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HARLEQUIN ICHTHYOSIS: AN AUTOSOMAL DERMATOLOGICAL DISORDER

Ashmeet Kaur[1], Harsharan Pal Singh[2*]

[1]Department of Quality Assurance, Delhi Institute of Pharmaceutical Sciences & Research, Pushp Vihar, New Delhi, India

[2] Department of Pharmacology & Toxicology, Noida Institute of Engineering & Technology, Greater Noida, Uttar Pradesh, India.

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***Correspondence for Author**
Harsharan Pal Singh.
Department of Pharmacology & Toxicology, Noida Institute of Engineering & Technology, Greater Noida, Uttar Pradesh, India.

ABSTRACT

Harlequin ichthyosis is a severe and extremely rare genetically inherited disorder of skin. It is a disorder with severe erythrodermtic ichthyosis which causes a distinct and life threatening appearance at birth. It is most severe form of congential ichthyosis. The baby born with a dense armor-like scales that covers the entire body. The armor cracks and splits apart which affects the shape of the eye-lids, nose, mouth and ears. The newborn is encased within a membrane which restricts the movement of the limbs and chest cavity. The restricted movement of the chest results in respiratory and circulatory failure. These babies are at serious risk of hyperthermia and hypothermia, dehydration, seizures, skin infection, poor feeding and hypernatremia. Thus, neonates die at an early stage of life. Pathogenetic mechanism involved behind this disorder is the mutation in the ABCA12 gene. Loss of function of ABCA12 leads to defective lipid transport via lamellar granules and malformation of the intercelluar lipid layer. This results in hyperkeratotis of the skin. This genetic disorder can be diagnosed by prenatal DNA analysis by chorionic villus or amniotic fluid sampling at early stages of pregnancy. The otherwise fatal disorder can be managed with utmost nursing care with combined efforts of paediatrician, dermatologist, geneticist, ophthalmologist, reconstructive surgeon along with full involvement of parents. This has led to increased survival incidences. These babies are subjected to contempt which adversely affects their psyche and self-esteem. Thus, social and professional support should be included as an essential part of the holistic management of such babies.

KEY WORDS: Autosomal recessive, congenital ichthyosis, microencephaly, hyperkeratotis.

INTRODUCTION

Ichthyosis is a disorder of keratinisation or cornification and it is caused due to abnormal epidermal differentiation or metabolism [1]. Ichthyosis could be either acquired or inherited. The autosomal recessive congenital ichthyosis is of the types, harlequin ichthyosis which is the most severe and often fatal form, lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma [1, 2].

Harlequin Ichthyosis is an autosomal recessive disorder. This is the most severe form of congenital ichthyosis with incidences of 1:300,000 births [2, 3]. The word ichthyosis is derived from a Greek word called as 'Ichthys' meaning fish-skin or fish-like skin. While Harlequin was a comedian who used to wear dresses with triangular shaped coloured patches. The disease derived its name as the skin of the babies forms large diamond-shaped scales and appears to be fish–like. Facial abnormalities include ectropion and eclabium. The fetus develops dysfunctioned lipid layer of skin which is characterised by dry, scaly with thickening of keratin layer of the skin [3].

The lamellar ichthyosis is characterised by the presence of large, pigmented without redness of the skin. Nonbullous congenital ichthyosis shows presences of finer whiter scales along with erythroderma or redness of skin [4, 5].

Pathogenesis of the Disorder

Through the evolution process, the ancestral vertebrates left the oceans to move to the terrestrial areas. Due to this they developed an air breathing respiratory system and a robust protective mechanism (keratinisation of the skin) which helps the body to adjust to the dryer environment [1, 6]. The air breathing respiratory system requires pulmonary surfactants to form a lipid–rich monolayer that coats the airway of the lungs and is essential for proper inflation and function of the lungs. Serious deficiency of these surfactants would lead to fatal deficiency of the newborn. The other adaption for life in dry environment is cutaneous keratinisation. Intercellular lipid layers in the stratum corneum, the most external layer of the skin are important for the barrier function of the skin. Severe malformation of the intercellular lipid layers in the stratum corneum of the skin leads to severe and frequently lethal disorder named Harlequin ichthyosis. [6, 7] Lipid processing in the skin is essential for the protective function of the stratum corneum. The barrier between the internal and the

