labor was within average references.

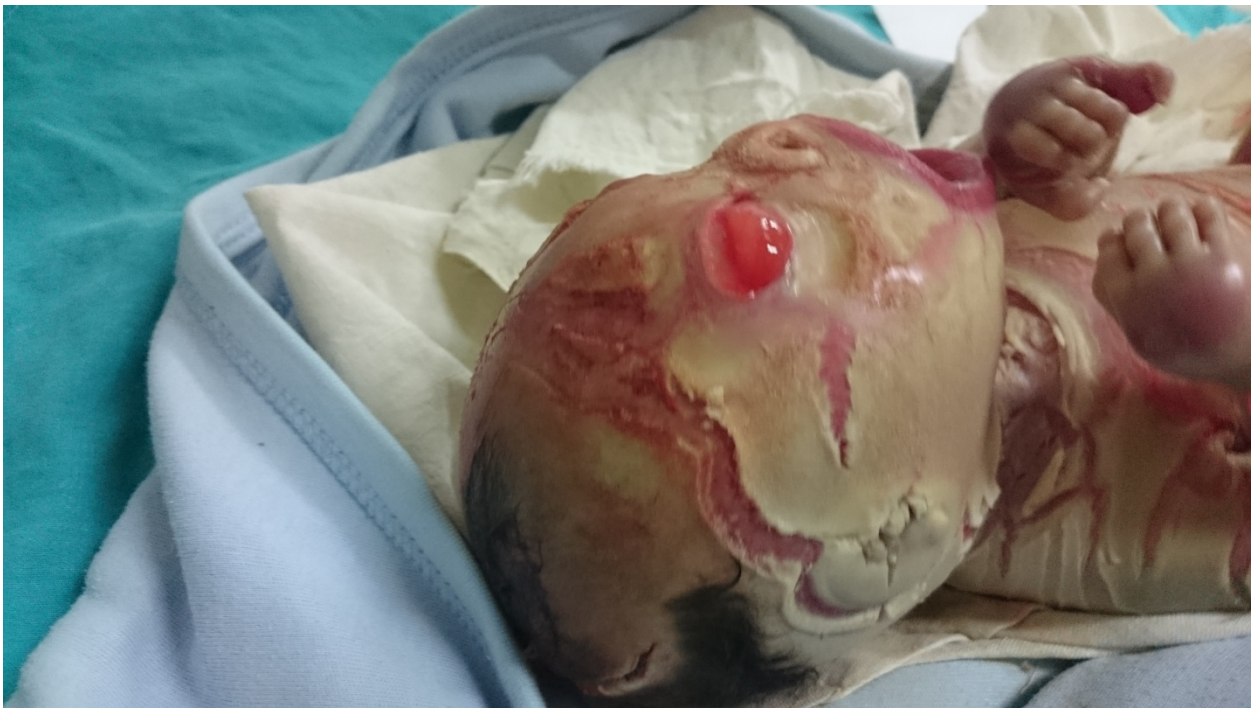

Figure 1: The head of the baby shows small area of scalp covered by hair, open mouth, flattened nose, rudimentary external ears, absent eye balls, eye opening covered by mucous reddish membrane.

A female baby, weighing 2900 gm was delivered by spontaneous vaginal delivery. The Apgar score was 7 and 9 at 1 and 5 min, respectively. The mother had not received regular antenatal care. The baby was the first child of non-consanguineous Egyptian parents. The parents had no family history of any inherited skin disorder.

Her birth weight, length, and head circumference were within normal averages. The baby exhibited thick skin with deep fissures. Hair was absent all over the body except for a small area of scalp. The facial examination revealed a fixed and open mouth, flattened nose, flat fontanels, small rudimentary external ears, absent eye balls, and eye openings covered by a reddish mucous membrane (Figure 1). The limb examination revealed flexion deformity in both upper and lower limbs (Figure 2). Ultrasound of both eyes showed bilaterally absent eye balls and the abdominal ultrasound was normal.

Figure 2: The body of the baby covered by thick skin with deep fissures with flexion deformity in both upper and lower limbs.

The baby was admitted to the neonatal intensive care unit (NICU) due to dehydration and failure of oral feeding. A nasogastric tube was inserted and oral feeding started. She was doing well till the 6th day of life when she developed a skin infection. Antibiotics were tried, but fulminant sepsis developed and the baby died at the 11th day of life.

