

# Management of Harlequin Ichthyosis and Associated Complications

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## Background

Harlequin Ichthyosis is a rare acquired autosomal recessive disorder most commonly associated with a mutation in the *ABCA12* gene. This mutation leads to a loss of function of epidermal lipid transport, which is crucial for lamellar granule maturation. With this disruption in lipid transport and ineffective lamellar granules, the epidermis does not adequately form or desquamate and becomes ineffective as a barrier from the environment. At birth, patients will present with leathery, thick scales separated by deep fissures. Other physical exam findings include ectropion, eclabium, absent/smaller ears, and contractures of fingers and toes. Diagnosis can be made with amniocentesis to test for *ABCA12* genetic mutation. However, early recognition of characteristic findings are difficult on fetal ultrasound. Ectropion, eclabium and contracture of fingers and toes can sometimes be appreciated on 3D ultrasound. However for some, diagnosis is not recognized until birth. Due to ineffective skin barrier, multiple disciplines are required in addition to dermatology in the management of these infants due to multiple complications. Prognosis initially was poor with most infants dying within the first few days of life. Prognosis has significantly improved with early neonatal care and adequate management with systemic and topical retinoids. This case studies evaluates the multiple subspecialties and care involved with these patients.

## Pregnancy and Delivery

- Pregnancy complicated by Fibroids, Uti, and Pre-Eclampsia to a 25 year old G1 now P1 mother at 38w+6d
- Patient had an anatomical ultrasound that was unremarkable and low risk quad screen.
- Patient had difficulty with descent; ROM lasted >24 hours after pushing 1.5 hours and no change in station , patient was delivered via C-section
- NICU team was present due to mother requiring magnesium during delivery for preeclampsia
- Infant cried immediately at delivery, however it was immediately recognized that infant had ichthyosis at birth with large scales and thick leathery skin with deep fissures in addition to ectropion bilaterally with conjunctival injection, eclabium, bilaterally ears scaling filling external ears.
- Patient was taken to the resuscitation island in a plastic bowel bag and immediately placed in an isolette
- APGARS 9 and 9
- Patient was stable on room air and transferred to the NICU floor



Pictures at birth depicting deep scales, fissures, and scales. Pictures Courtesy of Dr. Turchan and Dr. Hicks.

## Hospital Course and Complications

- **At birth**, patient was placed in an isolette with humidity at 70% while patient was covered in gauze with vaseline. Lacrilube was applied to the cornea bilaterally. Patient was started on morphine Q4hr. Due to prolonged rupture of membrane patient was started on amp and gent with sepsis rule out with blood cultures, which eventually were negative. Patient was under contact isolation requiring sterile gloves. Genetic testing was sent on DOL 1 and resulted many weeks later found to be homozygous for loss of function of *ABCA12* gene.
- **DOL 3**: Patient was started on small volume PO feeds during DOL 2 and tolerated well. Continued skin care management with vaseline and gauze dressing changes 2 times per day. No bathing at this time. Patient was started on systemic retinoids with acitretin 0.5 mg/kg/day and topical retinoid tazarac 0.1% on the hands, feet, and eyelids. Daily BMPs were followed.
- **DOL 4** added erythromycin eye ointment to treat conjunctivitis and humidifier decreased to 50% humidity due to elevated temperatures.
- **DOL 6** Patient underwent dermal tissue release of the hands and feet, this acutely improved perfusion to fingers and toes. Retinoid was increased systemic retinoid from 0.5mg/kg to 1mg/kg.
- **DOL 7** Methadone 0.1 mg/kg every 8 hours was added for better pain management. Versed and Tylenol were added PRN. Patient was started on bleach bath once a day w/ 1:10 Dakin’s solution to sterile water solution, with redressing with sterile water rinse and re-dress.
- **DOL 9**: Strictures were rereleased on distal upper and lower extremities. Lipid panel followed with CMP, found to be normal.
- **DOL 17**- ENT was consulted and recommended mineral oil BID, would like to debride external ear canals and will perform when discharged. Hearing screen was performed and failed. Methadone was not needed any longer.
- **DOL 18**: Patient had G-tube placed. Patient was taken out of his isolette.
- **DOL 19**: Vitamin D was closely monitored and patient was started on a zinc supplement. G-tube feeds commenced. Pain was better controlled with PRN morphine and versed.
- **DOL 22**: Patient experienced autoamputation of 2<sup>nd</sup> and 3<sup>rd</sup> digit, Vitamin D was 37 and goal was for vitamin D level >40mg/dL. Added 0.5ml vitamin D supplement. Patient no longer needed sterile gloves, however still under contact isolation. Tub bath now permitted with gentle cetaphil soap.
- **DOL 26-27**: Patient had been on excessive narcotics and scoring for withdrawal was initiated. Patient had elevated scores and was given PRN morphine.
- **DOL 29**: Pain has improved significantly, showing very low withdrawal scores, thought to be due to significantly impaired scales. Scoring was ended on DOL 33.
- **DOL 37**: Patient was found to be positive for MRSA colonization. Patient continues to work on PO feeds. Patient is still not back at birth weight, electrolytes have been stable during hospital stay.
- **DOL 40**: Fluid goal was increased to 170 ml/kg/day.
- **DOL 46**: Patient was discharged home with close follow up with multiple subspecialists including dermatology, ophthalmology, ENT, infectious disease, genetics, orthopedics, plastic surgery.



