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A RARE AND SEVERE ICHTHYOSIS OF NEONATES -HARLEQUIN ICHTHYOSIS

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ABSTRACT

Harlequin ichthyosis (HI) is an autosomal recessive form of congenital type. HI is an extremely rare and most severe form of ichthyosis. The condition is caused by mutation of the *ABCA12* gene resulting in impaired lipid transport in the outermost layer of the skin, the epidermis. During the neontatal period, harlequin ichthyosis manifests phenotypically as dramatic large polygonal plate-like scaling of the skin that cracks and can slough, revealing the underlying diffusely bright red skin. Other features include hypoplasia of the fingers, malformation of the ears and nose, and alopecia. Affected neonates often do not survive and mortality is commonly attributed to respiratory failure and/or sepsis. The ages of survivors ranged from 10 months to 25 years and death usually occurred in the first 3 months. HI infants need to be cared for in a neonatal intensive care unit immediately after birth. Several harlequin neonates have survived. They tend to have severe erythroderma and fine scaling, even with optimal management. Survivors can suffer from recurrent skin infections from epidermal fissuring, contractures due to their tight skin, metabolic abnormalities, developmental delay, and pulmonary issues. High quality management of immediate newborn care may improve survival. Introduction of oral retinoids and its timing remain controversial, but frequent application of emollients to improve barrier function is critical.

INTRODUCTION:

The word **"**Ichthy" comes from the Greek word for fish. This condition is called "Ichthyosis"because the thickened skin sometimes has the appearance of fish scales. Because each form of Ichthyosis is rare and there is an overlap of clinical features amongdisease types.

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Harlequin ichthyosis is a severe genetic disorder that mainly affects the skin. Infants with this condition are born with very hard, thick skin covering most of their bodies. The skin forms large, diamond-shaped plates that are separated by deep cracks (fissures). These skin abnormalities affect the shape of the eyelids, nose, mouth, and ears, and limit movement of the arms and legs. Restricted movement of the chest can lead to breathing difficulties and respiratory failure.The skin abnormalities associated with harlequin ichthyosis disrupt this barrier, making it more difficult for affected infants to control water loss, regulate their body temperature, and fight infections. It is also called as Harlequin

baby syndrome or HI or Ichthyosis Congenital, Harlequin Fetus Type[1, 8].Ichthyosis may be either inherited or acquired. There are approximately28 recognized forms of Ichthyosis .In ichthyosis, the barrier function of the skin is compromised and has a decreased ability to protect against bacterial, chemical, and mechanical assault and to prevent trans-epidermal water loss[2].The skin abnormalities associated with harlequin ichthyosis disrupt this barrier, making it more difficult for affected infants to control water loss, regulate their body temperature, and fight infections.Infants with harlequin ichthyosis often experience an excessive loss of fluids (dehydration) and develop life-threatening infections in the first few weeks of life. Like increased susceptibility to infection secondary to impaired skin integrity and dramatically increased metabolic demands due to increased epidermal turnover and evaporative heat and water loss[2,3]. Harlequin ichthyosis is extremely rare, and is the most severe form of the keratinizing disorders characterized by profound thickening of stratum corneum. Densearmour like scale covers the body.The new born appears to be encased in a tight thin membrane which allows little movement and holds the limbs in semiflexed position.Six major distinct clinical subtypes are known in hereditary non-syndromic ichthyoses. Starting with the most severe form, they are: harlequin ichthyosis,lamellar ichthyosis, congenital ichthyosiform erythroderma, epidermolytic ichthyosis(EI)and recessive X-linked ichthyosis to the mildest form of ichthyosis vulgaris.Superficial epidermolytic ichthyosis is an additional sub type similar to EI [4].The known causative molecules underlying ichthyosis include ABCA12, lipoxygenase-3, 12R-lipoxygenase, CYP4F22, ichthyin and steroid sulfatase, all of which are thought to be related to the intercellular lipid layers.ABCA12 is a known keratinocyte lipid transporter associated with lipid transport in lamellar granules and a loss of ABCA12 function leads to defective lipid transport in the keratinocytes, resulting in the most severe, harlequin ichthyosis phenotype[3,5].Other causative molecules for ichthyoses are transglutaminase 1, keratins and filaggrin.Harlequin ichthyosis is a severe genetic disorder that mainly affects the skin. Infants with this condition are born with very hard, thick skin covering most of their bodies.The underlying genetic abnormality in harlequin ichthyosis is a mutation in the lipid-transporter gene *ABCA12* on chromosome 2[6]. In this review we are providing the data regarding history, Pathophysiology, causes, signs and symptoms and treatment of HI.