Discussion

Harlequin ichthyosis is a rare and often fatal congenital disease. The data about this anomaly is very limited, coming almost entirely from case reports. The first case of HI was reported in 1750 by Reverend Oliver Hart who described a fetus with thickened and cracked skin over the whole body.2

Studies on the pathogenesis of this disease are novel. It has been found that HI is caused by mutations in the ABCA12 alleles.7 This ABCA12-mediated lipid-transfer system is essential to the transfer of lipids from the cytosol of the keratinocytes into lamellar granules. ABCA12 localizes throughout the entire Golgi apparatus to LGs at the cell periphery, mainly in the granular layer keratinocytes. ABCA12 works in the transport of lipids from the Golgi apparatus to LGs in the granular layer cells. At the transition from the stratum granulosum-the third layer of the epidermis-to the stratum corneum, the contents of lamellar bodies are extruded into the intercellular space to form protective lipid sheets that are responsible for the skin's hydrophobic barrier.2

In HI, the ABCA12-mediated transfer of lipid to lamellar granules is defective. The lamellar granules themselves are morphologically abnormal or absent. Normal extrusion of lipid from these granules into the extracellular space cannot occur, and lipid lamellae are not formed. This defective lipid "mortar" between corneocyte "bricks" results in aberrant skin permeability and lack of normal corneocyte desquamation.[4]

The inheritance of this anomaly is autosomal recessive, and affected babies are usually homozygous for the mutation, consistent with the autosomal recessive pattern of inheritance so in most cases there was consanguinity between parents,[8] but in our case there was no consanguinity between parents of our baby and there was no family history of any congenital anomalies.

Babies are usually born prematurely and do not have any brain or internal organ abnormalities[9]. However; in our case the baby was term delivered at 39 weeks with normal birth weight. Prenatal diagnosis could be the first step for early detection of the disease. A detailed family history, including questions about consanguinity between the parents, and the presence of other skin disorders in their children could be helpful for early diagnosis of the disease.[7]

Possible areas of early detection include microscopic examination of the amniotic fluid cells and an ultrasound for assessment of the shape of fetal mouth at the 17th week of pregnancy.[8] Skin biopsy at the 24th week of pregnancy, especially among the families with a history of HI, could also be helpful in prenatal diagnosis. Although ultrasonography can be useful in some cases, it could be inappropriate due to delayed phenotypic expression and the rarity of the disease.[3] Furthermore, sequence analysis of ABCA12 should be done first for the individuals with HI history.[9]

The following findings may be noted on physical examination in the newborn period:

- *Skin: Severely thickened skin with hyperkeratotic scale is present at birth. Deep, fissures separate the scales.*
- *Eyes: Severe ectropion is present. The free edges of the upper and lower eyelids are everted, leaving the conjunctivae and cornea at risk for desiccation and trauma.*
- *Ears: The ears are flattened with*

absent retroauricular folds. The pinnae may be small and rudimentary or absent. The external auditory canal may be obstructed by scale.

- *Lips: Severe traction on the lips causes eclabium and a fixed, open mouth. This may result in feeding difficulties.*

- *Nose: Nasal hypoplasia and eroded nasal alae may occur. The nares can be obstructed.*

- *Extremities: The limbs are encased in the thick, hyperkeratotic skin, resulting in flexion contractures of the arms, the legs, and the digits. Limb mobility is poor to absent. Circumferential constriction of a limb or digit can occur, leading to distal swelling, ischemic necrosis and autoamputation. Hypoplasia of the fingers, toes, and fingernails is reported. Polydactyly is described.*

- *Temperature dysregulation: Thickened skin prevents normal sweat gland function and heat loss. The infant is heat intolerant and can become hyperthermia.*

- *Respiratory status: Restriction of chest-wall expansion can result in respiratory distress, hypoventilation, and respiratory failure.*

- *Hydration status: Dehydration from excess water loss can cause tachycardia and poor urine output.*

- *Central nervous system: Metabolic abnormalities can cause seizures. CNS depression can be a sign of sepsis or hypoxia. Hyperkeratosis may restrict spontaneous movements, making neurologic assessment difficult.*

In our case the skin, ears, mouth and nose findings are typical for HI but the unique finding is that both eyeballs were absent as shown by the ultrasound of the eye sockets. Both upper and lower limbs showed flexion deformity. The digits also showed flexion deformity. There was no respiratory distress in our baby and she didn't need oxygen.

Affected infants usually do not survive for very long because of undernourishment caused by the rigidity of the lips, under ventilation and infections, but longer survival has been reported.[10]

In their review of clinical outcome in 45 cases of HI, Rajpopatet et al. reported a survival rate of 56%; 16 of 45 HI cases surviving for 7 years or longer and the longest surviving case reaching 25 years. Improved outcomes were linked to heterozygous mutations and early use (by day 7) of oral retinoid, whereas most neonatal deaths were attributed to sepsis and severe disease with homozygous mutations.[1]

In our case the baby was doing well with a nasogastric tube for nutrition till the 7th day of life when a skin infection occurred which developed into septicemia. Antibiotics were started when the skin infection occurred but the baby not respond to treatment, she developed septicemia and died at the

11th day of life. Oral retinoid hadn't been used due to a lack of experience as it was the first case of HI in our university hospital.

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