

## **Case report**

### **“A neonate with diamond-shaped yellowish scaling of the skin: a case report on Harlequin Ichthyosis”**

#### **Abstract:**

Harlequin Ichthyosis is an extremely rare genetic disorder of the skin with a mortality rate of 44%. It is inherited in an autosomal recessive pattern, pointing towards the role of consanguinity among parents as a contributing factor. We present a unique case of a Harlequin baby whose parents' marriage was nonconsanguineous with no family history of the disease on either side. The antenatal ultrasound scans were normal as well with oligohydramnios as the only prominent feature a week before delivery. Hence, leading to a low suspicion and delayed diagnosis of an already extremely fatal condition. A two-hour-old female baby presented with generalized yellow scales and fissures covering the body in a diamond-like pattern, along with ectropion, eclabium, abnormal digits, clubfeet, and contractures in the extremities. The chest and abdomen were covered with thick scales as well, but the ear and anal canal were patent. Based on these findings, a clinical diagnosis of Harlequin Ichthyosis was made. Supportive management with a multi-disciplinary approach was started, focusing on temperature regulation, nutrition supplementation, eye & skin care, and pain control. However, the next day the patient developed respiratory distress and was put on CPAP. Due to skin hyperkeratinization, intravenous access could not be maintained. Instead, umbilical catheterization was used as a source of nutrition and medicines. Her condition kept deteriorating leading to tachycardia, tachypnea, and sudden onset of apnea eventually leading to a need for intubation. Being aware of the associated complications and poor prognosis the parents decided to withdraw supportive care leading to death soon after. Since the characteristic findings on antenatal scans are usually not seen until the last trimester, we emphasize the importance of

early confirmatory diagnosis via genetic screening as delayed management leads to even worse outcomes. Additionally, we also recommend counseling the parents for future pregnancies due to the recurrence of the disease.

**Keywords:** Harlequin Ichthyosis, Collodion Baby Syndrome, Congenital Nonbullous Ichthyosiform Erythroderma, Nonbullous Lamellar Ichthyosis, case report.

### **Introduction**

Harlequin ichthyosis (HI) is an extremely rare autosomal recessive disorder affecting one in every 300,000 births.<sup>1</sup> It is caused by an interruption in the lipid and protease transfer to the lamellar granules in the epidermal granular layer due to mutations in the lipid transporter adenosine triphosphate binding cassette A12 (ABCA12) in the keratinocytes. Lamellar granules are essential for antimicrobial peptide transport and secretion. Their transport dysfunction impairs innate immunity causing an increased risk of skin infections in HI patients.<sup>2</sup> Neonates also become more prone to other complications, including dehydration, sepsis, and respiratory insufficiency, increasing the fatality rate of the disease to 44 percent.<sup>4</sup> As a result, early detection and treatment are critical in reducing neonatal mortality, manifesting primarily within the first two months of life. We present a sporadic case of a Harlequin baby with oligohydramnios as the dominant feature on a prenatal ultrasound scan a week before delivery. There was no family history of the disease, and the fetus was the result of a non-consanguineous marriage. Hence, fetal DNA analysis could not be performed, preventing early diagnosis in our case.

### **Case History:**

A two-hour-old female presented to the pediatric nursery for the evaluation of armor-like skin and the assessment of the anomalous condition of the newborn. The patient was born out of a non-

consanguineous marriage at thirty-four weeks of gestational age, weighing 2.5 kilograms, and delivered through cesarean section. Her mother, a 37-year-old female with gravida six and parity five, underwent an elective lower segment cesarean section due to breech presentation and decreased fetal movements. No anomalies were detected on earlier ultrasound (US) scans; oligohydramnios was found one week before delivery. Maternal medical history was unremarkable. As per the parental report, there was no history of abortion, stillbirths, or congenital malformations in previous pregnancies.

At the time of birth, the neonate had widespread, diamond-shaped, thickened, yellowish plates covering the entire body like armor (Figure 1). Erythematous fissures separated the scales that bled from the creases. Other evident facial features included ectropion, eclabium with a wide-opened mouth, small nose with a depressed nasal bridge, absent eyelashes and eyebrows, and small pinna with no identifiable ear canal (Figure 2). Contractures were present in the extremities with abnormally shaped digits and notable clubfeet.



Caption (Figure 1): Generalized thick, yellow, hyperkeratotic scales with deep erythematous cracks covering the entire body like armor.



Caption (Figure 2): Bilateral ectropion, eclabium, depressed nasal bridge, and thick encasement of face with scales seen on day 1 of birth.

