Journal of Exploratory Research in Pharmacology **2026** vol. 11(1) | e00040
DOI: 10.14218/JERP.2025.00040

Review Article

Harlequin Ichthyosis: A Comprehensive Review of Pathogenesis, Diagnosis, and Management

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Received: August 06, 2025 | **Revised:** September 02, 2025 | **Accepted:** October 17, 2025 | **Published online:** December 09, 2025

Abstract

Harlequin ichthyosis, one of the rarest and most severe skin disorders, is mainly characterized by extreme hyperkeratosis, severely impairing the natural barrier function of the skin. This congenital disease results from a mutation in the *ABCA12* gene responsible for lipid transport, whereby healthy skin development is assured. Harlequin ichthyosis is an autosomal recessive condition that requires parents to carry a defective gene copy for the disorder to manifest in their offspring. Babies born with Harlequin ichthyosis have thick skin plates that crack and flake off; they easily become dehydrated, infected, and may suffer from respiratory complications. With new improvements in neonatal care and systemic therapy, notably retinoid therapy, infants' survival rates have improved. This review provides an inclusive overview of the pathophysiology, clinical features, diagnostic methods, management, and potential future therapies for Harlequin ichthyosis. In addition, a discussion on genetic counseling and its importance in managing family risk factors is also included, as well as a look into cutting-edge research focused on gene therapy and potential curative treatments.

Introduction

One of the more severe forms of congenital ichthyosis, a family of genetic disorders involving the skin, is Harlequin ichthyosis (HI).[1] The very word describes its appearance, which is harlequin-like, evoking the costume that a harlequin would wear in a traditional theater play.[2] This rather superficial comparison does little justice, however, to the reality of the condition, which typically presents with serious medical issues from birth in affected babies.[3,4] HI is typically marked by the development of thick, armor-like skin plates separated by deep red fissures, leading to an almost complete loss of the skin's protective function.[4,5] Affected infants are thus at high risk for potentially life-threatening complications, including dehydration, bacterial infections, and respiratory distress due to the rigidity imparted by the skin surrounding the chest.[6] Historically, the disease was almost always fatal in the neonatal period, but outcomes have greatly improved due to advances in neonatal care, meaning that many patients live longer and more coherently.[7] Nevertheless, HI is a severely life-altering condition that demands constant medical intervention.

Keywords: Harlequin ichthyosis; Congenital ichthyosis; *ABCA12* gene; Lipid transport; Hyperkeratosis; Neonatal care; Retinoid therapy; Genetic counseling; Gene therapy; CRISPR.

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How to cite this article: Goel F, Sharma N, Kumar D. Harlequin Ichthyosis: A Comprehensive Review of Pathogenesis, Diagnosis, and Management. *J Explor Res Pharmacol* 2026;11(1):e00040. doi: 10.14218/JERP.2025.00040.

The genetic basis of HI has been identified as a mutation in the *ABCA12* gene, which transports lipids within cells.[8] This gene is essential for the normal formation of the skin's lipid barrier—a protector against water loss and a safeguard against dangerous pathogens entering the body.[9,10] Upon mutation of the *ABCA12* gene, the abnormal conformation causes a disruption of lipid transport; this does not function properly in forming the skin's barrier, hence resulting in characteristic hyperkeratosis of the affected individual.[11]

This review will cover the key features of HI, starting with the genetics and molecular mechanisms that form the basis for the disorder. From here, we move on to clinical presentation and how it is diagnosed, again concentrating on the different methods used to confirm the disorder both pre- and postnatally.[12] Management can be initiated in the newborn period with systemic retinoid therapy and then followed up with long-term maintenance.[13] The review will cover information on genetic counseling and the role that it plays in supporting affected families to understand the risk potential for recurrence in future pregnancies. Finally, we shall discuss current research and future directions—especially in areas of gene therapy and new therapeutic options that may help change the course of the disease.[14]

This review aims to provide a well-rounded understanding of the challenges posed by HI, regarding what individuals affected and their families face, as well as the efforts made to improve outcomes through research and clinical advancement.

