CASE REPORT

Delivery of a Harlequin Ichthyosis Baby : A case report

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Introduction:

Harlequin ichthyosis is very rare genetic skin disorder with severe morbidity and mortality. It is the severe form of autosomal recessive congenital ichthyosis (ARCI) which is often lethal in the neonatal period[1]. Patient may survive for several months or years in very rare case[2]. HI appears with severely thickened and scaly skin over the whole body. There are deep, erythematous fissures which separate large diamond shaped thick skin plates. In addition, ectropion, lack of development of the external parts of the nose and ears, eclabium and open mouth, hypoplastic fingers, anonychia and mobility limitation of the joints are some other clinical feature of HI[3,4]. Neonates with HI are at high risk for development of hypothermia, hyperesthesia, dehydration, respiratory distress, hypoventilation, malnutrition, hypernatremia, seizure and skin infections[5].

HI is associated with preterm birth and often leads to death due to neonatal complications such as fluid loss and septicemia[6].

The underlying genetic abnormality in HI has been identified as an alteration in the lipid–transporter gene adenosine triphosphate binding cassette transporter A 12 (ABCA 12) on chromosome -II[7].

Histological examination of the skin reveals characteristic abnormalities in the structure of lamellar granules and the expression of epidermal keratin[8].

Prenatal diagnosis would be the first step for early detection of the disease. Therefore, obtaining the family history, consanguinity between the parents, and the presence of other skin disorders in offspring would be very helpful for early diagnosis of the disease[4]. Microscopic examination of the amniotic fluid cells and ultrasound for assessment of the shape of fetal mouth at 17 weeks of pregnancy might be useful for the early detection. Prenatal diagnosis can also be feasible using skin biopsy at 24 weeks of pregnancy, especially among the families with a history of HI. Although ultrasonography can be useful in some cases but it might not be applicable due to delayed phenotypic expression and the rarity of the disease[3]. Furthermore, sequence analysis of *ABCA12* should be done first for the individuals with HI history[4].

Case report:

On October 10, 2017 a primegravidae aged 24 years was admitted to Holy Family Red Crescent Medical College hospital, Dhaka, due to preterm premature rupture of membrane and labour pain.

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Gestational age was approximately 33 weeks and 2 days based on both, the first day of the last menstrual period and early scan. The mother had received irregular antenatal cheek up and no remarkable complication was noted in the last ultrasound examination at 28 weeks of pregnancy. She underwent emergency cesarean section in view of footling presentation and a female baby weighing 1.7kg was delivered.Apgar score was 5 and 7 at 1 and 5 min, respectively. The baby was the first child of non-consanguineous parents. The parents had no family history of any inherited skin disorder. The baby exhibited thick white poreclin like skin with deep fissures. Hair was absent all over the body including scalp area. The facial examinations revealed a fixed and open mouth, flattened nose, flat fontanels, small rudimentary external ears, absent eye balls, and eye openings covered by a reddish mucous membrane (Figure 1). The limb examination revealed flexion deformity in both upper and lower limbs (Figure -2).

The baby was admitted to the neonatal unit. there was failure of oral feeding and the baby was dehydrated. A nasogastric tube was inserted for feeding but a peripheral intravenous line could not be secured. Later, the baby's skin was noticed to peel off leaving erythomatous failure. The baby died on 3rd day may be due to dehydration and fulminant sepsis.

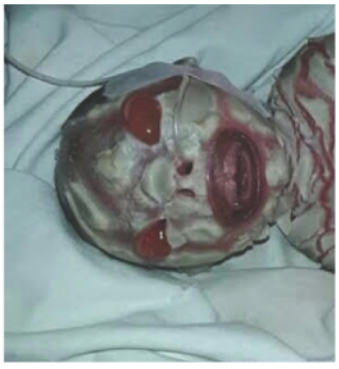

Figure – 1: Eye openings covered by a reddish mucous membrane.

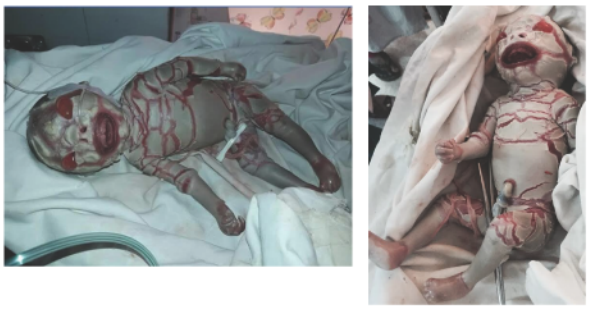

Figure-2: Flexion deformity in both upper and lower limbs

Discussion:

Ichthyoses (Greek icthys, meaning 'fish') represent a heterogeneous group of skin disorders that are characterised clinically by generalised scaling of the skin due to defective keratinisation and desquamation, and histologically by hyperkeratosis. They are usually distinguishable on the basis of inheritance pattern, clinical features, associated defects and histological changes. The autosomal dominant and X linked recessive ichthyoses are clinically less severe and rarely ever present at birth.