external environment for bodily defence are corneocytes. These corneocytes are attached to each other by corneo-desmosomes and embedded in the intercellular lipid lamellae, forming a cornified layer. The lipid lamellae are derived from lamellar granules, the major lipid-rich organelles present in the epidermal granular cells, originating from the trans-Golgi network. At the granular lamellar-stratum corneum interface, first the lamellar granules fuses with the membrane and discharges their contents into the intercellular lamellae. Then the complex enzymatic reactions lead to modifications of the lipid composition of the intercellular spaces which includes cholesterol, ceramides and free fatty acids. These modifications provide a highly effective water-permeability barrier. Due to the regulated proteolytic cleavage of the corneo-desmosomes, the corneocytes detaches from each other in the superficial layer of stratum corneum. The transport of endogenous lipid across the corneocytes cell membrane into the stratum corneum intercellular space through lamellar granules is mediated by ABCA12 proteins. The ABCA12 positive lamellar-granular cells only will fuse with the cell membrane to secrete lipid into extracelluar space to form the intercellular lipid layer. The most severe deficiency of ABCA12 protein causes in defective lipid transport via lamellar granules in keratinising epidermal cells, resulting in Harlequin ichthyosis phenotype. [7] The ABC transporter superfamily is one of the largest gene families which codes in highly conserved group of proteins that are involved in the energy dependent active transport of a variety of substrates across the membrane including ions, carbohydrates, peptides, amino acids, and lipids. ABC genes are widely distributed throughout the eukaryotic genome and are highly maintained between species. These transporters have nucleotide-binding folds located in the cytoplasm and utilises energy form the ATP to transport substrates across the cell membrane. The subfamily, of which the ABCA12 is a member, comprises 12 full transporter proteins and 1 pseudogene (ABCA11), these are essential for lipid transport and secretion. Three ABCA genes of the subfamily as ABCA12 are implicated in the development of several genetic diseases affecting cellular lipid transport as summarised in the table. While, the deficiency in ABCA12 is responsible for causing Harlequin ichthyosis.[6, 8]

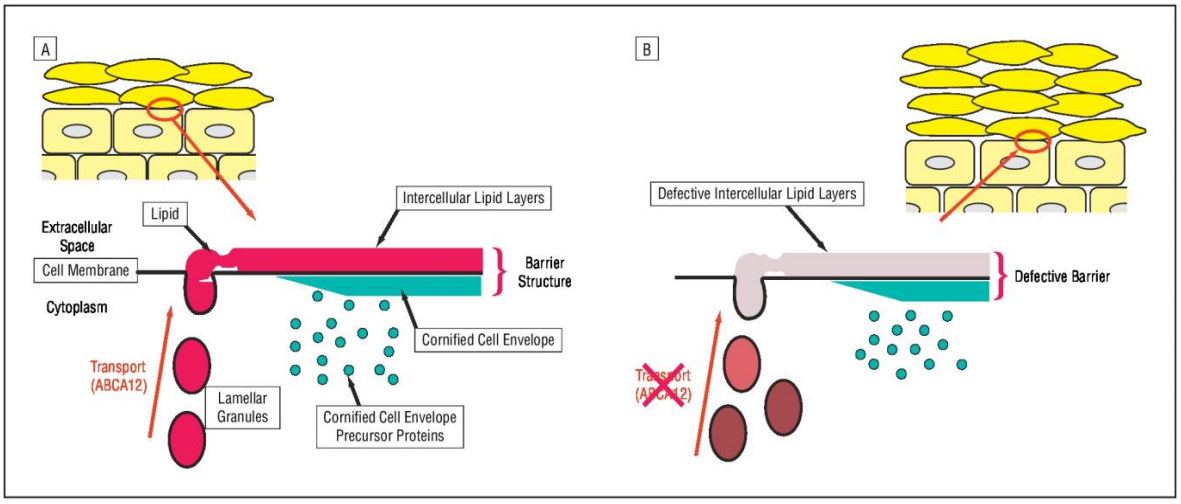

Figure 1: Pathogenesis of Harlequin ichthyosis (HI) caused by an adenosine triphosphate-binding cassette A12(ABCA12) deficiency. **A-** Model of formation of the normal intercellular lipid layers and cornified cell envelope in the stratum corneum. Formation of intercellular lipid layers in the stratum corneum is essential for correct epidermal barrier function. ABCA12 works in lipid transport via lamellar granules (LGs) to form an intercellular lipid coat. **B-** Model of malformation of the stratum corneum barrier in HI. Loss of function mutations in ABCA12 lead to defective lipid transport via LGs and malformation of intercellular lipid layers, resulting in loss of epidermal barrier function and abnormal hyperkeratosis.

(Reference: Akiyama M.; Pathomechanisms of harlequin ichthyosis and ABCA transporters in Human Diseases; ARCH Dermatol 2006; 142(7); 914-918.)