History:

Harlequin ichthyosis has been discovered in 1750 by Oliver Hat who was a cleric in Charleston, South Carolina.He described it as a medical condition which involved very hard and dry skin which appeared to be cracked in many portions of the body of the poor infant who was affected by the disorder.He also said that the scales on the skin resembled the scales of a fish. The child also had a large, round and open mouth and it had no external nose, just the holes in the place where the nose was supposed to be [7].The child's eyes were actually large lumps of coagulated blood and the poor toddler did not have any external holes. As were the case with the nose, there were only holes where the ears were supposed to be. The hands and feet of the child were described as very swollen and cramped up. Harlequin ichthyosis got its name for the facial expression commonly associated with the disorder and because of the scales, which are shaped like diamonds so they resemble the costume of Harlequin. During the recent years it has become possible to diagnose the disorder even before the child is born by utilizing morphologic analysis of amniotic fluid cells which can be obtained by amniocentesis.Fetal skin biopsy can also be used for the same purposes. The disease can also be easily recognized by means of an ultrasound and 3D ultrasound.The modern medical support made it possible for the affected infants to survive into childhood and adolescence[7,8].

Epidemiology:

Ichthyosis vulgaris and X-linked ichthyosis are the most common types of ichthyosis, with an estimated incidence of 1 in 250 births and 1:6000 male births.Autosomal recessive congenital ichthyoses, which include lamellar ichthyosis, congenital ichthyosiform erythroderma, and harlequin ichthyosis, are rare; their overall incidence has been estimated at approximately 1 in 200,000 births[9].

Frequency: International- More than 100 cases of harlequin ichthyosis have been reported. **Mortality/Morbidity**: The mortality for harlequin ichthyosis rate is high. With neonatal intensive care and the advent of retinoid therapy, some babies have survived the newborn period. They are still at risk of dying from systemic infection, which is the most common cause of death.

Race: No racial pre-limination of harlequin Ichthyosis.

Sex: No increased risk of harlequin Ichthyosis based on sex is known [(10)].

Different types of ichthyosis: Six major distinct clinical subtypes are known in hereditary non-syndromic ichthyoses(which are represented in table 1). Starting with the most severe form, they are: harlequin ichthyosis, lamellar ichthyosis, congenital ichthyosiform erythroderma, epidermolytic ichthyosis,recessive X-linked ichthyosis to the mildest form of ichthyosis vulgaris[(5)].

Causes of harlequin ichthyosis:

It is a Genetic disorder that is passed from parent to child or that occurs spontaneously.Harlequin ichthyosis is caused by certain mutations in the gene known as ABCA12 gene**.**The mutations in the gene occur; the production of the needed protein gets significantly decreased so the lipids cannot be transformed throughout the body properly. All of this leads to abnormal development of epidermis and the occurrence of hard thick scales on the skin.[(13)]Two copies of the gene in each cell need to be altered before this medical condition can be inherited so that is why it is medicinally considered as an autosomal recessive pattern.In most cases the parents of an affected infant carry a copy of the mutated gene without ever showing any symptoms or signs of harlequin ichthyosis.In recessive disorders, the condition appears when the person inherits the same defective gene for the same trait from each parent.If the individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease but will not show the condition.The risk of transmitting the disease to the children of a couple, both of whom are carriers for the recessive disorder, is approximately 25 percent per pregnancy.[(14)]Harlequin type ichthyosis is caused by disruptions or changes (mutations) to the ABCA12 gene located on chromosome 2 (2q34) [(15)].Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual.Pairs of human chromosomes are numbered from 1 through 22 and an additional 23rd pair of sex chromosomes, which include one X and one Y chromosome in males and two X chromosomes in females. Each chromosome has a short arm designated “p” and a long arm designated “q”. Chromosomes are further sub-divided into many bands that are numbered. For example, “chromosome 2q34” refers to band 34 on the long arm of chromosome[(12,16)].The numbered bands specify the location of the thousands of genes that are present on each chromosome.**Cold weather** is also an important factor which increases dry skin and leads to Ichthyosis.**Acquired Ichthyosis** is not inherited and occurs for the first time indult hood. It is usually associated with some general systemic diseases, such as under active thyroid, sarcoidosis, lymphoma, generalized cancer or HIV [(17)].

