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# HARLEQUIN ICHTHYOSIS: A REVIEW OF DERMATOLOGICAL EMERGENCY

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**ABSTRACT**

Harlequin ichthyosis (HI) represents the most severe and impactful type of autosomal recessive congenital ichthyoses (ARCIs). This condition arises from mutations in the ABCA12 gene, which disrupts the deposition of intercellular lipids in the stratum corneum, leading to significant defects in the skin barrier. Infants typically present at birth, often prematurely, exhibiting thick, yellow, hyperkeratotic skin plates with pronounced erythematous fissures, resulting in a distinctive facial appearance. Historically, harlequin ichthyosis has been viewed as a fatal condition, with treatment primarily focused on palliative care. However, recent observations indicate that with appropriate neonatal care and the early administration of oral retinoids, survival rates for affected infants are improving. The identification of ABCA12 mutations allows known carriers to pursue preventive preimplantation and prenatal genetic testing. Additionally, experimental research has demonstrated the potential for restoring lipid secretion in lamellar granules through corrective gene therapy. Ongoing studies are essential to explore alternative treatments to retinoids for managing HI.

**KEYWORDS**: Harlequin ichthyosis, Autosomal recessive congenital ichthyoses (ARCI), Genetic mutation, ABCA12 gene, Keratinization, Harlequin fetus, Armor-like layer of skin, Prenatal diagnosis, NICU.

## INTRODUCTION

Ichthyosis refers to a broad category of chronic skin conditions characterized by extensive scaling and a rough texture, often accompanied by dryness, cracks, redness, occasional itching, and, in some rare cases, suprabasal epidermolysis. The clinical manifestations of these monogenic disorders can either be isolated to the skin (nonsyndromic ichthyosis) or present alongside other organ involvement (syndromic ichthyosis).[1]

Harlequin ichthyosis (HI) is an exceptionally rare and severe type of autosomal recessive congenital ichthyosis (ARCI).[2] The majority of HI cases are linked to mutations in the ABCA12 gene[3]. This condition arises from pathogenic variants in the Adenosine Triphosphate Binding Cassette Transporter Protein A12 (ABCA12) gene located on chromosome 2.[4] The mutation leads to a compromised lipid barrier, resulting in hyperkeratosis, secondary hyperthermia due to ineffective sweating, and dehydration. The hyperkeratosis may also cause the formation of hyperkeratinic bands, which can lead to limb ischemia and autoamputation.[5] This disorder significantly disrupts the keratinization process, where the epidermal layer of the skin differentiates to create the stratum corneum, a process that begins around the 20th to 24th week of gestation.[6]

ARCI encompass a diverse range of disorders that are inherited in a recessive manner, characterized by the presence of congenital ichthyosis without any involvement beyond the skin.[1] Congenital autosomal recessive ichthyosis (CARI) typically manifests at birth, often presenting as a collodion baby. CARI may evolve into various related disorders.[7] The ARCI category includes several severe subtypes, such as harlequin ichthyosis (HI), lamellar ichthyosis, and non-bullous congenital ichthyosiform erythroderma. Individuals affected by these severe forms of ichthyosis often experience significant hyperkeratosis and scaling across extensive areas of their skin from birth, which can greatly impact their quality of life.[8]

1. Lamellar ichthyosis is identified by its dark, plate-like scales resembling armor. This condition is frequently linked to mutations in the gene responsible for producing the enzyme transglutaminase 1.
2. Another phenotype within the spectrum of congenital autosomal recessive ichthyosis (CARI) is congenital ichthyosiform erythroderma, which is characterized by widespread redness and fine, white scales.
3. Epidermolytic hyperkeratosis is an autosomal dominant condition marked by hyperkeratosis and blister formation, with at least six distinct clinical

phenotypes reported. This disorder may arise from mutations in the genes encoding keratin 1 and keratin 10, which are intermediate filament proteins.

4. Ichthyosis vulgaris is the most prevalent form of ichthyosis, inherited in an autosomal dominant manner. Its symptoms are typically mild and can vary significantly depending on environmental factors such as climate and humidity.
5. X-linked ichthyosis, resulting from a deficiency in the enzyme steroid sulfatase, primarily affects males and is characterized by widespread scaling that usually appears shortly after birth. This condition may also be associated with corneal opacities that do not impair vision.