Pathophysiology

The *ABCA12* gene encodes a transmembrane protein that is in-

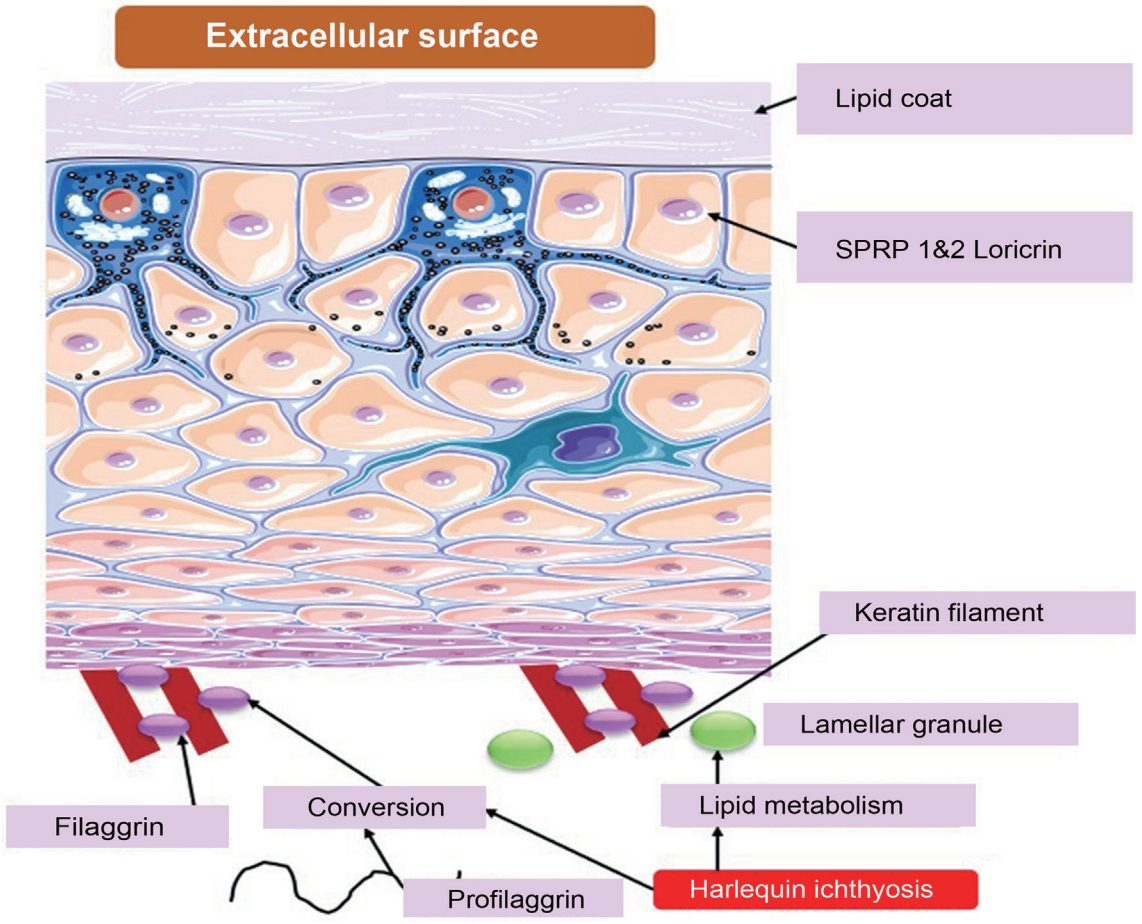

Fig. 1. The pathophysiology of genetic ichthyoses includes the composition of the cellular surface region of cornified cells. The components or chemicals that are linked to congenital ichthyoses are indicated in brackets. SPRP, small proline-rich protein.

volved in lipid transport into the lamellar granules of epidermal keratinocytes.[15] These lipids are required for the formation of the skin's lipid barrier, which protects against moisture loss by conserving water within the body, protecting the body from harm caused by pathogens and environmental agents, and maintaining homeostasis.[16] The ABCA12 protein belongs to the adenosine triphosphate (ATP)-binding cassette transporter family, a large group of proteins that move molecules across cellular membranes, drawing their energy from the hydrolysis of ATP.[17]

The normal epidermis is multilayered. The outermost part of the skin, the stratum corneum, is composed of dead keratinized cells embedded in a lipid matrix.[18] This provides a layer of physical barrier protection by restricting the ingress of injurious pathogens and the egress of moisture.[19] The appropriate formation of the *ABCA12* gene is important because it involves the transport of glucosylceramides and other lipids into the lamellar granules for secretion into the extracellular space between the corneocytes.[20] These are converted into ceramides, free fatty acids, and cholesterol, which together constitute the lipid matrix (Fig. 1).