Table. ABCA Subfamily Members, Their Functions, and Associated Disorders*

Member	Expression Organs and Sites	Function	Associated Disorders
ABCA12	Skin, epidermal keratinocytes	Lamellar granule lipid transport	Harlequin ichthyosis, type 2 lamellar ichthyosis
ABCA3	Lung, alveolar type II cells	Lamellar granule lipid transport	Fatal surfactant deficiency
ABCA1	Blood vessels	Cholesterol, phospholipids transport	Tangier disease, familial hypoalphalipoproteinemia, early-onset atherosclerosis
ABCA4	Eye, retinal rod cells	Retinoid transport	Stargardt disease, age-related macular dystrophy, retinitis pigmentosa 19, cone-rod dystrophy
ABCA2	Brain, oligodendrocytes	...	...
ABCA7	Spleen, hematopoietic tissue	...	...
ABCA5	Skeletal muscle	...	...
ABCA10	Skeletal muscle	...	...
ABCA6	Liver	...	...
ABCA9	Heart	...	...
ABCA8	Ovary	...	...
ABCA13	...	...	...

*Ellipses indicate unknown.

Table 1: ABCA Family submembers along with their function and associated disorders.

Harlequin ichthyosis is an autosomal recessive disorder caused by the mutation of the ABCA12 gene located on the chromosome 2q34. An ABCA12 protein comprises of 2595 amino acids and includes 2 ABCs containing 3 characteristic, highly conserved motifs

(Walker A, Walker B, and active transport signature). In addition, there are 2 transmembrane domains, each consisting of 6 hydrophobic membrane-spanning helices. ABCA12 protein has 5 mutation sites which results in either homozygous or heterozygous states. The three mutations, 1300C→T(R434X), 2021_2022delAA, and 5848C→T(R1950X), leads to truncation of highly conserved region of the ABCA12 protein[8]. The deletion mutation 4158_4160delTAC leads to in-frame deletion mutation of threonine residue at codon 1387(T1387del) within the first ATP-binding domain of the ABCA12 protein. The splice acceptor site mutation, IVS23-2A→G, results in two splice pattern variants. One variant loses 9 bp sequence and results in a 3 amino acid deletion which are located between the transmembrane domains and are highly conserved. While the other results in 170 bp sequence loss, which leads to a frameshift mutation. All of these mutations are thought to seriously affect either the function or specific critical structures of the ABCA12 protein.[8,9]

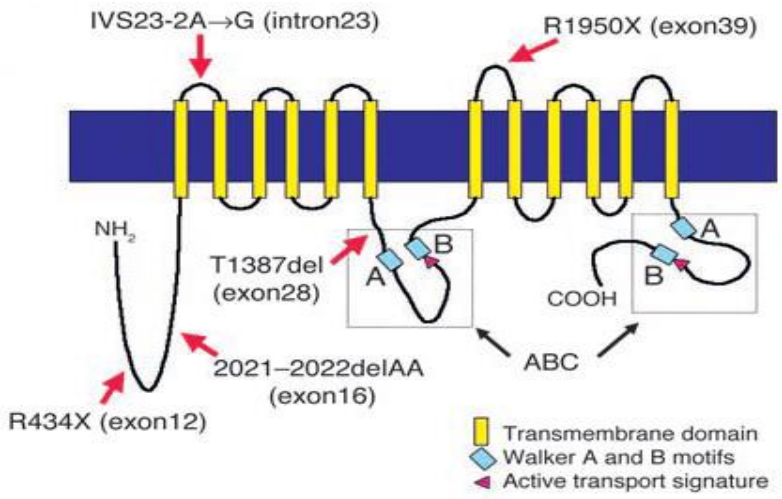

Figure 2: Structure of ABCA12 protein and the 5 mutation sites (red arrows) in HI patients. Dark- blue area is cell membrane; bottom of dark-blue area is cytoplasmic surface.
(Reference: Rothnagel JA, Dominey AM, Dempsey LD. Mutations in the rod domains of keratins 1 and 10 in epidermolytic hyperkeratosis. Science 1992; 257: 1128-1130. PMID: 1380725.)