Recent advancements in research have significantly enhanced our understanding of the underlying mechanisms of these severe congenital ichthyoses, leading to the discovery of several genes and molecules responsible for the genetic abnormalities. To date, seven loci linked to autosomal recessive congenital ichthyosis (ARCI) have been identified, including five causative genes and molecules. These genes include the transglutaminase 1 gene (TGM1), ABCA12, and two lipoxygenase genes, ALOXE3 and ALOX12B, along with ichthyin. Notably, ABCA12 has recently been recognized as a lipid transporter in keratinocytes, playing a crucial role in lipid transport within lamellar granules. A loss of ABCA12 function results in a compromised lipid barrier in the stratum corneum, leading to the HI phenotype.[8]

In humans, congenital skin keratinization defects lead to a distinct genodermatosis known as ichthyosis, derived from the Greek term "ichthys," which translates to fish. Among the various forms of ichthyosis, harlequin ichthyosis (HI) is recognized as the most severe subtype and represents the most critical congenital skin disorder with an unknown cause.[9]

ABCA12 is part of a large superfamily of ATP-binding cassette (ABC) transporters that facilitate the movement of diverse biomolecules across cell membranes. The ABCA subfamily is believed to play a significant role in lipid transport. Phylogenetically, ABCA12 is closely related to ABCA3, which is crucial for the transport and secretion of alveolar surfactant lipids by lamellar granules (LGs) in type II alveolar lung cells. In the skin, LGs are the predominant secretory granules found in the upper epidermal keratinocytes, and abnormal LGs are a key characteristic of the epidermis in HI lesions. Additionally, relatively minor missense mutations in ABCA12 have been linked to type 2 lamellar ichthyosis, a milder variant of the condition.[9]

HI is often referred to as "harlequin fetus" due to the propensity for affected infants to be born prematurely. These newborns are enveloped in a thick "armor-like" layer of skin that significantly limits their movement. The skin becomes dry and forms hard, diamond-shaped plaques separated by fissures, resembling protective plating. The typical facial features are severely distorted, affecting the lips (eclabion), eyelids (ectropion), ears, and nostrils. Historically, infants with HI faced a high mortality rate, often succumbing within two days of birth due to feeding difficulties, bacterial infections, or respiratory distress. However, advancements in neonatal intensive care and the potential benefits of oral retinoids have enabled some patients to survive.[10]

HI affects both males and females at an equal rate, impacting approximately one in every 500,000 individuals, which translates to about seven cases per year in the United States. According to another source, this condition occurs in roughly one in 300,000 births. It was first documented in 1750 by Reverend Oliver Hart in a dairy entry in America.[11]

There are three distinct subtypes of HI, differentiated primarily by the specific skin abnormalities observed. The issues with the lamellar structure of the epidermis arise not only from the mismanagement of lipid transport but also from significant desquamation due to the hydrophobic characteristics of the lipids.

- The first notable abnormality involves the irregular development of the lamellar granule structure, characterized by a deficiency of normal granules. Additionally, lipid droplets can be found in vacuoles and the stratum corneum. This abnormal lamellar structure can result in severe water loss due to the hydrophobic nature of the lipids.
- Another prevalent irregularity is the improper conversion of profilaggrin to filaggrin. This atypical process results in an overproduction of filaggrin and hampers the formation of a robust keratin complex.
- Other significant irregularities include variations in keratin expression and the presence of either regular or irregular keratohyalin granules.[6]

**ORIGIN OF THE NAME**

The term "harlequin" is derived from the distinctive facial features characterized by a triangular and diamond-shaped pattern of hyperkeratosis. In newborns, the mouth is significantly stretched open, resembling the smile of a clown.

**OTHER NAMES**

**CAUSES**

Harlequin ichthyosis results from mutations in the ABCA12 gene, which is essential for the proper development of skin cells by providing instructions for producing a crucial protein. This protein is vital for transporting fats to the outermost layer of the skin, known as the epidermis, thereby forming a protective skin barrier. A mutation in this gene leads to a compromised skin barrier.

This condition is inherited in an autosomal recessive manner. Recessive genetic disorders manifest when an individual inherits a defective gene from both parents. If a person receives one normal gene and one mutated gene, they become a carrier of the disorder but typically do not exhibit any symptoms.+

**CLINICAL FEATURES**

Newborns may present with severe ectropion, eclabium, flattened ears, and extensive, thick, plate-like scales covering the entire body. This condition can lead to dryness, infections, deep skin fissures, small and inflamed hands and feet, inability to close the eyes, respiratory challenges, and elevated sodium levels in the blood, which contribute to a rigid skin texture.[13]

In older children and adults, the following issues may arise:

