

Harlequin ichthyosis newborn: A case report

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Abstract

Harlequin ichthyosis is a rare and severe genetic skin disorder that occurs within the developing foetus. Harlequin ichthyosis is the most severe and devastating form of autosomal recessive congenital ichthyoses. It is caused by mutations in the lipid transporter adenosine triphosphate binding cassette A 12. Here, we reported a case of harlequin ichthyosis with no family history. No abnormalities were detected in prenatal sonography. A 24-year-old pregnant woman with premature rupture of membrane and labour pain was referred to a hospital in Shoushtar city, Iran. The mother delivered a male baby with harlequin ichthyosis. The infant baby died on the 5th day. Harlequin ichthyosis is associated with adenosine triphosphate binding cassette A 12 gene mutation; therefore, genetic screening and counselling for susceptible parents should be taken into account. Prenatal diagnosis of harlequin ichthyosis principally via sonographic techniques is important in managing the disorder.

Keywords

Dermatopathology, harlequin ichthyosis, healthcare delivery, case report

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Introduction

Harlequin ichthyosis (HI) is a rare and severe genetic skin disorder that occurs within the developing foetus.¹ HI is caused by mutations in the adenosine triphosphate binding cassette A 12 (*ABCA12*) gene and is inherited in an autosomal recessive fashion (5P,9P). Mutation in the *ABCA12* gene has been identified in a high percentage of HI children's chromosomes.^{2,3} HI represents the most severe form of non-syndromic ichthyoses associated with perinatal morbidity and potential lethality early in life.^{4,5} The incidence of HI is relatively low, ranging from 1/300,000 to 1/1,000,000.⁶ No significant association is found between sex and race with the incidence of HI.⁷ The disease has a 25% chance of recurrence in subsequent pregnancies.⁸ HI typically exhibits thick and plaque-like scales all over the body and is associated with ectropion, eclabium and ear deformities, sparse scalp hair, short limbs, hypoplastic digits, and complete absence of eyebrows and eyelashes.^{9–11} These infants are also at high risk for low body temperature, dehydration, respiratory, poor nutrition, low blood sodium, seizures and skin infection.^{12,13}

Due to respiratory failure, loss of fluid or skin infections, the probability of mortality for infants with HI is high.¹⁴ Infants with HI would die within 2 days of life,^{12,15} and in very rare cases, some infants may survive for several months

or years.⁸ Successful management of HI requires a multidisciplinary approach from the onset.¹⁶ With advanced therapy protocols, such as retinoids and novel procedures, the survival rates have increased in developed countries.^{4,7,17–19} This is, however, not so in developing countries. This study reports a case of a woman who delivered a foetus with HI at the age of 24 years.

Case report

A 24-year-old pregnant woman with premature rupture of membrane and labour pain was admitted to the Maternity ward of Al-Hadi Hospital in Shoushtar, Iran, on 26 October 2018, at 3:30 a.m. for her third pregnancy. The gestational age based on the first day of the last menstrual period (LMP) was 36 weeks and 2 days, and based on sonography was 36 weeks and 5 days. Sonography at 9 weeks and 4 days and at 25 weeks and 3 days of gestation found no abnormalities in foetal development. No prenatal genetic investigation and

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Figure 1. A boy baby with deep cracked skin, open wide mouth, abnormal eyes, and flatted nose and ear.

eventual genotypic characterization were carried out for the baby. In the 36th week of gestation (27 October 2018, at 11:50 a.m.), a live male infant was delivered via caesarean section due to a slow foetal heartbeat and continued labour pain. The baby was diagnosed with HI. His birthweight, length and head circumference was 2.700kg, 42cm and 36cm with Apgar 8,²⁰ respectively. Apgar's score in the 5th minute was measured as 10. The baby had ichthyosis of the scalp, face and neck with outward pouting of lips or fish mouth, compressed ear pinna and open eyes because of the outward turning of eyelids from the eyeball. The head was characterized by a scalp with partial hair loss (alopecia) (Figure 1). The newborn at birth was not evaluated for markers of inflammation, electrolytes and so on. The baby was sent to the neonatal intensive care unit (NICU) upon delivery. The nurses tried several times to get an intravenous line (IV) from the neonate, but they failed. Hence, 2 days later, the baby was transferred to the neonatal unit. According to the physician's recommendation, no antibiotics were administered. The skin management included eye softeners, saline compresses and gentle emollients. However, he died on the 5th day.