On physical examination at admission, her vitals were as follows; temperature 98.6 F, respiratory rate sixty-four breaths per minute, and pulse 140 beats per minute. The anterior fontanelle, when palpated, was open, soft, and flat. The chest was normal in shape, covered with thickened skin, and moved equally on both sides with respiration. There was bilateral equal entry of air with no intercostal or suprasternal recessions. The abdomen was soft, slightly distended, covered with scales, and moved with respiration. The umbilical stump was healthy and clamped with visible bleeding from the ends. Anal canal was found patent. The heart sounds were of normal intensity on auscultation. No added sounds or murmurs were heard. Peripheral pulses were palpable, with a capillary refill time of two seconds. Neurological examination revealed diminished rooting, sucking, and grasping reflexes due to wide-opened mouth, eclabium, and skin contractures, respectively. Moro reflex was absent. Tone was normal. Pupils were round, equal, and reactive to light bilaterally.

The patient underwent the following laboratory evaluations: complete blood count, electrolyte assessment, renal and hepatic function tests, and blood culture. These all returned within normal limits except for a deranged PT/INR.

Given the severity of the dermatological findings, the neonate was assessed by a pediatrician as well as a dermatologist, and a clinical diagnosis of Harlequin Ichthyosis (HI) was made. The patient was also reviewed by an otolaryngologist, an ophthalmologist, and a pediatric surgeon for their expert opinions on the various findings. Parents were counseled about the disease spectrum in depth.

The patient was kept in a high-humidity incubator, and oxygen was given via a non-rebreather mask. Nutrition was initiated via a nasogastric tube. Intravenous access was gained for the maintenance of fluid and electrolyte balance. Sterile moist gauzes, lubricants, and antibiotic ointment were applied for eye care. The cutaneous surface was washed with normal saline, and white soft paraffin and liquid paraffin were then generously applied all over the body surface twice a day. Retinoid capsules dissolved in olive oil were injected at a dose of 0.5/kg/day.

On day two, the patient started developing respiratory distress with suprasternal recessions, which prompted the discontinuation of the nasogastric tube to prevent aspiration. Continuous positive airway pressure (CPAP) was maintained by a bubble CPAP at 4cm of water. Intravenous access could no longer be maintained due to further thickening and crusting of skin; therefore, pediatric surgery was consulted to perform umbilical catheterization to continue nutrition and medications.

On day three, the patient developed tachycardia and tachypnea. Intravenous cefotaxime and amikacin were administered twice a day as prophylaxis for suspected sepsis. Labs revealed deranged PT/ INR for which Vitamin K was administered.

On the fourth day of life, the patient developed sudden onset of apnea coupled with bradycardia, necessitating cardiopulmonary resuscitation. The patient was successfully revived with high-quality CPR.

However, the patient's condition worsened within fifteen minutes, warranting intubation. Given the course of the disease and the associated poor prognosis, the family elected to withdraw supportive care. The patient died soon after. In addition to providing psychological support to the parents, genetic counseling was recommended for future pregnancies.

### **Discussion:**

Harlequin Ichthyosis has an autosomal recessive mode of inheritance, meaning that consanguinity between parents plays a pivotal role in its etiology.<sup>3</sup> In addition, previously performed studies on HI displayed a strong association of consanguinity between parents, older affected siblings, or siblings with any inherent dermatological condition with a subsequent Harlequin fetus.<sup>4</sup> Therefore, a detailed account of family history and information about previous pregnancies is crucial in perinatal diagnosis. However, in our study, the parents were not related to each other, and there were no other associations found within the family history either. Since fetal DNA analysis is only recommended for those with prior family history, the antenatal screening depends solely on ultrasonography for de novo mutations.<sup>1</sup> Thus, hindering early diagnosis in our case, considering the rarity and the overlapping features of the disease with other similar dermatological conditions.

After birth, the condition is diagnosed by viewing the characteristic anomalous features of the patient. Physical examination reveals generalized thick, yellow, hyperkeratotic scales with deep erythematous cracks, bilateral ectropion, eclabium, eyelid eversion, thick encasement, a flat nasal bridge, and contractures of all extremities, hyperflexion of fingers and toes due to hyperkeratosis.<sup>5</sup> These cutaneous constrictive bands cause restricted mobility and present as hyper-flexed toes with incurved and clenched fingers. This may lead to digital ischemia and gangrene, as reported if left untreated.<sup>6</sup> A clinical diagnosis was made after the aforementioned was observed in our fetus.