Clinical Features Shown By Hi Baby

The HI baby's whole body is covered with large, dry, thick, diamond shaped and yellowish armor-like plaques (plate like scales) called hyperkeratosis with reddish, moist, oozing fissures and cracks. These fissures lead to dehydration and infection. Skin fissures also causes hypothermia in infants. Because of their affected skin, temperature regulation gets disturbed as well as infants become prone to easy water loss from the body. They show severe cranial

and facial deformities. Poorly developed mouth, eye, and ears are characteristic to HI baby. Microencephaly is another sign. The dry and fissured skin restricts the chest movement which causes breathing difficulties. The typical clown-like open mouth shows circumferential erithematous discoloration. The eyelids are severely everted called ectropion, with occlusion of the eye and susceptibility to trauma. The lips are everted due to the dry skin and fixed without the grimace (eclabium). Eclabium and ectropion both often results in bleeding. The nose tips are flattened with anteversion of the nares. The swollen extremities are encased by the thickened stratum corneum. These are deformed in such a way that they cannot bend properly and are hypoplastic. [3, 6, 10]

Figure 3: Thick armor-like scales with fissuring area of erythema, ectropion and eclabium.
(Reference: : Javed T., Afzal M., Khan I., Harlequin fetus: a case report; Journal of Pakistan Association of Dermatologists 2005;15:348-350

The infants show minor features like absence eyebrows, eyelashes and scalp hairs, while the associated abnormalities include renal tube defects, altered thymic structures and pulmonary hypoplasia. [10]

HI usually causes prenatal death within the first few weeks. This mainly results due to respiratory compromise (due to mechanical limitation of the ribcage excursion), sepsis, hypothermia, dehydration, malnutrition, severe anaemia as well as renal failure. Though HI is extremely fatal, the rare cases of survival show variable neurological impairment, short stature and failure to thrive. The patient is at risk for severe keratitis due to ectropion of all the eyelids. [10, 11]

Prenatal Diagnosis

HI has very poor prognosis and it is often fatal. Therefore, prenatal diagnosis is of utmost importance. Before the identification of the causative gene, until 2005, for more than 20 years, the prenatal diagnosis was performed by microscopic examination of the skin biopsies of the foetus during the later stages of pregnancies. The biopsies were usually performed at 19-23 weeks estimated gestational age (EGA). At this stage the characteristic features reported in biopsies include lipid droplets in the cytoplasm of keratinised cells in the thickened orthokeratotic stratum corneum and abnormal or absent lamellar granules in both stratum granulosum stratum corneum as well as keratin plugs in the hair follicles and sweat ducts. These were sufficient for prenatal diagnosis of the disorder. [9]

Technically, the foetal skin biopsy for prenatal diagnosis is difficult. It requires excellent site selection, and is time consuming. This also requires significant knowledge of foetal skin development as well as the interfollicular epidermis at 19 week EGA or earlier is not adequately developed to exhibit the characteristic morphology of HI foetus.

With the discovery of underlying genetic cause of HI i.e. the mutation in the ABCA12 gene enabled the DNA-based prenatal diagnosis of HI by chorionic villus or amniotic fluid sampling in the early stage of pregnancy. This procedure is more reliable and have reduced burden on the mother.

Prenatal ultrasound (sonography) can also serve as a diagnostic tool. The HI baby shows the most common sonographic findings that are a large gaping mouth, dysplastic or swollen hands and feet, aplasia of the nose, and bulging eyes. The presence of skin particles floating in the amniotic cavity, intra-amniotic debris or floating membranes might be the indirect sign. Polyhydramnios has been proposed as a marker for congential ichthyosis. But a definite prenatal diagnosis is made by the previous two methods. [9, 12]

Treatment and Management

There is no standard, accepted therapy for this disease. The management of neonates with HI begins with stabilisation of the airway, breathing and circulatory compromise due to hyperkeratotic skin [12]. Then there is the use of humidified incubator, temperature regulation,

nutrition replacement, eye and skin care, pain control, physiotherapy, and infection control. The baby is nursed in a humidified crib to provide a moist environment. Nutrients, fluids and medications are given through umbilical vein because access through peripheral vasculature is difficult in these babies. Ectropion is managed with artificial tears and antibiotic ointments to provide protection from exposure and prevention of dessication of the cornea. At later stage it is corrected by surgery [13, 14]. Petrolatum-based creams and ointments are used to keep the skin soft, supple and hydrated, thus facilitating desquamation. Also, bathing and soaking can reduce the risks of skin infection, replenish moisture, in the skin and promote the softening and shedding of the thick stratum corneum. As the child grows, keratolytic agents (like alpha-hydroxy acid or urea preparations) can be used to promote thinning of the stratum corneum. These agents have high cutaneous absorption leading to systemic toxicity, which makes them unsuitable for use in neonates. The most widely used class of drugs in HI patients is retinoids and their derivatives (e.g. etritinate), which prevents cracking of the skin and promotes desquamation. This is helpful in hastening pliability. Pliability renders immense benefits in improving the movement range, prevention and early correction of contractures, including ectropion and eclabium. [14] Pain management is also important aspect. Pain caused by cracks makes it necessary to use anti-inflammatory drugs or keep the HI baby sedated with use of morphine. [15, 16] The parents of the must receive counselling after prenatal diagnosis about the potential risks affecting the offspring. They should also be educated about the potential complications involved with the disease. [17]