Pathophysiology:

*Harlequin ichthyosis: (HI)*Mutations in a gene known as ABCA12 (adenosine triphosphate [ATP]-binding cassette transporter, subfamily A, member 12, in chromosome region 2q35, underlie this disorder Patients with harlequin ichthyosis are usually homozygous for this mutation consistent with autosomal recessive inheritance.The ABC superfamily of genes encodes proteins that transport a number of substrates across cell membranes.ABCA12 is thought to encode a transmembrane protein that mediate lipid transport. This ABCA12 -mediated lipid-transfer system is thought to be essential to the transfer of lipids from the cytosol of the corneocyte into lamellar granules.Lamellar granules are intracellular granules that originate from the Golgi apparatus of keratinocytes in the stratum corneum. These granules are responsible for secreting lipids that maintain the skin barrier at the interface between the granular cell layer and the cornified layer.In harlequin ichthyosis, the ABCA12 -mediated transfer of lipid to lamellar granules is absent. The lamellar granules themselves are morphologically abnormal or absent.Normal extrusion of lipid from these granules into the intercellular space cannot occur, and lipid lamellae are not formed. This defective lipid “mortar” between corneocyte “bricks” results in aberrant skin permeability and lack of normal corneocyte desquamation[(2,6,18)].

Mechanism: The exact mechanism of this transport abnormality has yet to be elucidated. One hypothesis involves abnormal calcium-mediated signaling by means of calpains. Calpains are calcium-activated neutral proteases that are essential to normal epidermal differentiation. Calpains are consistently under expressed in patients with harlequin ichthyosis compared with the general population. The pivotal role of ABCA12 in harlequin ichthyosis is supported by in vitro data. Studies have demonstrated normalization of lipid transport when the wild-type ABCA12 gene is transferred to keratinocytes of patients with harlequin ichthyosis (figure1).Nonsense mutations in ABCA12 are seen in harlequinichthyosis.[(19)]

Typeof Ichthyosis	Clinical features
Ichthyosis vulgaris	At birth skin may appear normal, Skin gradually becomes dry, rough and scaly, with most signs and symptoms appearing by the age of 5. Can affect all parts of the body, including the face and scalp. Bends of arms and legs usually spared. Palms are excessively lined. Associated with atopic dermatitis
Lamellar ichthyosis	Often called collodion baby as at birth the baby is covered by a thickened collodion-like membrane which is then shed, Scaling occurs over the whole body, including creases and bends, May result in drooping lower eyelids (ec-tropion), Prenatal testing in subsequent pregnancies is available May be associated with mutation in transglutaminase 1 gene
Epidermolytic hyperke-ratosis	Skin is moist, red, and tender at birth Fluid filled blisters may occur which may become infected and give rise to a foul skin odor, Thick, generalized scaling occurs within a few days Biopsy shows epidermolytic hyperkeratosis
X-linked ichthyosis	Generalized scaling is present at or shortly after birth Scaling is most prominent over the extremities, neck, trunk and buttocks May cause corneal opacities, Associated with steroid sulphatase deficiency in fibroblasts and elevated plasma cholesterol sulphatase Only affects males, May be associated with testicular disease[10,11,12]

