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# A COMPREHENSIVE REVIEW OF GENETIC DISORDER: HARLEQUIN ICHTHYOSIS

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ABSTRACT

Harlequin ichthyosis is the most severe form of autosomal recessive congenital ichthyosis. The affected neonate is born with a massive, horny shell of dense, plate like scale and contraction abnormalities of the eyes, ears, mouth. HI case treated with acitretin, focusing on the multi-faceted management of the disease. It is usually treated with supportive care and prenatal diagnosis for early findings. The prognosis improves once the baby survives the first few weeks. Physical development may be delayed by the abnormal calorie needs their skin function demands, but mental and intellectual developments are expected to be normal.

## INTRODUCTION:

Harlequin ichthyosis (HI) is a rare form of congenital ichthyosis. Over the first months of life, the hyperkeratotic covering is shed, revealing a diffusely erythematous, scaly epidermis, dry, rough plates of skin with deep cracks in between skin which persists for the remainder of the patient's life.[1,6] The majority of affected individuals being homozygous for mutation in the ABCA 12 gene.[2,3] This condition presents with a wide range of severity and symptoms. The gene plays in the production of a protein that transports fats into the outer layer of the skin and helps in its development.[4] The ABCA 12 gene is believed to encode a transporter protein involved in the transport of epidermal lipids across cell membranes. Identification of this gene will make DNA-based prenatal diagnosis possible.[2]


## CAUSES

Harlequin ichthyosis was traced to the ABCA12 gene

- Genetic disorder that occurs due to a mutation in the ABCA12 gene.
- The ABCA12 gene is inherited by the baby from its parents.[5]
- Defected in the gene not allow the proper development of the skin.
- Individuals must inherit two recessive genes in order to show the disease, one from each parent, but the parents ("carrier") show no signs of the ichthyosis.[2]
- It can cause tissue injury resulting in necrosis and auto-amputation.[4]

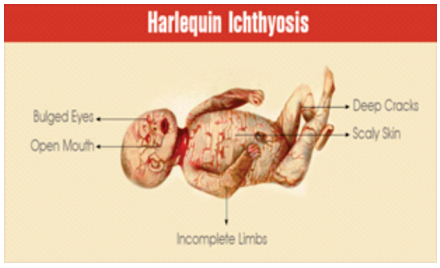
## SIGNS AND SYMPTOMS

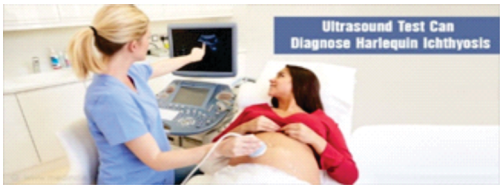
HI affects the skin. The baby is born with the following features:

- The skin is thick, dry and diamond-shaped plates separated by deep fissures
- The eyes appear bulging due to the pulling back of the eyelids revealing the red inner linings due to tightness
- The mouth appears open due to the pulling back of the lips leads to unable proper breathing and feeding.[4,6]
- The outer part of the ear may be absent, making the ears look like holes and nose appears flat
- The movement of the limbs may be restricted due to incomplete development.
- The hands and feet may be small, swollen, and partially flexed.[5,6]

## DIAGNOSTIC EVALUATION

- The physical examination of the baby, which reveals the typical appearance of the skin Genetic testing
- can detect the abnormal genes and confirm from prenatal diagnosis. Ultrasound during pregnancy
- may raise suspicion of the condition.
- Fetal cells obtained through a procedure called amniocentesis r chorionic villus biopsy can be subjected to genetic tests.[7,8]




- **PRENATAL DIAGNOSIS**
- Fetal DNA analysis and ultrasound technology have replaced the more invasive techniques of fetal skin biopsy.1 Fetal DNA analysis can be offered to parents who had a previous child with HI.
- Fetal genomic DNA is obtained from amniotic fluid via amniocentesis or chorionic villus sampling.[8] New research has shown that messenger RNA analysis using hair samples can also more easily and less invasively be used to identify ABCA12 mutations.[9]
- Prenatal ultrasonography may allow detection of signs suggestive of HI, including eclabium (turn outward lip), ectropion eye, rudimentary ears, contractures, and dense floating particles in amniotic fluid ("snowflake sign"). The application of 3D ultrasound theoretically offers a greatly improved analysis of facial morphology and may aid in prenatal diagnosis for detection of unusual features requires tertiary expertise, and they are not detectable until the second trimester, excluding the option of early termination.[10]

## MANAGEMENT

### MEDICAL MANAGEMENT

Intensive care management (Level III NICU) is largely supportive and involves a multidisciplinary team, including neonatology,

dermatology, genetics, ophthalmology, otolaryngology, orthopaedic and plastic surgery, nutrition, physical therapy, and nursing.

