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Harlequin Ichthyosis : A Rare Congenital Entity

JESIKA RIZVI TAMANNA[1], FIROZA BEGUM[2], NAHREEN AKHTER[3], TABASSUM PERVEEN[4]

Abstract

Harlequin Ichthyosis (HI) is an extremely rare genetic skin disorder. It is the most severe type of ichthyosis. It is characterized by thickened, dry, rough and armor like plates of skin with deep cracks in between. Alternative names for HI include- keratosis diffusafetalis, ichthyosis congenital, ichthyosis fetalis, harlequin fetus and ichthyosis congenital gravior. It is an autosomal recessive disorder with the majority of affected individuals being homozygous for mutation in the ABCA 12 gene. This condition presents with a wide range of severity and symptoms. Affected neonates usually do not survive beyond first few days of life. We are presenting prenatal diagnosis of a case of this rare condition.

Keywords: *Harlequin ichthyosis, genetic skin disorder, ichthyosis fetalis, ABCA 12 mutation.*

Introduction:

Harlequin ichthyosis (HI) is a lethal disease, [1,2] Incidence is 1 in 300000 births. HI is an inherited autosomal recessive disorder that characterized by congenital epidermis abnormality. The affected individuals are homozygous for ABCA 12 gene mutation. Though subjects with HI in very rare cases may survive for several months or years, there was a reported case of HI in Saudi Arabia, where the child has survived beyond 7 years. [3] HI appears with severe thickened and scaly skin on the entire body. In addition, ectropion (everted eye lids), lack of development of the external parts of the nose and ears, eclabium (everted lips) and open mouth, hypoplastic fingers, anonychia and mobility limitation of the joints are some other

clinical features of the HI.[2,4,5] Patients with HI are at high risk for hypo/hyperthermia, dehydration, respiratory distress, hypoventilation, malnutrition, hypernatremia, seizure, and skin

infection.[2,6] HI is associated with preterm birth and often leads to death due to neonatal complications such as fluid loss and septicemia.[3] This study reports a case of 32 weeks of pregnancy with undue enlargement of abdomen with respiratory distress .Sonographically suspected as HI with polyhydramnios and finally delivered a HI baby.

Case Report:

A 20 years old primigravid Bangladeshi patient presented to our OPD at her 32weeks of pregnancy with undue enlargement of abdomen with respiratory distress. Her 2D ultrasonography showed polyhydramnios and otherwise normal. Then to exclude congenital anomaly she was advised for 3D ultrasonography and the report showed abnormal facial features with eversion of eye lids(ectropion), eversion of lips(eclabium), exposed dentium caverna,(fig 2) clenched fist, deformed foot, flat nose and polyhydramnios. With probable diagnosis of HI she was admitted under Fetomaternal medicine department, BSMMU. There was no history of consanguinity and family history of HI baby. Patient with her guardian were explained about poor prognosis of the baby. The family opted to terminate the pregnancy and she was induced with prostaglandin and delivered a male baby with features of HI. The skin of the baby was split into plaques of rigid fixed skin, separated by deep red

fissures (fig 1). The tightness of the skin pulls around the eyes and mouth, forcing the eyelids and lips to

1. Registrar (Gynae & Obs), Bangabandhu Sheikh Mujib Medical College and Hospital, Faridpur.
2. Professor & Former Chairman of Fetomaternal Medicine Department ,BSMMU,Dhaka.
3. Professor & Former Chairman of Fetomaternal Medicine Department ,BSMMU, Dhaka
4. Professor & Chairman of Fetomaternal Medicine Department ,BSMMU, Dhaka

Address of Correspondence: Dr. Jesika Rizvi Tamanna, Registrar (Gynae & Obs), Bangabandhu Sheikh Mujib Medical College and Hospital, Faridpur. E-mail: jesika.tamanna83@gmail.com

turn inside out revealing the red inner linings (ectropion and eclabium respectively).

The chest and abdomen of the infant was restricted by the tightness of the skin, making breathing difficulty. The ears appear to be missing, hands and feet were tight and constricted, fingers and toes were hypoplastic with tapered distal end which were held in flexed contracture. Movements were restricted. The baby was attended by neonatologist, resuscitation was done, baby was wrapped with saline soaked gauge but the baby died within 15 minutes due to respiratory distress. For confirmation DNA based analysis for ABCA 12 mutation was adviced but the parents refused for financial problem. The parents were psychologically supported and as there is 25% chance of recurrence , genetic counselling was recommended for future pregnancies.