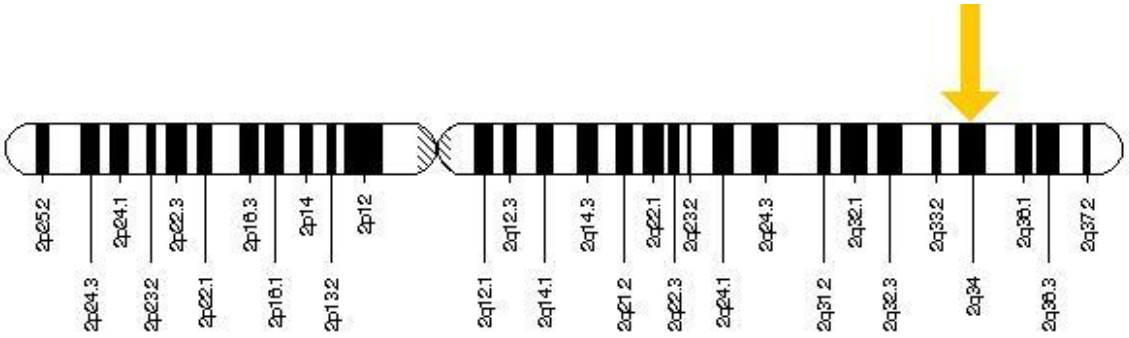

Figure 1: mutations in abca12 gene

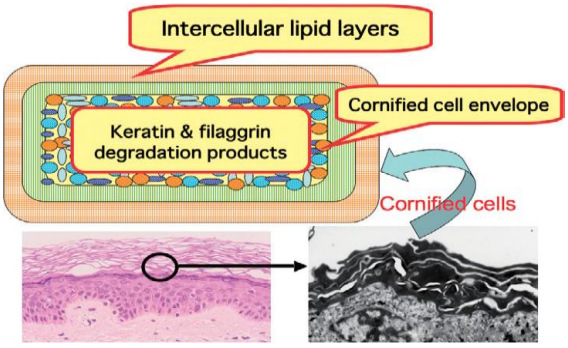

Figure 2: Cornified cells of skin [23]

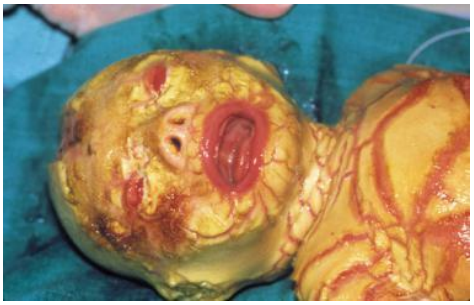

Figure3: Harlequin Effected Baby [3]

Formation of the intercellular lipid layers is essential for epidermal barrier function, and the defective formation of those layers is thought to result in a serious loss of barrier function,and to lead to extensive hyperkeratosis.ABCA12 has beenhighlighted, because it was recognized as a key molecule in keratinocytes lipid transport.Among the severe ARCI diseases, HI is the most devastating congenital ichthyosis, with affected new-borns showing large, thick, plate-like scales over the whole body with severe ectropion, eclabium and flattened ears.ABCA12 is a keratinocyte lipid transporter, and demonstrated that *ABCA12* mutations lead to the HI phenotype. Another group independently reported that *ABCA12* mutations underlie HI by linkage analysis[16,20].*ABCA12*mutations were also found to underlie LI and CIE cases. ABCA12 is a member of a largesuperfamily of the ATP-binding cassette (ABC) transporters that bind and hydrolyser ATP totransport various molecules across a limiting membrane or into a vesicle. All ABCA subfamilymembers are thought to be lipid transporters. ABCA12 is a keratinocyte trans membrane lipidtransporter protein associated with lipid transport in lamellar granules to the apical surface ofgranular layer keratinocytes.Ultra structurally, lamellar granule abnormalities are apparent in HI patient epidermis.Several morphologic abnormalities have been reported, e. g., abnormal lamellar granules in thegranular layer keratinocytes and a lack of extracellular lipid lamellae in the stratum corneum.They reflect defective lipid transport by lamellar granules and the malformation ofintercellular[6,4,21].Major components of skin barrier in stratum corneum consist of intercellular lipid layers, cornified cellenvelope and keratin/filaggrin degradation products. lipid layers in the stratum corneum in HI.In addition, cultured epidermal keratinocytes froman HI patient carrying *ABCA12* mutations demonstrated defective glucosylceramide transport,and this phenotype was recoverable by an *in vitro ABCA12* corrective gene transfer.Based onthese findings, we were able to shed light on the patho-mechanisms of HI with the underlying*ABCA12* mutations leading to a loss of ABCA12 function.Lamellar granules are lipid transportingand secreting granules in the epidermal keratinocytes[22].Mutations in the lipid transporter proteinABCA12 cause defective lipid accumulations into lamellar granule, resulting in malformationof the intercellular lipid layers of the stratum corneum.The fact that ABCA3 (a member ofthe same protein superfamily as ABCA12) functions in pulmonary surfactant lipid secretion viathe production of similar lamellar-type granules within lung alveolar type II cells furthersupports this concept.We subsequently transplanted cultured keratinocytes from patients with HI and succeeded inreconstituting HI skin lesions in immunodeficient mice.These reconstructed HI lesions showedsimilar changes to those observed in HI patients' skin(figure 2).HI patients often die in the first one or two weeks of life. However, once they survive beyondthe neonatal period, HI survivors' phenotypes improve within several weeks after birth[1,2, 3].

