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Harlequin Ichthyosis in a Preterm Neonate Born to a Consanguineous Couple: A Case Report and Prenatal Diagnostic Challenges

Dr Parul Jaiswal[1], Dr Meenal Patvekar[2], Dr Akshay Jagtap*[3]

[1]Junior resident, Department of obstetrics and gynaecology, Dr. D. Y. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, PIMPRI, PUNE-018

Email ID: paruljaiswaldr14@gmail.com

[2]Professor and unit head, Department of obstetrics and gynaecology, Dr. D. Y. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, PIMPRI, PUNE-018

Email ID: mpatvekar@gmail.com

[3*]Senior Resident, Department of obstetrics and gynaecology, Dr. D. Y. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, PIMPRI, PUNE-018

Email ID: dr.akshayj01@gmail.com

***Corresponding**

Dr Akshay Jagtap

Senior Resident, Department of obstetrics and gynaecology, Dr. D. Y. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, PIMPRI, PUNE-018

Email ID: dr.akshayj01@gmail.com

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ABSTRACT

Harlequin ichthyosis (HI) is a rare, severe autosomal recessive disorder affecting the epidermal barrier due to ABCA12 gene mutations. It presents with thick, hyperkeratotic skin, severe ectropion, eclabium, and limb deformities, often leading to perinatal complications. This case report describes a 19-year-old unregistered primigravida at 35 weeks of gestation with a history of consanguineous marriage, presenting with preterm premature rupture of membranes (PPROM) and obstetric pain. A vaginally delivered female neonate weighing 2.2 kg exhibited classical HI features, including fissured skin, underdeveloped auricles, cyanosis, and bradycardia. Despite advances in prenatal imaging, early detection remains challenging, particularly in resource-limited settings. Ultrasound findings such as thickened skin, fetal akinesia, and polyhydramnios can suggest HI, but definitive molecular diagnosis via amniocentesis or chorionic villus sampling is not widely accessible. Maternal risks include polyhydramnios, preterm labor, and increased cesarean delivery rates, requiring vigilant antenatal monitoring. Genetic counseling is critical for affected families, emphasizing the 25% recurrence risk in future pregnancies. This report underscores the need for enhanced prenatal screening protocols and multidisciplinary management strategies for high-risk pregnancies in consanguineous settings. This report presents a case of prenatal suspicion and postnatal confirmation of HI, highlighting the diagnostic limitations, obstetric challenges, and genetic implications. By addressing the gaps in prenatal care and raising awareness about carrier screening and reproductive options, gynecologists can play a crucial role in supporting high-risk pregnancies and reducing the recurrence risk in future generations.

Keywords: *Harlequin Ichthyosis, Prenatal Diagnosis, ABCA12 Mutation, Consanguinity, Genetic Counselling*

1. CASE PRESENTATION

A 19-year-old unregistered primigravida at 35 weeks of gestation presented with PPROM and labour pains. She belonged to a rural background with no prior antenatal visits. Her medical and surgical history was unremarkable, but the marriage was consanguineous (first-degree relatives). There was no known family history of genetic disorders.

On admission, she was hemodynamically stable with regular uterine contractions. Fetal heart rate monitoring showed a non-reassuring pattern. Urgent ultrasound revealed severe oligohydramnios and a growth-restricted fetus measuring below the 10th percentile. Fetal skin thickening and reduced limb movement suggested a congenital skin disorder, but no definitive prenatal diagnosis was possible due to late gestation and lack of previous scans.

Labour was augmented, and she delivered vaginally a female neonate weighing 2.2 kg, measuring 39 cm in length with a 35 cm occipitofrontal circumference. Apgar scores were 3 and 5 at one and five minutes, respectively. The neonate presented with classical HI features, including thick, armor-like hyperkeratotic skin with deep fissures, ectropion and eclabium, a flattened nasal bridge, underdeveloped auricles, severe limb contractures with restricted movement, cyanosis, bradycardia, and respiratory distress (Figure 1).

Figure 1: Presentation of classical HI features in the neonate.

Despite resuscitation efforts, the neonate experienced progressive respiratory failure due to restricted chest wall expansion. NICU admission was considered, but due to resource limitations, only supportive care including hydration and topical emollients was provided. Genetic counselling was offered, and ABCA12 mutation testing was advised. The postpartum period for the mother was uneventful.

Given the autosomal recessive inheritance, the couple was counselled regarding the 25% recurrence risk and advised on prenatal diagnostic options, including CVS at 10–12 weeks or amniocentesis at 15–18 weeks in future pregnancies. This case underscores the critical need for antenatal care, especially in consanguineous marriages, to enable early suspicion and diagnosis of autosomal recessive disorders.

2. DISCUSSION

Harlequin ichthyosis (HI) is a rare, life-threatening congenital skin disorder caused by mutations in the ABCA12 gene, which plays a crucial role in lipid transport and epidermal barrier formation. It is inherited in an autosomal recessive manner and has an estimated incidence of 1 in 300,000 births [1, 2]. The disorder is characterized by thick, Armor-like hyperkeratotic plaques, severe ectropion (everted eyelids), eclabium (everted lips), and contracted limbs, leading to high perinatal mortality [2, 3].