The parents had a distant relationship and had no similar condition of HI in the previous pregnancy or family history. They had a healthy child. In her second pregnancy, she had delivered a stillborn male infant at 38 weeks' gestation due to diminished foetal movement and delay in reaching a hospital.

Discussion

HI is the most severe autosomal recessive genetic disorder, which occurs due to mutation in the ABC transporters ABCA12, a cell membrane transporter associated with lipid transportation.^{1,20} Foetuses carrying this mutation have defective lipid secretion within epidermal keratinocytes, resulting in a loss of the skin lipid barrier and the development of HI.²⁰ The prevalence of the disorder is 1 in 300,000 live births.^{15,17,21,22}

The likelihood of mortality for infants with HI is high, their prognosis is poor, and most neonates die a few days after delivery due to respiratory distress, infection, heat loss and dehydration.¹⁰ However, the survival rate is related to the type of mutations. Infants with the compound heterozygote mutation survive more than those with the homozygote mutation.²³ In a study by Elkhatib and Omar,²⁴ the age range of HI patients who survived the early neonatal period ranged from 10 months to 25 years, and the average survival rate was estimated at approximately 55%. In this study, the baby died on the 5th day. In previous studies conducted in Iran and Eritrea, infants with HI died after only a few days (range = 2–14 days).^{25–28} With the recent advances in neonatal care in developed countries, many affected babies can now survive to adulthood.^{4,18} Iran is yet to attain this stage of advancement, but with awareness creation and improvement in newborn care, this category of newborns may have better chances of survival.

Since the risk of pregnancy recurrence is 25%, prenatal ultrasound and genetic analysis are highly important.^{10,29} Ultrasonography is a common clinical method used to diagnose HI.³⁰ Next generation sequencing (NGS) is a technology that can be used to diagnose rare genetic disorders like congenital ichthyosis. Indeed, this technology is designed to reveal causal mutations in groups of genes associated with one or more genetic diseases.³¹ NGS has changed the landscape of genetic testing, especially in rare inherited diseases,³¹ and has significantly improved clinical diagnosis compared to traditional sequencing methods.^{32,33} Fioretti et al. conducted a study to identify the genetic cause of the disease in four Italian patients using NGS targeting 4811 genes. They demonstrated that multigene NGS in clinical settings is a powerful technology for diagnosing rare heterogeneous genetic disorders, such as autosomal recessive congenital ichthyoses.³⁴ Although NGS is the standard technique for detecting HI, clinical investigation and ultrasonography are necessary for a safe diagnosis.³⁵ Foetal DNA analysis can be offered to parents who had a previous child with HI.³⁶ A study suggested that messenger RNA analysis using hair samples can also more easily and less invasively be used to identify ABCA12 mutations.³⁷ In some cases, prenatal ultrasonography may allow the detection of signs suggestive of HI, including eclabium, ectropion, rudimentary ears, contractures and dense floating particles in amniotic fluid.³⁸