A multidisciplinary approach, including dermatologists, ophthalmologists, geneticists, and pediatricians, is needed to deal with the numerous complications and associated comorbidities of the disease. In fact, an important aspect of the multidisciplinary approach is to counsel the parents, provide them with psychological support, and discuss their concerns and fears, as the general outlook of the neonate might terrify them. They should be encouraged from the beginning to take part in the neonate's care and to have a strong parent-child relationship. Skin-to-skin contact is essential; hence, parents should be trained to bathe the child and apply topical medication.<sup>7, 8</sup> Breastfeeding should also be initiated; however, care should be taken to avoid it if the risk of aspiration exists, as seen in our patient. All these measures will help to make sure that the parents are mentally ready to take care of the child.

Early management of HI includes a humidified incubator, temperature regulation, nutrition supplementation, eye care, pain control, and skin therapy. A humidified incubator with rigorous temperature regulation is essential to reduce the transcutaneous water and heat losses caused by the dysfunctional epidermal permeability barrier. Since remarkable caloric drain in HI infants can cause growth retardation, nutritional replacement is crucial, and up to 25% additional calories per day might be required compared to a healthy neonate.<sup>6,9</sup> Ectropion can be initially treated with artificial tears and antibiotic ointment. Pain management is important as the deep cutaneous fissures are agonizing, and painful truncal fissures might restrict deep breathing, increasing the risk of pulmonary complications and developmental delay.<sup>10-12</sup>

Skin care is of utmost importance. Patients should be bathed to soften and expedite the shedding of the thick stratum corneum to reduce the risk of skin infections. Emollients should be applied to the skin several times a day to protect the infant against foreign pathogens and reduce transcutaneous water

loss. Systemic retinoids are the treatment of choice and should be started as soon as possible. They increase the shedding of the hyperkeratotic plates. Acitretin is the favored retinoid because it has a shorter half-life and a better safety profile.<sup>13</sup> However, since the epidermal barrier is compromised and cutaneous absorption is enhanced, topical keratolytic should be avoided as potential systemic toxicity may occur. Systemic retinoid therapy causes sufficient keratolysis, making the use of potentially toxic topical keratolytic unnecessary.

Sepsis is quite common in the first month before the healing of deep fissures has occurred and is the leading cause of death in these patients. Therefore, a strict check should be kept for signs of sepsis, and aggressive treatment of bacterial or fungal infections is important. However, there is no proven benefit of antibiotic and/or antifungal prophylaxis; they may even be detrimental as they favor the growth of *P. aeruginosa* in burn wounds and enhance the risk of candidemia.<sup>14</sup>

HI has a poor prognosis, and the survival rate depends on the severity of the disease. With a mortality rate of 44%, neonatal demise occurred between day one and day fifty-two, as reported previously. Fulminant sepsis, respiratory failure, or their combination comprise 75% of these deaths.<sup>4</sup> Thus, it is imperative that antenatal screening is performed, and a pertinent history is taken to enhance the perinatal management provided as well as to prepare the parents for the possible outcomes. Prenatal diagnosis of HI can be made using antenatal ultrasonography. Sonographic findings such as a large open mouth, a flat nose, abnormal position of limbs, ectropion, and later; intrauterine growth restriction, short limbs, echogenic amniotic fluid, floating membranes, and polyhydramnios can be found.<sup>15</sup> The three-dimensional US aids in the better visualization of these features and hence the early diagnosis. However, these phenotypic findings are not detectable before the third trimester, and a confirmatory diagnosis can only be made after testing for the ABCA12 gene in the affected fetus. Early diagnosis via

genetic screening may aid in counseling the parents for future pregnancies and the recurrence of the disease.

### **Conclusion:**

Harlequin Ichthyosis is a rare congenital skin keratinization disorder with an autosomal recessive pattern of inheritance. Genetic counseling and genetic screening for ABCA12 mutation with prenatal investigations, e.g., amniocentesis or chorionic villus sampling, is essential in susceptible families. Antenatal ultrasonography can aid in prenatal diagnosis. Neonates are given symptomatic treatment, and nutrition is maintained. Prophylactic antibiotics play no role in improving the prognosis of the disease, which is poor.

### **Declarations**

**Authors' contributions:** MK made significant contributions toward the design and interpretation of the study and drafted the original manuscript as well as made critical revisions. SIS conceptualized the study, contributed to its acquisition, wrote the original draft, and critically revised the study; ZW made substantial contributions toward the design and acquisition of the study data, and wrote the original draft. OP was involved with the acquisition and interpretation of the study and contributed to the original work. All authors read and approved the final manuscript and are equally accountable for all aspects of the work, ensuring integrity and accuracy, according to the current ICMJE authorship criteria.

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