In HI, mutation of the *ABCA12* gene disrupts this process of lipid transport, and the lipid barrier therefore cannot be structured appropriately.[21] Such an outcome leads to areas of the skin becoming prone to hyperkeratosis—that is, abnormal overproduction of keratin. In hyperkeratosis, the outer layer of the skin is abnormal, again due to the overproduction of keratin; this protein forms the structural component of skin, hair, and nails.[22] It is exaggerated in HI, thereby forming rigid, plate-like scales that cover large portions of the body.

Failure of the lipid barrier of the skin also prevents the shedding of dead cells (desquamation), causing layers of keratinized cells to build up on the outer skin surface. This accumulation is one of the factors in the formation of the thickened skin plates characteristic of HI. The deep fissures formed between these plates are thought to result from mechanical stress on the rigid, unyielding skin during fetal movement and from subsequent effects after birth.[23]

Lipid barrier dysfunction caused by HI is not a condition limited to the skin alone.[24] Under an ineffective barrier, there is a severe loss of important moisture, thus causing dehydration. In addition, the cracked nature of the skin allows easy entry of bacteria; hence, the risk of infection is very high for affected individuals.[25] Since the skin in neonates is relatively taut over the chest, this can impair breathing, resulting in respiratory distress and potentially leading to respiratory failure. The baby cannot control water loss or protect against pathogens, so this condition is immediately life-threatening at birth and requires immediate and ongoing medical therapy.[26]

Signs and symptoms

HI generally presents with a very striking and severe phenotype

at birth, and so it can be easily identified by its typical features.[27] Knowledge of the clinical features of HI is important for immediate medical intervention, since the infants carry a significant risk of complications in the neonatal period.[28]

Newborn appearance and early symptoms

Infants born with HI present with a plethora of hallmark characteristics, primarily the formation of large, tight plates of thickened, hyperkeratotic skin over most of the infant's body, with deep erythematous fissures separating them.[29] This fissure eruption is both a diagnostic feature and dangerous for the infants, since it creates easy routes for pathogenic entry.[30] The skin appears abnormally thick, more like armor,[31] and often is configured as if it were a harlequin pattern of diamond shapes. Such plates are rigid, inelastic, and prone to cracking. Thickness may range from a few millimeters to more than a centimeter, and thus, normal skin flexibility is impossible.[32]

Deep red fissures or cracks divide the thick skin plates. The fissures not only challenge the protective function of the skin but, more importantly, provide a source of continual fluid loss, and therefore, infant dehydration may occur.[33] Infants with HI characteristically have irregular facial appearances. The conjunctiva is exposed due to ectropion, predisposing the infant to infection and irritation.[34] Feeding is usually complicated by eclabium, meaning that the lips are everted. Flattening or malformations of the ears are common, and the nose appears flattened due to narrowing of the skin around the face.[35] Because of its stiffness, the movement of the joints is highly restricted, especially around the limbs. Infants appear to have poor mobility of the arms, legs, and hands, which generally influences motor skills and muscular development during the early years of life.[36]

Complications of HI

Major complications secondary to HI are numerous and potentially life-threatening, requiring prompt, sustained care.[37] These include, but are not limited to, the following:

The hardness of the overlying skin may limit full lung expansion and even cause distress and failure in severe cases, especially in neonates, who depend on pliable skin to allow normal movements of breathing.[38] Infants with HI often have feeding disorders due to limited oral movements from the tight skin around the mouth.[39] This condition is termed eclabium. As they cannot open the mouth wide enough, it may be quite difficult to breastfeed or bottle-feed.[40] Nutritional supplementation is usually provided through feeding tubes.