- Harlequin ichthyosis demands a proper skin care regimen to keep the skin moisturized and to prevent cracking and fissuring that may lead to infection.[3]
- Most harlequin infants will need one-on-one nursing care for the first several weeks of life. Most of the fatalities from this condition occur in the first few days of life, many of the successes attributed to etretinate use in the medical literature may be equally due to the high quality of care in the immediate new-born period and to a less severely affected new-born.
- The baby should be kept in humidified incubator to maintain its body temperature and provide humidified air. The environment should be sterile to prevent infection till the baby's condition stabilizes
- Adequate fluids and electrolytes should be given to prevent dehydration
- Administration of oral etretinate (1 mg. /kg. body weight) may accelerate shedding of the thick scales. It takes a week or two for etretinate to work loosening the scales with gradually peel off.
- Antibiotic treatment may be necessary to prevent infection at this time.
- Surgery may be required to relieve skin tightening and improve function of limbs
- Regular follow-up of the patient will help to diagnose and treat any problems arising from the condition or its treatment
- Some new-borns with harlequin ichthyosis will not survive, even with the best of care, because of the severity of their condition.

## SKIN CARE

Skin barrier dysfunction in neonates is especially problematic, given the large body surface-to-weight ratio.[13] Skin care should include once to twice daily cleansing to hydrate and promote shedding of the stratum corneum.[12] some suggest daily buffered dilute hypochlorite baths.11It is process by dampening roll gauze with warmed 0.125% sodium hypochlorite mixed 1:10 with warmed sterile water. The optimal pH is 8 to 8.5. The gauze can be applied as a wet wrap, occluded with a plastic wrap layer for 10 to 20 minutes.[9] A bland emollient should be applied immediately after wet wrap removal. Products, such as jelly, coconut oil, sunflower seed oil, are considered safe.[15,16] The authors recommend handling infants with sterile, latex-free gloves to minimize spread infection.[10]

## RETINOID THERAPY

The use of systemic retinoid therapy is standard-of-care in the management of HI, following a reported 83% survival among 25 treated infants compared with 24% survival of 21 infants who did not receive an oral retinoid.[8] However, these results must be interpreted with some caution, because half of the untreated infants died within 3 days after birth, which is earlier than when retinoid therapy is usually available for administration. Another study documented a 92% survival rate among 12 infants treated with retinoid compared with 50% among those not treated.[16]

Several oral retinoids have been used for HI as well as congenital ichthyoses, including etretinate, isotretinoin, and acitretin.[12,15,18] The first successful neonatal use of acitretin in HI was reported in 2001[18] at a dose of 1 mg/kg per day, started on day 10 of life. Acitretin administration has been the retinoid most often used by the authors. Additionally, compounding isotretinoin rapidly isomerizes the 13-cis molecule to all-trans retinoic acid, which may have greater toxicity than the aromatic acitretin.[18]

Treatment initiation within the first 7 days of life is recommended for all infants who can tolerate the medication.[9] However; neonatal acitretin administration has been hindered by a lack of commercially available liquid formulations in the United States.

## NUTRITION:

HI neonates has increases caloric demands for skin turnover [7,11] Once an adequate suck and swallow has been established, breastfeeding should be encouraged to enhance bonding between mother and child.[10,12] Inadequate suck to maintain caloric needs has been noted in infants with HI, and long-term supplemental tube feeding may be required. Vitamin D deficiency and rickets have been reported in neonates with ichthyosis[16,17] and increased risk of neonatal sepsis.[17]

## FAMILY COUNSELLING

- There are approaches that can foster bonding between the family and infant. Touch should be encouraged. Sharing photographs of survivors to family members has been a beneficial intervention[17]
- Healthcare teams to educate and prepare families before discharge for the prolonged care that will be necessary at home. Several Web sites are available for family and patients, including the Foundation for Ichthyosis & Related Skin Types (FIRST) at http://firstfoundation.org
- Physical and occupational therapy is key to optimizing range of motion in infancy and childhood as the hyperkeratotic skin can lead to constriction of limbs and digits, affecting fine and gross motor skills.[3,12] Some infants and children may display impaired cognitive and social functioning, making speech and language therapy necessary.[1,6]

## COMPLICATIONS

- Loss of water, resulting in dehydration
- Life-threatening infections.
- Inability to regulate body temperature
- Breathing difficulties and respiratory failure

## CONCLUSION

HI is a rare skin disorder. It follows autosomal recessive mode of inheritance. Prenatal diagnosis should be offered to women with previously affected babies. An understanding of the ABCA12 mutation and skin barrier disruption provides a basis for therapy. The surviving children are now in their teenage years, with several in their twenties display dry, reddened skin, which may be covered by large thin scales, and sparse hair. Supportive care from health team is required for effective management in the absence of data to the contrary, the authors believe it is advisable to institute early retinoid therapy.

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