In obstetric practice, prenatal diagnosis of HI remains a significant challenge, especially in resource-limited settings lacking access to genetic testing and advanced imaging. Although second-trimester ultrasound findings, such as thickened skin, fetal akinesia, and polyhydramnios, may raise suspicion for HI, definitive diagnosis requires molecular analysis via chorionic villus sampling (CVS) or amniocentesis [4]. Early detection is critical for genetic counselling, reproductive decision-making, and delivery planning. Maternal complications in HI pregnancies include polyhydramnios, preterm labour, and increased caesarean rates due to fetal anomalies or distress [5]. The psychological burden on families is considerable, warranting comprehensive prenatal support.

Ultrasound imaging plays an essential role in the prenatal detection of HI. 2D ultrasound can reveal features like fetal akinesia, limb contractures, and polyhydramnios due to impaired swallowing. 3D/4D ultrasound enhances visualization of facial deformities such as ectropion and eclabium, as well as the characteristic armor-like skin plaques [6, 7]. Serial imaging should be performed in high-risk pregnancies, especially in consanguineous couples. Postnatal diagnosis may be supported by electron microscopy (EM) and histopathology. EM demonstrates defective lamellar granules in keratinocytes, while skin biopsy reveals massive hyperkeratosis, parakeratosis, and a thin granular layer [8]. These findings help confirm the diagnosis when genetic testing is unavailable or inconclusive.

The pathogenesis of HI involves mutations in ABCA12 that impair lipid transport in keratinocytes, disrupting the epidermal

barrier. This leads to transepidermal water loss, dehydration, electrolyte imbalance, increased susceptibility to infection, and restricted respiratory movements, all of which contribute to early mortality [9]. Genetic counseling is crucial for families affected by HI. Carrier screening and prenatal diagnosis through CVS or amniocentesis are critical in future pregnancies.

Preimplantation genetic diagnosis (PGD) via IVF offers an option to avoid recurrence. Counseling should also provide psychosocial support and address culturally sensitive issues, particularly related to consanguinity.

Comparatively, cases of HI reported in India and globally have shown similar patterns of consanguinity, late or missed prenatal diagnosis, and early neonatal death. A few cases with early antenatal suspicion through detailed 3D/4D imaging and immediate neonatal intensive care have reported survival up to weeks or months, especially in tertiary care centers. Our case adds to the limited Indian data on unregistered pregnancies, emphasizing the added vulnerability due to poor antenatal access. Kataria et al. described a preterm neonate with classical features of Harlequin ichthyosis, born to consanguineous parents. The infant exhibited hallmark signs including thick, armor-like scales with deep fissures, ectropion, eclabium, flattened nasal bridge, hypoplastic ears, and absence of scalp and facial hair. Limb swelling led to restricted joint mobility. The condition is linked to mutations in the *ABCA12* gene, which disrupt lipid transport in epidermal cells. Despite supportive care, the neonate succumbed within seven hours of birth [10] Salehin et al. reported a case involving a 31-year-old woman in her third pregnancy who delivered a female infant with clinical features consistent with Harlequin ichthyosis, including thickened, fissured skin, ectropion, eclabium, cyanosis, and immature external features. The baby weighed 2.1 kg and required intensive care, but despite the initiation of supportive treatment, the parents opted for discharge on the day of birth [11]. Sharma et al. reported a male neonate born at 36 weeks via emergency cesarean section due to fetal distress. The infant exhibited characteristic features of Harlequin ichthyosis, including thick, hyperkeratotic skin with deep fissures, ectropion, eclabium, hypoplastic digits, absent palmar and plantar creases, and limb contractures. He required immediate respiratory support and was admitted to the NICU. Upon seeing the infant, the family recalled a similar presentation in a previous child who had died within 24 hours of birth [12].

Given the autosomal recessive inheritance of HI, genetic counseling is essential for families with a confirmed diagnosis or a history of the disorder. Couples with previously affected child or consanguineous marriages have a 25% recurrence risk in subsequent pregnancies [9]. Carrier screening using targeted genetic testing for ABCA12 mutations is recommended for both parents. In future pregnancies, prenatal genetic diagnosis through chorionic villus sampling (CVS) at 10 to 12 weeks or amniocentesis at 15 to 18 weeks can detect the presence of pathogenic mutations [13]. If both parents are confirmed carriers, preimplantation genetic diagnosis (PGD) during in-vitro fertilization (IVF) may offer the opportunity to select unaffected embryos for implantation. Counseling sessions should include discussions on the prognosis of HI, the possibility of palliative care in severe cases, and the availability of advanced supportive management for affected neonates. Additionally, psychological support for parents and siblings is crucial to address the emotional and ethical challenges associated with the diagnosis. Genetic counseling also serves as a platform to raise awareness about the risks of consanguineous marriages and the importance of early prenatal screening.

Overall, the effective diagnosis and management of HI require a multidisciplinary approach involving obstetricians, genetic counselors, maternal-fetal medicine specialists, and neonatologists. By providing families with comprehensive information, healthcare professionals can facilitate informed decision-making and optimize perinatal care.

The lack of antenatal care, absence of early ultrasound screening, and unregistered pregnancy status further complicated the timely identification of this condition. Proper antenatal screening, genetic counseling, and multidisciplinary care coordination are essential in high-risk pregnancies, particularly in consanguineous marriages where the likelihood of autosomal recessive disorders is increased.

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