The fissured surface of the skin results in an inability of the skin to retain moisture and leads to significant fluid loss.[41] For this reason, dehydration is always a concern, particularly in the neonatal period, when fluid balance is already precarious.[42] The disrupted barrier allows pathogens that are normally held outside the epithelium, such as bacteria, to penetrate easily, and infections are very common and serious complications of the disease.[43] The skin fissures, especially if deep or open, become an ideal site for bacterial colonization. Sepsis, a severe systemic infection, is one of the top killers in infants with HI.[44]

Since the skin of these babies cannot retain moisture, it also cannot regulate their internal body temperature.[45] This means that babies suffering from this condition are highly prone to either hypothermia or hyperthermia. Thus, newborns need to be closely monitored with respect to controlled temperatures to prevent further complications.[46] HI does not significantly affect neurodevelopment but may cause secondary complications in the form of severe dehydration, infection, or respiratory distress, leading to hypoxia and impairment of brain function.[47]

Long-term clinical features

Long-term management of survivors in the neonatal period consists of improving skin flexibility as well as minimizing the thickening caused by hyperkeratosis.[48] While many features of HI will evolve with time as the child grows, many will remain lifelong issues.[49]

In the growing HI child, hyperkeratosis persists, though it may be rather mild with vigorous treatment.[50] Systemic retinoids have been reported to decrease the severity of hyperkeratosis. However, they do not result in complete removal of the disease.[51] The repeated cracking of the skin plates may lead to permanent scarring.[52] Furthermore, the skin becomes more fragile and thus may be damaged further. Therefore, careful management with emollients and therapeutic agents is required to minimize damage.[53]

Ectropion typically persists into adulthood, subjecting the eyes to drying and irritation and possibly resulting in infection.[54] In severe cases, surgery may be required to correct the ectropion before irreversible corneal damage occurs.[55] The skin defects resulting from HI are visible; therefore, they can result in social withdrawal, emotional stress, and disturbances in body image.[56] Psychoemotional support is part of long-term treatment, particularly at puberty, when disorders in body image are more pronounced.[57]

Diagnosis

The diagnosis of HI can be made, if only for diagnostic purposes, in the prenatal or immediate postnatal period by clinical presentation and genetic testing.[50] For this reason, rapid diagnosis is critical so that early intervention and planning of intensive neonatal care may be initiated.[58]

Prenatal diagnosis

Among others, HI can be prenatally diagnosed in families with histories of such disorders.[59] Early detection enables parents to prepare the newborn for severe medical care directly after birth.[60] In families with a previous history of HI, genetic tests can be carried out in the womb on fetal DNA to confirm mutations in the *ABCA12* gene.[61] Genetic tests involve the examination of the fetus's DNA content through amniocentesis or chorionic villus sampling. These procedures occur roughly in the middle of pregnancy.[62] Routine prenatal ultrasounds can sometimes detect signs associated with very early HI, such as skin thickening or polyhydramnios due to a failure of the fetus to swallow.[63] However, ultrasonic examination results are usually nonspecific and therefore cannot be considered definitively conclusive. Magnetic resonance imaging can further provide details on the skin condition of the fetus as well as general development, though it is usually not necessary unless other abnormalities are suspected.[64]

Postnatal diagnosis

The diagnosis of the condition is often based on the appearance of the infant at birth, and it is characterized by thickened, fissured plates of skin that distinguish the disorder from other forms of ichthyosis or congenital skin conditions.[1] Examination by a neonatologist or dermatologist would show typical physical abnormalities of the skin, such as hyperkeratosis, fissures, ectropion, eclabium, and joint contractures.[65] Such characteristics are often sufficient to allow clinical diagnosis of HI. Genetic testing after birth can confirm the diagnosis by identifying mutations in the *ABCA12* gene.[66] This not only establishes the diagnosis but is also useful in

distinguishing HI from other forms of congenital ichthyosis, such as lamellar ichthyosis or epidermolytic ichthyosis.[67]

Differential diagnosis

A number of other skin conditions share many features with HI, especially in the neonatal period.[68] Differential diagnosis excludes such conditions, which are often of lesser intensity but share many overlapping features.[69] These conditions, similar to HI, present with thickened skin, but scaling is much less severe, and infants do not present with the same life-threatening complications as those with HI.[70] They are characterized by widespread blistering and erythema at birth, rather than the rigid, armor-like plates seen in HI.[30] Some babies are born encased in a shiny, tight membrane called a collodion membrane.[71] Although this may resemble the thickened skin associated with HI, the collodion membrane peels off, showing normal or mildly ichthyotic skin underneath.[72]

Management

This presentation highlights yet another variation of lamellar ichthyosis, the extent of which varies considerably between patients. It is therefore crucial to have an aggressive and multifaceted management approach, especially in the neonatal period, when the risk of mortality is at its highest.[29] Management focuses on decreasing the impact that hyperkeratosis exerts with regard to quality of life enhancement and the prevention of complications, infections, and scarring.[73]