Early retinoid therapy and the administration of antibiotics may improve the prognosis of HI.³⁹ It has been shown that in neonates with HI, early use of systemic retinoids can promote accelerated shedding of the hyperkeratotic plates, and continued use reduces scales and improves ectropion and eclabium.⁴⁰ A study in 2021 reported that systemic retinoids administration might have effective auxiliary therapeutic effects on the reparation of eyelid anatomy in HI infants.⁴¹ Cosio et al.⁴² reported that retinoids (e.g. trifarotene) could increase tolerability and treat acne and congenital ichthyosis. Rajpopat et al. assessed the clinical outcomes of 45 cases of HI. They suggested the early introduction of oral retinoids can improve survival. Of the 45 babies, an oral retinoid drug was given to 24, and 20 (83%) survived.³⁸ Some studies reported in some cases, the use of acitretin can inhibit wound healing.^{21,38} In a case study, an HI neonate was treated at 4 months of age after receiving intensive neonatal care and acitretin at 0.5 mg/kg per day.⁴ In a novel randomized controlled trial study, vitamin D intake was proposed as a promising alternative for managing congenital ichthyosis compared to acitretin.⁴³ However, despite the protective effects of retinoids on ischemic injury, some studies do not suggest retinoid therapy in infants (and recommend not to preclude them to a surgical intervention).⁴⁴ Tsvilika et al. suggested that, although applying topical retinoids have been suggested as an alternative to surgery, no satisfactory results have been seen in most cases. They also pointed out that Vitamin D intake should be considered to avoid the retinoids' side effects.⁹

Surgical interventions can also be used for the management of HI. Tsvilika et al., in a narrative review, assessed the effect of surgical interventions on the management of HI. In their review, surgical interventions were reported to treat eyelids and the digits' necrosis.⁹ Previous research suggested early surgery has a beneficial therapeutic effect in HI cases.^{44,45} No evidence was found that early surgery resulted in less ectropion at 6–12 months of age.^{46,47} The surgical procedure is not without risks.⁴⁸ Surgical wounding may increase infection.⁴⁷ Surgical procedures may pose a risk factor for iatrogenic injury.⁴⁵ HI surgical and general management can be quite challenging. Further studies are needed on this matter.⁹

Patients with HI should be hospitalized in a tertiary care centre with a level III NICU. Intensive care management is largely supportive and includes a multidisciplinary team, including nursing personnel, physical therapy specialists, an orthopaedic team, plastic surgeons, ophthalmologists, otolaryngologists, geneticists, dermatologists and neonatologist.^{4,49,50} The nursing team, especially the nurses play a primary role in maintaining skin integrity, preventing infections in hospital and extra hospital care, and providing family and caregivers with guidelines and support required.⁵¹ Moraes et al. suggested that implementing the nursing process, especially the care plan, is essential for the multidisciplinary success of the treatment. The nursing

team must act intensely to reduce the chances of infection during hospitalization.⁵¹

The primary care for infants with HI is postnatal blood circulation, the establishment of an airway and breathing. Saline compresses and gentle emollients should be used to keep the skin soft and to accelerate the desquamation.²⁵ Research suggested that affected neonates should be maintained in an incubator with additional humidity.^{51,52} Constant monitoring of the kidneys and liver is important. Urine output, daily weight and serum electrolytes should be monitored. Also, an important factor for increased survivability during neonatal management is the prevention of infections.⁹

Conclusion

HI is a rare genetic skin disorder. HI should be considered as a severe chronic disease that is not invariably fatal. HI management is complex. Therefore, a multidisciplinary approach and robust communication between the medical team, healthcare providers and family members are necessary for the long-term care of these patients. Also, because HI is very painful, a proper balance between pain relief and avoidance of serious side effects, which is a major challenge for caregivers, is required. Prenatal diagnosis of HI principally via sonographic techniques is important in managing the disorder. Moreover, since most infants do not survive neonatal, parents should be given appropriate support by healthcare workers and psychologists. The number of survivors is increasing with improved neonatal care, the early introduction of oral retinoids and surgical interventions.

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Author contributions

M.N. and M.S. collected the patient information. All authors were active in drafting, editing and approving the final manuscript. All authors read and approved the final manuscript.

Availability of data and material

Data sharing is not applicable to this article as no data sets were generated or analysed during this study.

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Ethical approval and consent for publication

This case report was approved by the Ethics Committee of the Shoushtar Faculty of Medical Sciences (reference no. 010).

Informed consent

Written informed consent was obtained from the legally authorized representatives of the child for his or her anonymized information to be published in this article.

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