Above is another view of patient at birth. Below is patient prior to discharge.



Below is patient at most recent dermatology appointment.



## Discucssion

- As seen below, management of this patient requires many specialists involvement. Below is broken down analysis by specialty of management specific to this patient and special considerations involving a handful of cases of Harlequin Ichthyosis studied worldwide.
- **Dermatology**: Patient is at high risk of morbidity and mortality due to ineffective skin barrier. Management involved early introduction of systemic retinoids and topical retinoids which have shown significant improvement for survival rate. Patients require lifelong intense skin care routine requiring bleach baths and BID application of Vaseline and gauze covering. Ongoing treatment with systemic retinoid debated, however this patient was on systemic retinoid w/ acitretin which was discontinued few months after birth.
  - LFTs, Lipid panel, BUN, and creatinine need to be monitored monthly while on retinoids, especially acitretin.
  - Topical exfoliates such as sacylic acid lead to increased risk of mortality and are not recommended
  - Pain management is crucial.
  - Thermoregulation is often difficult for these patients, even well into life.
- **ENT**: Patient had a large amount of debris in the ears leading to hearing difficulties. Vacuuming of external ear canal necessary for care. Debridement should be done carefully as to not further disrupt the skin barrier. Patients need close follow up with audiology as well due to high risk of hearing difficulties mostly secondary to skin in external ear canal.
- **Ophthalmology**: Due to ectropion, increased risk of keratosis, conjunctivitis, and corneal abrasions. Generous application of lacrilube to prevent complications and for treatment of conjunctivitis with erythromycin. Often times patients also require upper eyelid reconstruction, which this patient requires later in life. Surgery has to be carefully considered and planned due to the increased risk of infection.
- **Pulmonary**: This patient was adequately ventilating and did not require support, however is often a complication for patient’s due to significant pain associated with scales and fissures. Often times patients will require respiratory support.
- **Nutrition and GI**: These patient are susceptible to electrolyte imbalances due to insensible water loss. Patient also requires increased caloric goals for weight gain due to this insensible loss.
  - Rickets is another complication involved with these patients however unclear etiology. May be secondary to nutritional deficiencies or retinoid use. This is clinically followed with regular vitamin D levels. This patient was given a vitamin D supplement to assist in preventing this complication.
  - The patients also often times have difficulty with feeds due to eclabium, with inability to properly PO. Often times these patients will require NG tubes or G-tubes, as our patient required a G-tube. Patient will continue to work on PO feeding.
- **Pediatric orthopedics and Plastic surgery**: Due to contractures and requirement for repeated tissue releases as was seen during hospital stay with our patient. Occasionally, a compartment syndrome can occur which can progress to autoamputation. Physical therapy and occupational therapy are required well into life due to difficulty with contractures.
- **Infectious Disease**: Sepsis is very serious complication in patients with Harlequin ichthyosis and increased risk of morbidity and mortality. It is imperative there is a low threshold for sepsis work up and involvement of infectious disease. This patient had MRSA colonization, however remained clinically stable, and no intervention was performed.
- **Genetics**: Important to evaluate exact mutation, in this case *ABCA12* homozygous recessive- this is the most severe of the mutations.
- **Psychology and Palliative care**: Palliative care important and psychology as well due to life long concerns with appearance and need for further support in this difficult disease.

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