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# Keratosis diffusa fetalis: A rare case report

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**Abstract**
Harlequin Ichthyosis is the most severe form of congenital Ichthyosis presenting at birth. It is characterized by thick, fissured armor-plate hyperkeratosis, ears and nose deformities, ectropion, eclabium with fish mouth appearance, flexion deformities of all joints and hypoplastic digits. It is a very rare disorder with autosomal recessive inheritance. Perinatal mortality is high and the survivors develop severe erythroderma subsequently. We report a case of Harlequin Ichthyosis not only because of its rarity but also its tendency to occur in consecutive pregnancies. We recommend to have a genetic screening and counseling in all high risk couples e.g. consanguinity marriages as well as having more studies to diagnose and determine the best mode to deliver a baby with HI.
**Conclusion:** Early diagnosis and genetic counseling of the parents is an important step in managing Harlequin Ichthyosis. We recommend to have a genetic screening and counseling in all high risk couples e.g. consanguinity marriages, and with family history of Harlequin icthyosis or previous child born with Harlequin icthyosis preimplantation genetic diagnosis can be done by screening for ABCA12 gene in both affected baby and parents.

**Keywords:** Keratosis diffuse fetalis, Harlequin icthyosis, gene mutation, congenital autosomal

## Introduction
Disorders of cornification (ichthyoses) are a group of rare inherited disorders characterised by the presence of excessive amounts of dry surface scales. It is a disorder of keratinisation or cornification. Abnormal epidermal differentiation or metabolism is the basic pathology in these disorders. Histopathological examination of skin biopsy will show hyperkeratosis in these neonates. Harlequin ichthyosis (HI)/ Keratosis diffusa fetalis is the most severe and rare form of congenital ichthyosis.
Since the disease causes considerable amount of disfigurement it may cause profound psychological trauma in parents or other caregivers. Children who survive post-infancy may face stigmatization and discrimination owing to abnormal appearance of skin. More than 200 cases have been reported throughout the world. Antenatal diagnosis in suspected cases can be confirmed using electron microscopy of fetal skin biopsy and DNA-based diagnosis with chorionic villus sampling or amniocentesis. There is no cure for this condition and only supportive treatment can be given to prolong life.

## Case report
A G4P2L2A1 with previous 2 FTVD (Both female babies alive and healthy) aged 26 years registered with a private practitioner, reported to SS institute of medical sciences, labor room with 34 weeks 3 days of gestation with preterm premature rupture of membranes in latent labor with breech presentation. A history of 2$^{nd}$ degree consanguinity was noted. Her ANC was uneventful, anomaly scan done at 22 weeks was normal. Patient and attenders were counselled regarding mode of delivery and they opted for LSCS with tubectomy. She underwent emergency lower segment cesarean section with abdominal tubectomy in view of breech presentation and delivered a female icthyotic baby weighing 1.9 kg on, July 07 2019. Her postnatal course was uneventful. She was discharged on postnatal day-6 after suture removal.
The baby had white porcelain-like skin covering the body like armor with deep creases all over the body as shown in. Bleeding was noticed from the creases. The baby had a weak cry at birth. Eyelids and lips were everted showing ectropion and eclabion, respectively. Nasal hypoplasia with two nostrils was seen. The mouth was open with thick lips as seen in Figure 1.

The fingers and toes were flexed and fixed flexion deformity noticed, as seen in Figure 3. The ears were small with closed pinna. The heart rate and respiratory rate were normal. The baby was sent to the neonatal intensive care unit for further management. Patient and attenders refused admission to NICU inspite of extensive counselling and further care.

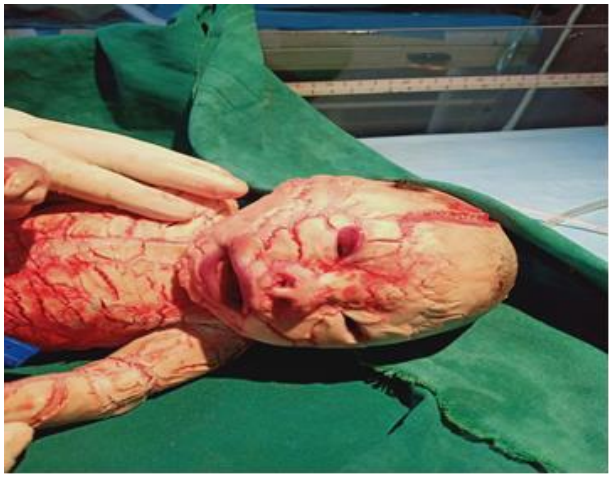

**Fig 1:** Showing Harlequin fetus with characterstic clown like facies, with ectropion, eclabium and under developed nose. Note the coat of armour like appearance with shiny plates and fissures