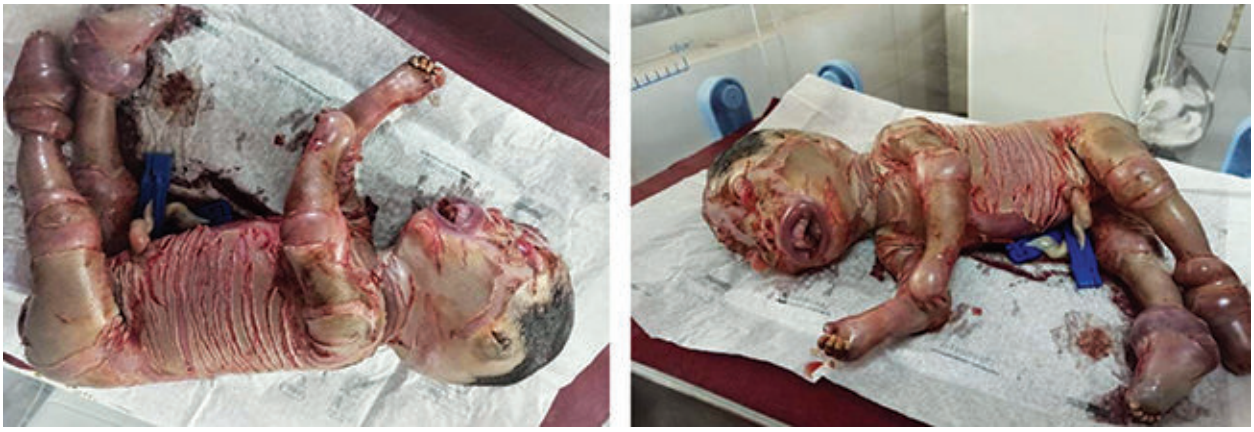

Fig.-1: *The patient with deep cracked skin, open wide mouth, everted eye lids, and flatted nose and ear*