Neonatal intensive care

A baby with HI should be directly admitted to the neonatal intensive care unit for close follow-up and intensive treatment.[74] The main objectives during this period are to avoid infections, maintain fluid balance, ensure proper respiration and feeding, and provide other supportive measures. The most important aspect of care is to keep the skin hydrated. Frequent application of emollients helps prevent cracking and reduce water loss.[75] It is also important to provide humidified environments and fluid replacement therapy to combat dehydration.[76] Due to the impaired skin barrier, systemic antibiotic therapy is necessary for preventing and treating infection. In high-risk cases, prophylactic antibiotics can be administered to the infant to prevent sepsis.[77]

Respiratory support

Infants with HI commonly experience respiratory compromise because the tight, inelastic skin covering the chest limits lung expansion.[78] Such infants are susceptible to respiratory distress or failure, which may manifest during the neonatal period.[79] In the most severe cases, if the skin plates are too restrictive, mechanical ventilation may be needed to support breathing. Ventilators provide controlled oxygenation and support to deliver sufficient amounts of oxygenated air to the infant—an absolute necessity in the early days of life.[80] The infant may sometimes require bypassing the upper airway; in chronically affected infants, a tracheostomy is sometimes necessary for effective long-term mechanical ventilation.[23]

Nutrition support

Eating can be difficult for the newborn with HI, largely due to eclabium (turned-outward lips) and limited mobility of the mouth and jaw.[81] Nutrition and hydration are critical supports needed for growth and skin healing. Nasogastric or orogastric feeding tubes may be introduced to infuse nutrition directly into the stomach, bypassing oral feeding if it becomes too difficult or insufficient.[82] This ensures the baby receives all the calories and nutrients needed for growth, avoiding complications caused by tight skin around the mouth. Infants with severe feeding problems or who are not tolerating enteral nutrition may require total parenteral nutrition through an intravenous route,[83] wherein total parenteral nutrition bypasses the gastrointestinal tract and provides necessary nutrients directly into the bloodstream.

Skin care and long-term management

Long-term care of the patient with HI involves management of the hardened skin, prevention of complications such as infections and skin breakdown, and improvement in quality of life.[84] Skin care must be constantly undertaken and is an integral part of daily life for individuals with HI. Emollients should be applied regularly and liberally to maintain the skin in a moistened condition, thus avoiding cracking. Emollients are ointment-based, such as petroleum jelly, and protect the skin by locking in moisture and forming a protective coat.[85]

Topical application of keratolytic agents, such as urea or salicylic acid, can be utilized. These agents dissolve dead and thickened skin cells, thus thinning them.[86] Oral retinoids, such as acitretin, are well-known drugs that can reduce the hyperkeratotic thickening characteristic of patients with HI.[87] Retinoids restore normal skin turnover, decreasing keratin build-up and improving the overall appearance of the skin. Long-term retinoid therapy can be associated with potentially dangerous adverse effects, such as liver toxicity, bone abnormalities, and teratogenicity.[88] Cuts or lesions should be attended to promptly to prevent infection and promote healing.[89] Aseptic techniques, including topical antibiotics, sterile dressing, and protection of the skin without causing further damage, are required in wound care.[90]

Psychosocial support and rehabilitation

Besides its physical effects, HI also tends to cause psychosocial problems due to its pronounced body structure and chronic condition.[91] Emotional and psychological support is an integral part of comprehensive care, especially during adolescence and adulthood. Psychological counseling helps patients cope with the emotional implications of a visible skin disorder.[92] Adolescents are particularly affected by issues of body image and social discrimination, which may develop into anxiety, depression, and isolation.

HI patients may require assistance with integration into schools or workplaces. Online and in-person support groups can help patients feel part of a community, increasing their potential to connect with others facing similar challenges.[93] Loss of joint mobility due to skin tightness may require physical therapy. In addition to routine stretching and exercises designed to maintain as much joint and muscle function as possible, the patient should remain flexible and avoid contractures.[94]

Prognosis

Historical prognosis

Historically, the outlook for infants with HI was grim, as most affected infants did not survive beyond the first few weeks of life.[95] Until recently, almost all infants who presented with HI succumbed to infections, dehydration, and respiratory failure in the first few days or weeks of life.[96] With an inability to provide advanced neonatal care and due to the lack of effective treatments, survival into infancy, let alone childhood, was very rare.[7]

Present outcome with advances in care

The outcome for patients with HI has indeed greatly improved with advances in neonatal intensive care, antibiotic therapy, and systemic retinoid treatments.[68] With appropriate medical care, most infants with HI now live into their teenage and adult years, albeit with severe issues concerning their skin condition and overall health.[8] Modern medicine has significantly improved the survival rates in infants with HI. Early and aggressive treatments for infections, dehydration, and respiratory problems have become major interventions to improve outcomes.[97] Infants who survive this critical neonatal period now have a much greater chance of long-term survival.