- Hearing impairment caused by scale accumulation in the ears
- Frequent skin infections
- Limited finger mobility due to tight skin
- Thickened nails and sparse or thin hair resulting from scalp scales
- Uncommon facial features due to skin stretching
- Risk of overheating due to scales that hinder the sweating process.[11]

**DIAGNOSIS**

The diagnosis of HI is typically straightforward due to the distinct and severe clinical features present at birth. A definitive diagnosis requires the identification of significant lipid droplet accumulation in the granular layer keratinocytes and cornified layer cells of the skin in affected infants.[13] To confirm the diagnosis, testing for mutations in the ABCA12 gene in the fetus is essential. DNA-based analysis for prenatal testing is both reliable and definitive.[8] For women who have previously had an affected child, prenatal diagnosis through Chorionic Villus Sampling (CVS) and analysis of amniotic fluid cells is recommended.[4]

Prenatal diagnosis serves as a crucial initial step for the early identification of the disease. Gathering family medical history, assessing consanguinity between parents, and noting any other skin disorders in their children can significantly aid in the early diagnosis. Microscopic examination of amniotic fluid cells, along with ultrasound evaluation of the fetal mouth shape at 17 weeks of gestation, may also facilitate early detection. Additionally, skin biopsy at 24 weeks of pregnancy can be a viable option, particularly for families with a history of HI. While ultrasonography can be beneficial in certain situations, it may not always be applicable due to delayed phenotypic expression and the rarity of the condition. Moreover, sequence analysis of the ABCA12 gene should be prioritized for individuals with a history of HI.[3]

If the condition goes undiagnosed before birth, several neonatal complications can arise. Infants may experience breathing difficulties and respiratory infections due to limited chest expansion and prematurity. The presence of thickened, cracked skin can disrupt temperature regulation and heighten the risk of infections. A wide mouth may lead to feeding challenges. Affected infants often struggle to maintain electrolyte balance, with dehydration being a common complication. Establishing intravenous access can be challenging, so umbilical cord cannulation is typically recommended for fluid monitoring and medication administration.[4]

**TREATMENT**

Harlequin ichthyosis currently has no cure, making effective management essential following initial treatment.

**Initial Treatment**

Infants diagnosed with harlequin ichthyosis require immediate admission to a neonatal intensive care unit (NICU). This may involve placement in a heated incubator with elevated humidity levels. Tube feeding can be implemented to prevent malnutrition and dehydration, while specific lubricants and protective measures are necessary to maintain eye health.[11]

**ONGOING CARE**

**Medical Care (Post-Delivery)**

- Ensure the stability of the patient's airway, breathing, and circulation, with IV access established (peripheral access may be challenging, necessitating umbilical cannulation).
- Utilize a humidified incubator for premature infants.
- Conduct regular monitoring of temperature, pulse, respiration (TPR), and oxygen saturation (SpO2).
- Prepare for early intubation if required.
- Perform frequent skin cultures for laboratory analysis.
- Screen serum electrolyte levels.
- Maintain a sterile environment to prevent infections.
- Encourage physical bonding between parents and the infant.
- Topical retinoid Tazarotene can be advantageous.
- Diluted bleach baths may reduce the likelihood of skin infections.
- Administer baths twice daily and apply wet sodium chloride compresses frequently.
- Provide IV fluids as needed.[11]

**Nursing Management**

- Apply retinoids to facilitate the shedding of hard, scaly skin.
- Use topical antibiotics to avert infections.
- Dress the skin with bandages to minimize infection risk.
- Insert a tube into the airway to assist with breathing.
- Utilize lubricating eye drops or protective devices for the eyes.[12]

**Consultation**

1. Neonatologist
2. Dermatologist
3. Medical geneticist
4. ENT specialist
5. Plastic surgeon
6. Ophthalmologist

**COMPLICATIONS**

Complications can manifest as issues related to the eyes and ears, discomfort and itching, skin infections, stunted growth, vitamin D deficiency, abnormalities in hair and nails, heightened sensitivity to temperature extremes, and physical limitations.[14]

**Ophthalmic Complications**

The primary goal of managing ophthalmic issues is to ensure normal visual development and safeguard the integrity of the ocular surface while reducing the likelihood of corneal epithelial defects. Regular eye examinations are recommended, ideally incorporating age-appropriate vision assessments and either slit lamp or alternative portable evaluations of the ocular surface. Cycloplegic refraction should be performed to rule out any significant, correctable refractive errors. The frequency of these examinations may range from monthly to once or twice a year.[14]

**Ear Complications**

Hearing loss is the predominant concern associated with ear complications, potentially hindering language and communication development. This issue often arises from the accumulation of scales and blockage in the external auditory canal, which is further exacerbated in young children due to the smaller size of their ear canals.