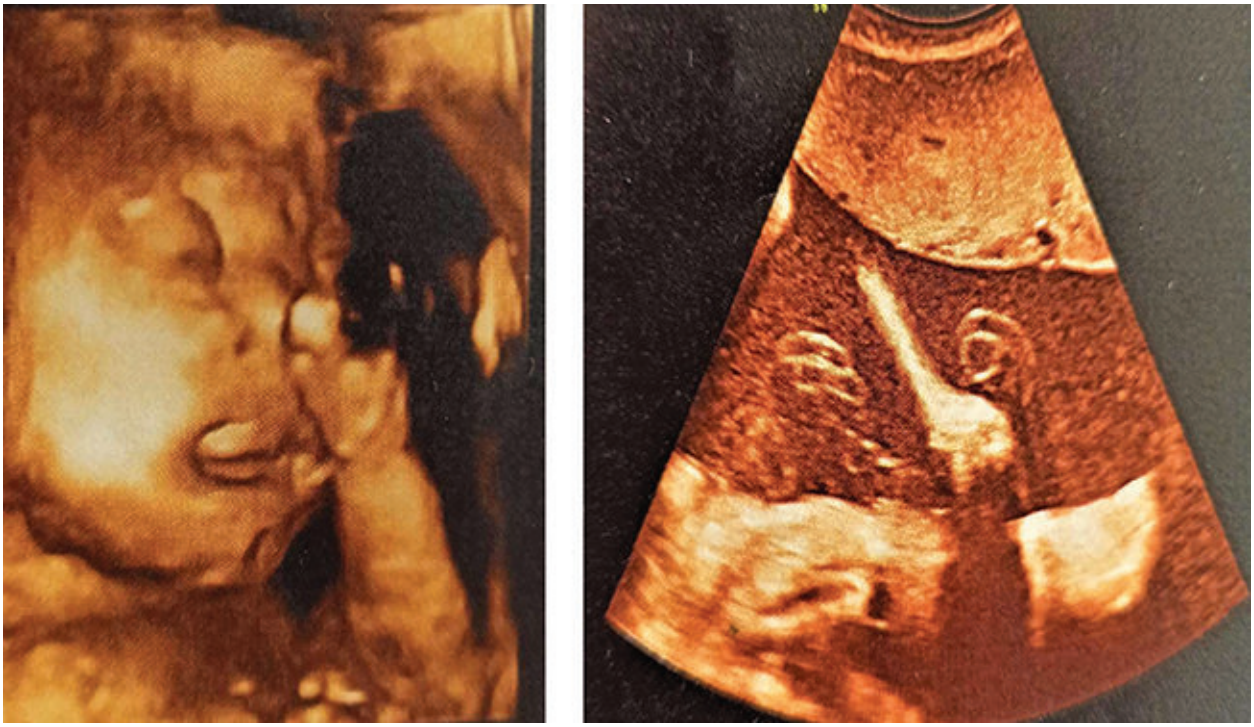

Fig.-2: *3D USG showing ectropion, eclabium, flat nose, clenched hand*

Discussion

HI is an inherited autosomal recessive disorder that characterized by congenital epidermis abnormality.[4,5] The first case was reported in 1750 by Reverend Oliver Hart.The affected individuals are homozygous for non-sense mutation in ABCA 12 gene (adenosine triphosphate-binding cassette transporter, subfamily A, member 12) on chromosome 2q33- q35 resulting in premature termination of protein translation [4]. Its OMIM number is

242500. The ABCA 12 gene plays a crucial role in transporting lipids to various body cells.

These lipids are essential for physiological development of the epidermis .[4,6] and the normal development of the skin.[2] At birth, infants are covered with hard hyperkeratotic armor, composed of large, thick, yellowish brown, and very sticky plates.[6,7] After birth, deep red fissures occur on these hard and inflexible plates that extend to the dermis, resulting in a joker-like skin. Infants with HI might have microcephaly, ectropion, and eclabium.[4] External auditory meatus and nostrils appear rudimentary and immature.[8] In addition, patients with HI have respiratory failure as a result of restricted chest expansion and skeletal deformities. Feeding problems may result in low blood sugar, dehydration, and kidney failure. In addition, temperature instability and infection would be common.[4,6] Almost all these clinical features were observed in the current case.

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] Diagnosis can be confirmed by testing for mutation in ABCA12 gene in the affected fetus. DNA based analysis for prenatal testing is reliable and conclusive [13]. Prenatal diagnosis with Chorionic Villus Sampling (CVS) and amniotic fluid cells analysis is advised in women with previous affected baby. Amniocentesis at 17 weeks may show intracellular lipid vesicle in shed keratinocytes and this is the investigation of choice. Skin biopsy is not currently recommended for prenatal diagnosis [11,12]. Antenatal USG, especially 3D USG [14] is another modality of prenatal diagnosis but late phenotypic expression of the disease poses a challenge for timely detection and further management. Similarly in our case there was no remarkable findings upto 28 weeks USG but later at 32 weeks sonographic abnormalities were identified.

The mortality of HI is high and most of the subjectss die within a few weeks of birth because of secondary complications such as infection and dehydration.[4] However, survival contributes to the type of mutations; subjectss with the compound heterozygote mutation survive more than those with the homozygote mutation.[9] In addition, advances in the postnatal treatments and cares improve the prognosis of the disease. A comprehensive case series of 45 patients assessed by Rajpot et al [4,9] suggested early oral retinoids, aid in the shedding of hyperkeratotic scales with overall survival rate more than 50%. The patients' quality of life improves with supportive cares. In addition to the routine care such as

checking vital signs, patients should be kept in a warm and humid incubator. Hydration should be performed.[10] As accessing to the peripheral vessels can be difficult, an umbilical venous catheter might be needed. Taking shower twice per day, saline compress and

soothing emollients must be used to keep the skin soft and to accelerate the desquamation.

Water and electrolyte disturbances must be managed as well. Environment must be cleaned

up to prevent infection; hence, repeated cultures of the skin would be essential to detect the hazardous micro-organisms.[4] In addition, genetic counseling and molecular investigation of the ABCA12 gene should be considered.

Conclusion:

HI is a rare skin disorder. It follows autosomal recessive mode of inheritance. Prenatal diagnosis should be offered to women with previously affected babies. DNA analysis for ABCA12 mutation will clinch the diagnosis. Characteristic features on prenatal USG tend to appear late so the scans should be repeated even when the second trimester anatomy scan is normal and can help in a situation when a DNA diagnosis is unavailable. We suggest that mutation screening of the ABCA12 gene and genetic counseling of families would be important especially in families with a consanguinity marriage.

Consent

Informed written consent has been taken from the patient and will be provided on request.

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