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CASE REPORT

Twin Neonates with Harlequin Ichthyosis in a Rare Monochorionic Dizygotic Pregnancy: A Medical Enigma

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ABSTRACT

The condition Harlequin ichthyosis (HI) is a severe but rare form of congenital ichthyosis. It is due to mutation in the ABCA12 gene. Harlequin ichthyosis is an inherited, autosomal recessive disorder. Our case study reports the first ever birth of twins affected by Harlequin ichthyosis to the parents with a strong family history in Pakistan. Family history played a major role in our case, as there was a strong history of HI in the relatives. There are around 200 case reports published worldwide about HI, but to our knowledge, this is the first case ever reported of twin birth of Harlequin ichthyosis in Mansehra, Pakistan

Keywords: Autosomal recessive, Congenital, Harlequin ichthyosis, Mutation, Twin Pregnancy.

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Introduction

The condition Harlequin ichthyosis (HI) is a severe but rare form of congenital ichthyosis. HI is due to mutation in the ABCA12 gene. The process of keratinization is mainly affected in this disorder. During the process of keratinization, the epidermal layer of skin differentiates to form the stratum corneum[1].HI is an inherited, autosomal recessive disorder; it is one of the most severe form of congenital ichthyosis. Newborn with HI presents with thickening of keratin layer along with plate like scaling of the skin separated by erythematous fissures[2]. The prevalence of the disorder is approximately 1 in 300,000 infants with almost 200 cases reported worldwide.[1] Prenatal diagnosis primarily depends on ultrasound findings, analysis of amniotic fluid, and molecular testing of umbilical cord blood. However, because the disease manifests later in pregnancy and has subtle early features, many affected fetuses miss the ideal window for detection. This makes prenatal diagnosis particularly challenging, especially when there is no known family history.[4] The standard for the detection of HI nowadays is next-generation sequencing (NGS).[5] In addition to disease management, comprehensive psychosocial support should be provided to parents through counselling by psychologists and social workers. Given that most affected infants do not survive beyond the neonatal period, families must be prepared to emotionally manage the high likelihood of loss. Affected newborns typically present with pronounced eclabium and ectropion,

underdeveloped digits, and incomplete formation of facial structures, including the eyes, nose, and ears. They also exhibit impaired thermoregulation and markedly restricted limb movements.[6] Our case study is unique as it reports the first ever birth of twins affected by HI in Mansehra, Pakistan.

Case Presentation

An 18 year old pregnant woman with $G_2P_1Al_1Ab_0$ came to a private clinic in Mansehra with complaints of Pervaginal bleeding and discharge for care and management of her second pregnancy. She already had 1 live birth via Caesarean section. Her antenatal scan showed diamniotic, monochorionic twins at gestational age 29+4 weeks with no gross fetal anomalies. Liquor was adequate, Fetal cardiac activity (FCA) positive for both fetuses. Gestational age was also confirmed through the last menstrual period, which resembles the scan. She underwent an emergency C-section due to premature rupture of the membrane and a previous 1 C-section scar. Twins were delivered through routine C-section without any complications. Both twins had thick white skin with intervening deep skin creases covering the whole body, a distinctive feature of Harlequin Ichthyosis(HI). The twins also had other HI features, including:

1) Severe ectropion is present in the eyes.
2) Ears flattening and absence of retroauricular folds.
3) A fixed open mouth caused by the traction of the lips.
4) The patient has obstructed nares with nasal hypoplasia.[7]

Parents had a consanguineous marriage and a family history of a similar disorder to uncle's twins. However, the firstborn baby of the couple was normal and alive. There was marked bilateral ectropion with immature eyes, deformed auricles, and eclabium with a persistent open mouth. The upper limbs, lower limbs, and extremities of both fetuses were hypoplastic. They had a weak cry.

Figure 1: Twins with severe Harlequin Ichthyosis.

Figure 2: Severe cracked and thick skin with hyperkeratinization, flatted nose, wide mouth, deformed eyes, and ears.

The first fetus expired after 10 mins of birth, while the second fetus was nursed in the NICU. Parenteral nutrition was initiated for the live fetus on the first day, as the baby couldn't initiate the suckling reflex and the inability of the NG tube to be inserted due to a flattened, deformed nose and blocked nostrils. Antibiotics and electrolytes were given through the intravenous route. Skin was moisturized with bland emollients and wet dressings. The second neonate couldn't survive long and died on the second day after delivery.

Discussion

Harlequin ichthyosis represents the most severe subtype of autosomal recessive congenital ichthyosis and is characterized by excessive keratin accumulation in fetal skin. Twin pregnancy with one normal fetus and second with HI had been reported in Pakistan, but both twins affected by HI is first ever case reported in Pakistan, and extremely rare

worldwide with few cases reported so far.[8] Prenatal diagnosis in developing cities remains a challenge due to limited genetic testing facilities. Also, because the disorder manifests later in gestation and its early features may be subtle, the ideal diagnostic window is often missed in ultrasonographic imaging, making antenatal detection particularly challenging in pregnancies without a known family history.[4]

Management begins with immediate admission of the neonate to the Neonatal Intensive Care Unit (NICU). Beyond intensive supportive care, affected infants often require multiple surgical interventions, including reconstructive procedures and skin grafting, to address extensive skin damage as well as deformities involving the eyelids and extremities.[8] Harlequin ichthyosis is associated with a high mortality rate, and management focuses on addressing complications on an individual basis. Nutritional support through tube feeding is often necessary until eclabium improves and oral feeding becomes possible. Early ophthalmologic evaluation is important for managing ectropion, which is prominent initially but usually improves as the thick scales are shed. Frequent application of emollients such as petrolatum is essential, and constrictive hyperkeratotic bands should be gently released to prevent compromised blood flow to the digits.[4]

Surgical treatment options are few, with autologous skin grafting being the most commonly used approach. However, due to the high risk of sepsis and skin infections, any invasive procedure must be performed with great caution.[9] The highest mortality in harlequin ichthyosis occurs within the first three months of life, primarily due to respiratory failure or sepsis, accounting for about 75% of cases. Around one-third of affected infants experience recurrent skin infections, and nearly 44% struggle to maintain a normal weight.[10]

Conclusion

We conclude that these twins' clinical and pathological abnormalities are of Harlequin ichthyosis (HI), which is the rarest and most severe form of congenital ichtyosis and first ever twin case. It is a life-threatening genetic disorder with poor prognosis and high mortality rate. In families with a history of HI, we advise detailed counselling of couples regarding the mutation and its effect on the neonate, as genetic testing facilities are limited and out of reach in developing cities. Family history played a major role in our case as there was a strong history of HI in the uncle's twins. There are around 200 case reports published worldwide about HI, but to our knowledge this is the first case ever reported of HI in Mansehra.

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