We advise that children under the age of 6 undergo hearing assessments at least every six months. Additionally, referrals to an ear, nose, and throat (ENT) specialist should be made if there are symptoms such as itching or pain in the ear, ear discharge, a sensation of fullness in the ears, or any hearing loss. There are various techniques available for earwax removal and addressing ear canal blockages, including the use of different types of ear drops.[14]

**Pruritus**

The underlying mechanisms of itching in congenital ichthyosis (CI) have not been thoroughly investigated and may be linked to skin inflammation. Consistent application of topical treatments, such as wet wraps with emollients, can alleviate itching by providing a cooling effect.[14]

**Growth Failure and Nutritional Deficiency**

Children with chronic illnesses often experience growth failure. Factors such as increased epidermal turnover, ongoing skin inflammation, and protein loss from the skin, particularly in patients with severe inflammatory ichthyoses like Netherton syndrome (NS), may lead to significantly elevated resting energy expenditure in CI.[14]

**Vitamin D Deficiency**

The presence of scales can thicken the skin, likely hindering the penetration of ultraviolet (UV)B rays. The inherent barrier dysfunction associated with ichthyosis may also interfere with the synthesis of previtamin D in the skin. This deficiency can be severe and may present with clinical and radiological signs of rickets. While vitamin D deficiency has been noted in various forms of CI, autosomal recessive congenital ichthyosis (ARCI) and epidermolytic ichthyosis (EI) may carry a higher risk.[14]

**DISCUSSION**

Harlequin ichthyosis (HI) is an uncommon autosomal recessive genetic disorder marked by severe congenital skin abnormalities. The majority of cases are caused by mutations in the ABCA12 gene, which is vital for lipid transport to skin cells and normal skin development. Infants born with this condition exhibit thick, yellowish-brown, hyperkeratotic skin plates that creates a rigid, armor-like covering. These plates develop deep red fissures, resulting in a distinctive facial appearance. Additional common characteristics include microcephaly, ectropion (the outward turning of the eyelids), eclabium (the outward turning of the lips), and underdeveloped nostrils and ear canals. The condition poses significant risks, such as respiratory failure due to limited chest expansion, as well as feeding challenges that can lead to dehydration, hypoglycemia, and kidney issues. Furthermore, temperature regulation problems and a heightened susceptibility to infections exacerbate the severity of HI.

Timely diagnosis is essential for effective management of HI, with prenatal screening being a key component in early detection. A comprehensive family history, including parental consanguinity and any similar skin disorders among relatives, can help identify pregnancies at risk. An ultrasound around the 17th week of gestation can evaluate fetal facial features, while microscopic examination of amniotic fluid cells may provide additional information. For families with a known history of HI, a skin biopsy at 24 weeks can be particularly beneficial. Genetic testing, particularly sequencing of the ABCA12 gene, is crucial for confirming the diagnosis. Although ultrasonography can be helpful in some instances, it may not always yield

effective results due to the delayed onset of the disease's symptoms.

The outlook for individuals with HI is typically unfavorable, marked by a high mortality rate during the initial weeks of life due to complications like infections and dehydration. Nevertheless, the likelihood of survival can improve based on the specific genetic mutation present, with compound heterozygous mutations linked to more favorable outcomes. Recent advancements in neonatal care and postnatal therapies, especially the prompt administration of oral retinoids, have led to a notable increase in survival rates, now surpassing 50%. Providing supportive care is essential, which involves creating a warm and humid environment, ensuring proper hydration, and utilizing an umbilical venous catheter when peripheral access is difficult. Regular bathing, saline compresses, and the application of emollients are beneficial for softening the skin and facilitating desquamation. It is also crucial to monitor for electrolyte imbalances and to prevent infections through routine skin cultures. Families affected by HI should consider genetic counseling and molecular testing of the ABCA12 gene to enhance management strategies and inform future reproductive decisions.

## CONCLUSION

Harlequin ichthyosis is caused by a significant functional deficiency in the ABCA12 gene. The ABCA12 and ABCA3 genes are essential for lipid transport, which is critical for human adaptation to arid land environments. Gaining insight into the genetic abnormalities and mechanisms associated with this condition is crucial for proper diagnosis, genetic counseling, and prenatal testing. Although Harlequin ichthyosis is a serious and persistent disorder, it is not invariably life-threatening. Improvements in neonatal care and the prompt administration of oral retinoids have contributed to a growing number of survivors.

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