CONCLUSION

Harlequin ichthyosis is a devastating disorder with high mortality rates. Prolonged survival is possible with extreme neonatal care. Though, the survival rates appeared to increase yet the persistent dermatosis is a lifetime suffering for the individual. Thus, this makes early prenatal diagnosis to allow appropriate counselling highly essential. Also, the abnormal appearance of these babies subjects them to contempt by others affecting their psyche and self-esteem. Therefore, social and psychological support should be included in the holistic management regime of these babies.

REFERENCES

1. Judge MR. Collodion baby and Harlequin ichthyosis. Harper J, Oranje A, Prose N. Textbook of Pediatric Dermatology. Second edition. Malden, Blackwell Publishing, 2006; 118-125.

2. Judge MR, McLean WHI, Munro CS. Disorders of keratinization. Burns T, Breathnach S, Cox N, Griffiths C. Rook's Textbook of Dermatology. 7th ed. Malden, Blackwell Publishing, 2004; 34.1-34.111.
3. Dale BA, Holbrook KA, Fleck man P. Heterogeneity in harlequin ichthyosis, an inborn error of epidermal keratinization: variable morphology and structural protein expression and a defect in lamellar granules. J Invest Dermatol 1990; 94: 6-18 (Abstract). PMID: 1688598.
4. Kam E, Nirunsuksiri W, Hager B. Protein phosphatase activity in human keratinocytes cultured from normal epidermis and epidermis from patients with harlequin ichthyosis. Br J Dermatol. 1997; 137: 874-882 (Abstract) PMID: 9470902.
5. Rothnagel JA, Dominey AM, Dempsey LD. Mutations in the rod domains of keratins 1 and 10 in epidermolytic hyperkeratosis. Science. 1992; 257: 1128-1130. PMID: 1380725.
6. Akiyama M.; Harlequin ichthyosis and other autosomal recessive congenital ichthyosis: the underlying genetic defects and pathomechanism; Journal of Dermatological Sciences, 2006; 42(2); 83-89.
7. Akiyama M.; Pathomechanisms of harlequin ichthyosis and ABCA transporters in Human Diseases; ARCH Dermatol 2006; 142(7); 914-918.
8. Akiyama M., Sugiyama-Nakagiri Y, Sakai K., Mutation in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer; The Journal of Clinical Investigation. 2005; 115: 1777-1784.
9. Akiyama M., Titeux M., Sakai Y., McMillan JR., Tonasso L, Calvas P, Jossic F, Hovanian A., Shimizu H.; DNA-based prenatal diagnosis of harlequin ichthyosis and characterisation of ABCA12 mutation consequences; Journal of Investigative Dermatology, 2007; 127(3):568-573.
10. Sundaramoorthy MS., Expecting the most unexpected-A harlequin baby! A case report and literature analysis; Our Dermatol Online, 2012; 3(4): 321-325.
11. Chen H.; Harlequin Ichthyosis; Atlas of Genetic Diagnosis and Councelling; Springer US, 2012; 999-1001.
12. Prasad AN, Harlequin Baby; Medical Journal of armed forces India 2011; 67(1); 88-89.
13. Schmuth M., Martinz V., Janecke AR., Fauth C., Schossiq A., Zschocke J., Gruber R.; Inherited ichthyosis/generalised Mendelian disorders of cornification; European Journal of Human Genetics, 2013;21(2):123-133.

14. Hashemzadeh A., and Heydarian F., Harlequin Ichthyosis; Acta Medica Iranica, 2009; 47(1); 81-82.
15. Patil P. Patil A., Verma J., Ghosh G, Recurrent Congenital Ichthyosis in Newborn: A case report; International Journal of Medical Research and Review 2013; 1(2):71-73.
16. Dubey AK., Tuibeqa IV., Pio NB. Harlequin ichthyosis: A rare dermatological disorder; International Journal of Case Report and Images 2014; 5(8): 590-594.
17. Rossie G., Mesia D., Management of harlequin ichthyosis in low-income countries; Annals and Tropical Paediatrics, 2011; 3(3): 247-249.