**Fig 2:** The fingers and toes were flexed and fixed flexion deformity, incurved toes, short foot length and clenched fist typical of Harlequin fetus

## Discussion

Harlequin icthyosis is a congenital disorder characterized by an autosomal recessive inheritance and incidence of about 1 in 300,000 births [1]. Usually, it has fateful prognosis and most of HI babies die in first weeks of life. Majority of the cases are reported due to ABCA12 gene mutation which is a gene responsible for transporting lipid to the epidermis in order to form a healthy normal skin. Infants at birth usually have thick, fissured armor-plate hyperkeratosis, ears and nose deformities, ectropion, eclabium with fish mouth appearance, flexion deformities of all joints and hypoplastic digits. Furthermore, restricted chest expansion and skeletal deformities may result in respiratory failure. Hypoglycemia, dehydration or even renal failure is common in these patients mainly due to feeding problems. In addition, hypo- or hyperthermia as well as infections are common. Most of these clinical features are present in this case. The hallmark of the diagnosis are the family history, consanguinity and other skin disorders. In our case also, the couple was consanguineous.

The maternal triple-marker screen is part of the standard clinical obstetric practice and is used routinely to diagnose Down syndrome, trisomy 18, and open neural tube defects. The most common cause for extremely low levels of unconjugated estradiol, one of the markers screened in the triple test, is X-linked ichthyosis. In this condition, there is placental insufficiency of steroid sulfatase, and therefore defective steroidogenesis. In case maternal serum screening reveals isolated low levels of unconjugated estradiol, amniocentesis or CVS sampling must be performed to confirm the suspicion of X-linked ichthyosis. Since there are 25 % chances of recurrence in future pregnancies, it is a challenge for the obstetricians and the radiologists to enable timely diagnosis. Three dimensional (3D/4D) ultrasonography may show certain features like rudimentary ears, flexion contractures, and floating particles in the amniotic fluid suggestive of Harlequin Ichthyosis. Even if there is no history of HI in family, features like large and gaping mouth, aplasia of the nose, abnormal limbs, and bulging eyes on 3D scans may help in diagnosis. Two-dimensional ultrasonography can also demonstrate features of harlequin ichthyosis but not until late in the second trimester, when enough keratin buildup is present to be sonographically detectable. Short feet may be an early marker for harlequin ichthyosis [2].

Apart from imaging, fetal skin biopsy also has a role in prenatal diagnosis. On light microscopy, premature keratinization can be identified by 20th to 22nd week. Electron microscopy may show atypical intraepidermal vesicles at 16 weeks. Amniocentesis at 17 weeks may show intracellular lipid vesicles in clump shed keratinocytes [3]. DNA-based prenatal testing by direct sequence analysis and restriction enzyme digestion analysis using fetal genomic DNA from amniotic fluid cells at 16 weeks gestation is also available for HI, and it is the investigation of choice for prenatal diagnosis of this condition. Detailed genetic counseling is therefore required for affected families. Preimplantation genetic diagnosis can be done by analyzing ABCA12 gene if the family already had a previous child with Harlequin icthyosis history. Extended family members should be advised to avoid consanguineous marriages because of the genetic risk. The mortality rate for Harlequin Ichthyosis is high, with worldwide figures approaching 50%. However, with neonatal intensive care and oral retinoid therapy (acitretin in the dose of 0.5-1 mg/kg/day orally), more babies survive the newborn period than in the past. A topical retinoid (tazarotene) can also be used to treat local and mechanical circulatory problems caused by hyperkeratosis. In a review of 45 cases by Rajpopat *et al.* it was found that twenty five cases of HI (56%) survived, ranging in age from 10 months to 25 years and there were twenty deaths (44%) from day 1 to day 52 either due to respiratory failure or fulminant sepsis [4].

## Conclusion

With improvement in supportive clinical care, the use of oral retinoid and regular moisture of the skin the survival rate of patients with HI has increased. However, early diagnosis and genetic counseling of the parents is an important step in managing such patients. We recommend to have a genetic screening and counseling in all high risk couples e.g. consanguinity marriages, and with family history of Harlequin icthyosis or previous child born with Harlequin icthyosis preimplantation genetic diagnosis can be done by screening for

ABCA12 gene in both affected baby and parents.

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