Harlequin icthyosis is a rare and often fatal congenital disease. The data about this anomaly is very limited, coming almost entirely from case reports.The incidence of this disease is 1 in 300,000 births. The first case of HI was reported in 1750 by Reverend Oliver Hart who described a fetus with thickened and cracked skin over the whole body[2].

Studies on the pathogenesis of this disease are novel. It has been found that HI is caused by mutations in the ABCA12 alleles[7]. It is essential to transfer of lipid from cytosol of the keratinocytes into lamellar granules. ABCA12 localizes throughout the entire Golgi apparatus to LGs at the cell periphery, mainly in the granular layer keratinocytes. ABCA12 works in the transport of lipids from the Golgi apparatus to LGs in the granular layer cells. At the transition from the stratum granulosum –the 3rdd layer of the epidermis –to the stratum corneum, the

content of the lamellar bodies are extruded in to the intercellular space to form protective lipid sheets that are responsible for the skin's hodrophobic barrier[2].

In HI, the ABCA12-mediated transfer of lipid to lamellar granules is defective. The lamellar granules themselves are morphologically abnormal or absent. Normal extrusion of lipid from these granules into the extracellular 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[4].
The inheritance of this anomaly is autosomal recessive, and affected babies are usually homozygous for the mutation, consistent with the autosomal recessive pattern of inheritance so in most cases there was consanguinity between parents[8], but in our case there was no consanguinity between parents of our baby and there was no family history of any congenital anomalies.Babies are usually born prematurely and do not have any brain or internal organ abnormalities9.however; in our case the baby was delivered prematurely with low birth weight.

The following findings may be noted on physical examination in the newborn period:

- Skin: Severely thickened skin with hyperkeratotic scale is present at birth. Deep, fissures separate the scales.
- Eyes: Severe ectropion is present. The free edges of the upper and lower eyelids are everted, leaving the conjunctivae and cornea at risk for desiccation and trauma.
- Ears: The ears are flattened absent retroauricular folds. The pinnae may be small and rudimentary or absent. The external auditory canal may be obstructed by scale.
- Lips: Severe traction on the lips causes eclabium and a fixed, open mouth. This may result in feeding difficulties.
- Nose: Nasal hypoplasia and eroded nasal alae may occur. The nares can be obstructed.
- Extremities: The limbs are encased in the thick, hyperkeratotic skin, resulting in flexion contractures of the arms, the legs, and the digits. Limb mobility is poor to absent.Circumferential constriction of a limb or digit can occur, leading to distal swelling, ischemic necrosis and autoamputation. Hypoplasia of the fingers, toes, and fingernails is reported. Polydactyly is described.
- Temperature dysregulation: Thickened skin prevents normal sweat gland function and heat loss. The infant is heat intolerant and can become hyperthermia.
- Respiratory status: Restriction of chest-wall expansion can result in respiratory distress, hypoventilation, and respiratory failure.
- Hydration status: Dehydration from excess water loss can cause tachycardia and poor urine output.
- 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.

In this case the skin, ears, mouth and nose findings are typical for HI . Both upper and lower limbs showed flexion deformity. The digits also showed flexion deformity. There was respiratory distress in our baby and she needed oxygen.
Affected infants usually do not survive for very long because of undernourishment caused by the rigidity of the lips, under ventilation and infections, but longer survival has been reported.10
In their review of clinical outcome in 45 cases of HI, Rajpopatet et al. reported a survival rate of 56%; 16 of 45 HI cases surviving for 7 years or longer and the longest surviving case reaching 25 years. Improved outcomes were linked to heterozygous mutations and early use (by day 7) of oral retinoid, whereas most neonatal deaths were attributed to sepsis and severe disease with homozygous mutations[1].

In our case the baby had respiratory distress from the day of delivery and supported with O2 inhalation.A nasogastric tube for nutrition was introduced. Skin infection occurred which developed into septicemia. Antibiotics were started when the skin infection occurred but the baby not respond to treatment, she died at the 3rd day of life. Oral retinoid hadn't been used due to a lack of experience as it was the first case of HI in our hospital.

Learning points

- The babies born with harlequin ichthyosis (HI) need intensive care management and persistent efforts from a team of neonatologist, dermatologist and neonatal intensive care unit nurses.
- Careful management and monitoring of patients for complications may improve outcome in neonates born with HI; patience is a virtue as long periods are required for significant recovery.
- Genetic counselling to the parents is of crucial importance to avoid situations such as rejections and child abuse.

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