Signs and Symptoms:

a. Skin: Severely thickened skin with large, shiny plates of hyperkeratosis scale is present at birth. Deep, erythematous fissures separate the scales.

b. Eyes: Severe ectropion is present. The free edges of the upper and lower eyelids are everted, leaving the conjunctivae at risk for desiccation and trauma.

c. Ears: The pinnae may be small and rudimentary or absent.

d. Lips: Severe traction on the lips causes eclabium and a fixed, open mouth. This may result in feeding difficulties.

e. Nose: Nasal hypoplasia and eroded nasal ale may occur[6].

f. Extremities: The limbs are encased in the thick, hyperkeratosis skin, resulting in flexion contractures of the arms, the legs, and the digits. Limb motility is poor to absent. Circumferential constriction of a limb can occur, leading to distal swelling or even gangrene. Hypoplasia of the fingers, toes, and fingernailsis reported Polydactylis described.

g. Temperature dysregulation: Thickened skin prevents normal sweat gland function and heat loss. The infants are heat intolerant and can become Hyperthermic.

h. Respiratory status: Restriction of chest-wall expansion can result in respiratory distress, hypoventilation, and respiratory failure.

i. Hydration status: Dehydration from excess water loss can cause tachycardia andpoor urine output.

j. Central nervous system: Metabolic abnormalities can cause seizures. CNS depression can be a sign of sepsis or hypoxia. Hyperkeratosis may restrict spontaneous movements, making neurologic assessment difficult[2,4].

Infants born with Harlequin ichthyosis are covered in thick plate-like scales of skin. The tightness of the skin pulls around the eyes and the mouth, forcing the eyelids and lips to turn

inside out, revealing the red inner linings.The chest and abdomen of the infant may be severely restricted by the tightness of the skin, making breathing and eating difficult.The hands and feet may be small and swollen, and partially flexed. The ears may appear to be misshapen or missing, butPre-mature birth is typical, leaving the infants at risk for complications from early delivery(figure 3).These infants are also at high risk for difficulty breathing, infection, low body temperature, dehydration, and hypernatremia (elevated levels of sodium in the blood).Constriction and swelling of the mouth may interfere with the suck response and infants may need tube feeding. The baby's corneas need to be lubricated and protected if the eyelids are forced open by the tightness of the skin [17].

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Complications:

Among neonates with congenital ichthyosis, infants with harlequin ichthyosis, collodion babies, and those with epidermolytic ichthyosis and Netherton syndrome are among those at highest risk for complications during the postnatal period.Beyond complications of prematurity, impaired barrier function serves as the primary source of morbidity and mortality during this time[12,3].Increased transepidermal water and heat loss lead to hypernatremia dehydration, other electrolyte imbalances, disrupted thermoregulation and calorie malnutrition. Fissuring and denudation can provide a means of entry for microorganisms, leading to skin infections and sepsis.For neonates with collodion membrane or harlequin ichthyosis, immobilization can result in impaired ventilation, hypoxia and pneumonia as well as difficulty sucking or feeding.In addition, constricting bands of skin can at times compromise perfusion and lead to peripheral edema and ischemia.Finally, infants with ectropion are at risk for exposure keratitis[22].