HI is typically a lifelong disease, and patients can live into adulthood. Their skin condition and its consequences require lifetime medical treatment, though quality of life varies with the severity of the disease and the effectiveness of proper treatments, which greatly benefit the patient.[98] Most patients are able to live relatively normal lives with proper care, though the cosmetic nature of the disease can impact social interaction and mental health as well.[99]

Challenges in adulthood

Issues of concern during adulthood include ongoing skin care, potential long-term adverse effects of retinoid therapy, and psychosocial impacts from the presence of a chronic skin condition.[100] Although retinoid therapy is associated with long-term complications, it offers considerable benefits in the management of hyperkeratosis.[101] Long-term use of retinoids is known to cause problems such as bone abnormalities and liver toxicity. Patients on long-term retinoid therapy must undergo frequent monitoring of their bone density and liver function.[13] The barrier function of the skin is already compromised and not very robust in patients with HI; therefore, they continue to be at risk for chronic skin infections even with the most meticulous care. Such infections are often difficult to manage and sometimes require frequent courses of antibiotic therapy.[102] Adults with HI may face ongoing psychosocial challenges, especially regarding employment, social interactions, and integration into society.[103] Support for their mental health can be achieved through mental health services and sustained follow-up in support groups.

Genetic counseling

This condition is inherited in an autosomal recessive pattern. Because it is a recessive disorder, each of the parents must carry one defective copy of the gene for their child to inherit the disorder.[104] Genetic counseling helps bring this kind of inheritance to the attention of a family and assess the risk of recurrence in future pregnancies, as well as prenatally diagnosable options.[105]

Inheritance pattern

HI is an autosomal recessive disease, meaning both parents must be carriers of one copy of the mutated *ABCA12* gene.[106] In general, carriers of the *ABCA12* gene are asymptomatic, but if both parents are carriers, there is a 25 percent chance of having an affected child in each pregnancy.[107] In couples who have had a child with HI, the risk of recurrence in future pregnancies is 25%.[108] There is also a 50% chance that the child will be a carrier of the gene,[109] and a 25% chance that the child will not inherit the gene mutation at all. A genetic test can detect whether parents are carriers of the *ABCA12* mutation. It plays a very important role in family planning, as informed couples can make decisions regarding future pregnancies.[110]

Prenatal genetic testing

Prenatal genetic testing can provide an early diagnosis of HI in couples known to be carriers of the *ABCA12* mutation.[111] This allows parents to make informed choices regarding the pregnancy and prepare for a delivery requiring intensive medical care for the affected infant.[112] These are studies in which fetal DNA can be obtained and screened for mutations in the *ABCA12* gene.[66] Amniocentesis is usually performed between weeks 15 and 20, while CVS is performed earlier, between 10 and 13 weeks.[113] PGD is an alternative offered to people undergoing *in vitro* fertilization. PGD offers the possibility of screening embryos for the *ABCA12* mutation before implantation to ensure that only non-affected embryos are selected for implantation.[107]

Reproductive options

With the help of genetic counseling, those at risk can learn about their reproductive options in the event of HI in their offspring.[114] Under circumstances of their choice and health, there are procedures couples can consider after taking prenatal tests and preimplantation genetic diagnosis.[115] Couples who carry the *ABCA12* gene mutation may consider using an embryo or sperm donor from a noncarrier to rule out all possibilities of the child being born with HI.[116] The couple can then conceive a child free of the genetic mutation that causes HI. This is another option for families who do not want to face the risks of their child inheriting HI or any other genetic disorder.[117] This option altogether eliminates the genetic risk and may satisfy families who want to expand. Genetic counseling can assist a couple in weighing all their choices, thereby creating avenues for informed decision-making concerning their private, ethical, and medical situation.[118] Counseling would involve addressing the psychological and practical concerns associated with each option, guiding families through their choices.