Diagnosis:

Up to now the preborn diagnosis them was based on the biopsy of fetal skin carried out in an advanced phase of the pregnancy. (In past the fetal biopsy was executed through the feto-scopy and it had a mortality rate that was between 4-7%.Today it is executed under echography guide between 17a and 20thweek of gestation, with a biopsy clamp. The samples should be aimed at the zone of cute affected by the eventual dermatological lesion.You have to introduce the needle and then the biopsy clamp: the teeth of the clamp are opened, it is pushed out on the cute fetal and the sample is carried out[18,23].The diagnosis is made with a conventional histological examination and with the electron microscope, analyzing the structure and the ultrastructure of the cute and resorting to the Immunohisto-chemical analyses.The most important indication to the fetal cutaneous biopsy is the diagnosis of the genodermatosis, hereditary diseases of the skin with high morbidity and mortality, including Harlequin ichthyosis. Harlequin Ichthyosis the preborn test based on DNA will replace the fetal biopsy. This analysis may be made before the tenth week of gestation by a normal chorionic villus sampling, or even before with the non-invasive analysis of the DNA of fetal cells in maternal circulation[5,21]. Finally, knowledge of the exact mutations (gene ABCA12) in this serious disease is the basis for the subsequent development of tools for pre-implantation genetic diagnosis [assisted reproductive technology that allows carriers to select healthy embryos].In the neonatal period, a likely diagnosis can often be made on clinical grounds alone. It is important to note, however, that it is not necessary to make a definitive diagnosis at this point, as management is generally not specific to the particular form of ichthyosis present. Within the first year of life, many cases that were not clear at birth become more clinically recognizable, as patients display the characteristic cutaneous phenotype, such as in EI or lamellar ichthyosis, or develop associated findings, for example neurologic findings in the setting of Sjögren-Larsson syndrome.Genetic diagnosis becomes particularly useful in the setting of future family planning, and we suspect that it may become more common and important in the coming years, as the genetics of these disorders begins to be better characterized and pathogenesis-based therapies are developed[9,24].

Treatment:

There is no cure for ichthyosis.The main goal of treatment is to moisturize and exfoliate. This helps prevent dryness, scaling, cracking and build-up of skin. People with this type of ichthyosis need to bathe, moisturize and exfoliate their skin on a daily regular basis. Dermatologist will prescribe or recommend moisturizing creams and ointments to keep the condition under control.In severe cases they may prescribe oral retinoids such as acitretin orisotretinoin. This can help to reduce scaling[4].Oral antibiotics may be prescribed if secondary infection occurs. People with ichthyosis have normal lifespan. However they may need to spend several hours.The baby may require intensive care monitoring of fluid and electrolytes. Specific treatments of the skin can minimize the formation of vesicles and increase the healing of erosions to decrease the friction and mechanical trauma should be used in lubricants, protective padding

and special bandages.The baby is prone to erosion with large bacterial infections and sepsis, the use of topical and systemic antibiotics chosen with care, can minimize the extent of infection[3,25].

Standard therapies:

✓ The thick, plate-like skin of Harlequin type ichthyosis will gradually split and peel off over several weeks.
✓ Antibiotic treatment may be necessary to prevent infection at this time.Administration of oral etretinate (1mg/kg body weight) may accelerate shedding of the thick scales.
✓ Most Harlequin infants will need one-on-one nursing care for the first several weeks of life.
✓ After the thick plates peel off, the skin is left dry and reddened, and may be covered in large thin scales.
✓ The skin symptoms are treated by applying skin softening emollients. This can be particularly effective after bathing while the skin is still moist.
✓ Skin barrier repair formulas containing ceramides or cholesterol, moisturizers with petrolatum or lanolin, and mild keratolytics (products containing alpha-hydroxy acids or urea) can all work to keep the skin moisturized and pliable, and prevent cracking and fissuring that can lead to infection[20,21,22,23].

CONCLUSION:

Ichthyosis, while fairly rare, is a condition that requires significant attention in the neonatal period. Successful management of ichthyosis in the newborn can be achieved through a thoughtful, directed and interdisciplinary approach. An understanding of the disrupted barrier in these patients provides a basis for management, and simple measures, including daily bathing and liberal emollients, serve as mainstays of treatment.

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