Psychological impact of genetic counseling

Genetic counseling not only performs a clinical-diagnostic function but also provides families affected by HI with meaningful emotional support. The news that one's child is suffering from such a serious genetic disorder as HI, or that one carries the gene responsible for such a condition, can be emotionally difficult and painful.[4] Genetic counselors are trained and capable of providing empathetic support and helping develop self-esteem in families who feel guilty, fearful, or uncertain.[119] Counseling may be required for parents who have already faced challenges with a child with HI and are contemplating further pregnancies.[120] After genetic screening, in some cases, the verdict on future pregnancies may still be unclear, especially when both parents are carriers.[121] Counselors guide families through the anxiety and ambiguity that accompany any genetic risk, equipping them with the necessary tools to manage the emotional burden of such uncertainties.[122] Continuous efforts in research on HI, especially improvements in genetic technologies and therapeutic approaches, offer hope for better treatments and eventually a cure for the disease.[123] Research is now more focused on understanding the molecular mechanisms of HI, improving strategies for clinical management, and developing gene-based therapies.[124]

Understanding the molecular mechanisms of HI

Better insight into the genetic and molecular causes of HI will be

beneficial in designing new therapeutic interventions. Studies are currently underway to understand how mutations in the *ABCA12* gene affect lipid transport within the skin layers and how such alterations lead to the hyperkeratosis characteristic of HI.[66] Current research based on the *ABCA12* gene concentrates on the role of the encoded protein in lipid transport across the skin layers.[125] These studies may inform potential therapeutic interventions by compensating, in cases of HI, for dysfunctional lipid transport across the skin. Besides genetic research, a proper understanding of skin biology and lipid metabolism is required to understand how the barrier function of the skin is compromised in HI.[126] Such discoveries may guide new therapies focused on restoring the lipid barrier or on hydration and repair of the epidermis.

Future directions

Gene therapy and gene editing

Gene therapy and gene editing are promising lines of research in the treatment of HI.[127] This approach seeks to rectify, at the level of genetic material, the mutated gene causing the disease in question; it holds out hope for a potentially more curative or even therapeutic intervention. The approach is to introduce a normal copy of the *ABCA12* gene into skin cells with the aim of restoring normal lipid transport and skin barrier function.[128] Gene therapy is still in its infancy but has shown great promise in preclinical models of other genetic skin disorders; therefore, researchers maintain hope for such applications in HI. Clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 is a highly potent gene-editing technology that enables the exact modification of a DNA sequence.[129] Using CRISPR could correct the mutation at the DNA level in the *ABCA12* gene involved in HI. Early results on the use of CRISPR in skin diseases have been promising, but there are technical and ethical challenges to be overcome before it can be applied in clinical settings.[130] Another promising area of research is represented by the use of stem cells to treat HI. Such therapies aim to stimulate regeneration by introducing stem cells that can differentiate into functional skin cells capable of producing the required lipids for the skin barrier.[131] This approach could provide lasting improvements in cutaneous function.

New therapeutic strategies

Besides gene-based treatments, novel pharmacological approaches are now being researched to improve the management of HI.[132] These aim to make current treatments more efficient, with minimally severe symptoms, while improving the quality of life for patients with HI. Researchers have explored small molecules that modulate lipid metabolism to improve skin barrier function. These treatments attempt to circumvent the negative effects of *ABCA12* mutations on lipid transport through the overexpression of alternative pathways or by directly supplying synthetic lipids to restore the barrier function of the skin.[133] Advances in drug delivery technologies may improve the efficacy of topical HI treatments by enabling deeper penetration of therapeutic agents within the skin.[134] Nanotechnology-based delivery systems, for example, could achieve targeted efficacy by directly reaching the affected regions of the skin and also provide fewer adverse effects compared to oral retinoids.[135]

Clinical trials and new treatments

Included among these are multiple clinical trials being conducted to evaluate new treatments for HI.[136] These studies are designed to evaluate the safety and effectiveness of new therapies, including gene-based treatments, new formulations of retinoids, and other strategies to manage hyperkeratosis. Another approach could involve new preparations of retinoids that provide the same benefits as current therapy but with minimal adverse effects. For instance, topical formulations of retinoids may exert effects on localized sites without the systemic toxicity associated with oral retinoids.[137] With the development of gene therapy, clinical trials will be needed to determine its safety and long-term efficacy.[138]

Ethical issues in gene therapy and genetic testing

As research advances toward gene therapy and gene-editing treatments, many ethical points must be considered, particularly regarding prenatal genetic testing and the use of gene editing for inherited conditions such as HI. Embryo editing via CRISPR-Cas9 and other gene-editing tools raises ethical concerns, including potential adverse effects or off-target effects. Ethical principles must be instituted to ensure these technologies are used responsibly, with patients and families fully informed and consenting to all risk-benefit profiles.[139] With the emergence of new treatments comes the issue of access and affordability. Many individuals with rare genetic disorders such as HI are hindered from accessing the latest state-of-the-art therapies, especially in low-resource settings.[140] Equitable access to life-saving therapies is an important ethical consideration for future research and policy-making.[141]

Limitations

Incomplete understanding of pathophysiology beyond ABCA12

While ABCA12 mutations are central to HI, emerging evidence suggests additional modifiers epigenetic factors, lipid metabolism regulators, and inflammatory pathways remain poorly characterized. The review may not fully capture these rapidly evolving molecular insights.

Scarcity of longitudinal outcome data

Long-term follow-up studies on survivors are limited. Information on neurodevelopment, psychosocial burden, quality of life, fertility, and adult complications is sparse, reducing our ability to describe lifelong disease trajectory.

Geographical and ethnic bias in existing literature

Most published data come from specific regions with advanced neonatal care. Underreporting from low-resource settings limits understanding of the true global burden, variability in phenotype, and differences in therapeutic access.

Limited evaluation of novel and experimental therapies

Although advancements like gene therapy, lipid replacement strategies, and stem-cell approaches are emerging, evidence remains preliminary. This review may not fully assess the safety, scalability, and clinical feasibility of these therapies.

Variability in treatment protocols across centers

Neonatal management strategies including retinoid therapy, infection control, and supportive care vary widely. Lack of standardized guidelines makes it difficult to compare outcomes or recommend uniform best practices.

Underrepresentation of patient and family perspectives

Psychosocial and caregiver challenges, adherence issues, stigma,

and long-term mental health impacts are often minimally addressed in the literature and thus limited in the review.

Limited Data on retinoid safety and pharmacokinetics in neonates

While systemic retinoids are widely discussed, robust data on long-term safety, dosing optimization, teratogenic risks, and organ toxicity in newborns remain lacking.

Rapidly evolving genetic technologies

Advances in whole-genome sequencing, prenatal diagnostics, and gene-editing tools occur faster than literature updates. The review may not capture the most recent technological developments.

Conclusions

HI is a rare and severe extreme genetic skin condition. Historically associated with high mortality rates, advancements in neonatal care, systemic retinoid therapy, and supportive treatments have brought about excellent progress regarding survival and, most importantly, greatly enhanced quality of life. However, it remains a lifelong challenge because even the simplest complications of the skin can easily lead to infections. Gene therapy, stem cell-based therapies, and gene-editing technologies like CRISPR will likely become future modalities that can correct the root genetic defect and thus cure the disorder. Still in their experimental stages, such therapies may soon pave the way for innovative approaches to the treatment of genetic skin diseases. Counseling has played an important role for affected families with regard to HI inheritance patterns, enabling them to make decisions concerning future pregnancies.

In a nutshell, though challenging, HI remains a condition with promising advances both in clinical terms and in cutting-edge research, giving hope to change the outlook for individuals suffering from this rare and devastating disorder. Further investment in research, clinical trials, and ethical oversight promises a brighter future for patients dealing with this condition, giving them improved treatments, outcomes, and a chance of cure in the long term. This review now provides a comprehensive and in-depth exploration of HI in fulfillment of the goal of a detailed analysis of the condition's pathophysiology, diagnosis, management, prognosis, genetic counseling, and future research directions.

Acknowledgments

We would like to extend our sincere gratitude to CNDR, MIET for the excellent facilities throughout the production of this essay.

Funding

This study did not get any grants from any agency.

Conflict of interest

All authors declared the absence of any financial or personal conflicts pertaining to this work.

Author contributions

Manuscript writing and figure preparation (DK), manuscript finalization (FG), supervision (NS). All authors have approved the final version and publication of the manuscript.

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