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Case Report

Harlequin ichthyosis: report of three cases

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ABSTRACT

Harlequin Ichthyosis is the most severe form of congenital ichthyosis. It characteristically presents as large thickened plate like scaly skin lesions over whole body at the time of birth. Few patients survive beyond neonatal period. Mortality is due to respiratory failure, hypo/hyperthermia, infections, electrolyte imbalance and dehydration. Prevention of Harlequin Ichthyosis can be done by prenatal genetic testing and counselling of parents. We are hereby reporting three cases of Harlequin Ichthyosis in newborns.

Keywords: ABCA-12 gene, Congenital Ichthyosis, Harlequin Ichthyosis, Retinoids

INTRODUCTION

Harlequin Ichthyosis (HI) is the rare lethal form of hereditary skin disorder with autosomal recessive inheritance. Reported incidence is 1 in 3,00,000 live births.[1] Only approximately 200 cases of HI are reported in literature. At the time of birth, large thickened scaly skin lesions with multiple erythematous fissures are present over whole body. Other clinical features may include ectropion, eclabium, open and wide mouth, hypoplastic flat nose, rudimentary ear appendages, hypoplastic fingers and toes, anonychia and joint contractures.[2] Diagnosis is mainly clinical, but can be confirmed by genetic testing and skin biopsy. Oral retinoids are effective when started early after birth.[3] Prognosis is very poor, most of the patients die during first few days of life. Very rarely do patients survive for months or years.

Case Histories

Case-1: A 35-year-old pregnant woman, 5th gravida, was admitted to our institute. A male full-term newborn, with birth weight 2.44 kg was delivered by normal vaginal delivery. There was history of consanguineous marriage. Her previous four siblings were normal. The newborn had thick scaly lesions with multiple fissures over whole body at the time of birth. Ectropion, eclabium, open and wide mouth, hypoplastic flat nose, rudimentary ear appendages, hypoplastic fingers and toes, anonychia and joint contractures were also present (Figure-1). Heart rate was

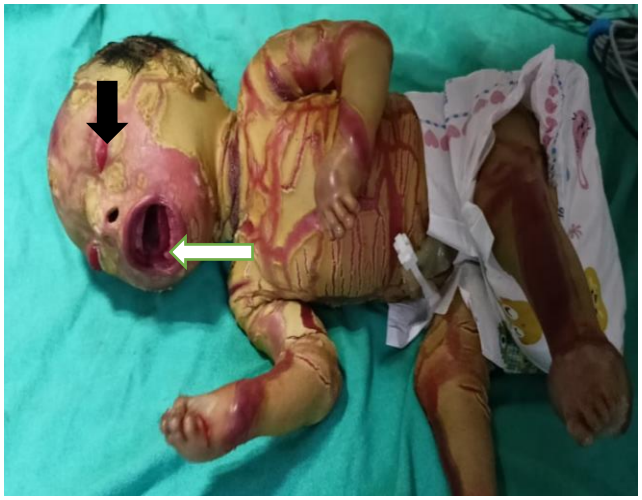

Figure-1 (Case-1): Typical clinical features of Harlequin Ichthyosis. Ectropion (black arrow), eclabium (white arrow), open wide mouth, rudimentary ear appendages, hypoplastic fingers and toes, anonychia and joint contractures (Coat of armor appearance)

130/minute and respiratory rate was > 60/min at the time of birth. Clinical diagnosis of HI was made. The newborn was admitted in NICU of our institute. He was kept in high humidity environment. Umbilical venous catheter was inserted for intravenous fluid and empirical antibiotics.

Trophic feeds were also started. Oxygen support was also given. Non-occlusive dressing with lubricants and/or saline compresses was done. Emollient and topical retinoids were applied. Isotretinoin (oral retinoid) was started at the dose of 1 mg/kg/day. Lubricant was used to protect the eyes. All blood investigations, including sepsis screening tests, blood culture, renal function tests and serum electrolytes were normal. Parents did not give consent for skin biopsy. Despite the intensive care, the newborn had impending respiratory failure on third day and was kept on ventilator. The newborn died on fifth day of life due to respiratory failure.

Case-2: A female preterm out-born newborn, 34 weeks gestation age, with birth weight 1.97 kg was born to a 22-year-old woman, 2nd gravida, by normal vaginal delivery. The newborn was admitted in NICU of our institute. There was history of consanguineous marriage. Her sibling was normal. The newborn had similar characteristic clinical features of HI as in Case-1. She also had conjunctival protrusion with chemosis (Figure-2). Intensive neonatal care was started on admission. Counselling of parents about the disease course and prenatal diagnosis for next child were done. The newborn had signs of sepsis and respiratory failure on fifth day of life. Second line antibiotics were started and patient was kept on ventilator. Despite the intensive care, the newborn died on sixth day of life due to respiratory failure and sepsis.

Figure-2 (Case-2): Typical clinical features of Harlequin Ichthyosis. Creamish scales with deep erythematous fissures over whole body (white arrow). Ectropion with conjunctival protrusion with chemosis (black arrow), eclabium, open wide mouth, rudimentary ear appendages, hypoplastic fingers and toes, anonychia and joint contractures (Coat of armor appearance)

Case-3: A male full-term newborn, 38 weeks gestation age, with birth weight 2.56 kg was born to a 24-year-old primigravida mother by normal vaginal delivery at our institute. The newborn had characteristic clinical features of HI. He also had conjunctival protrusion with severe chemosis and oral mucosa protrusion (Figure-3). The newborn was admitted to NICU of our institute. There was no history of consanguineous marriage. Counselling of parents about disease course and prenatal diagnosis for next child was done. Intensive neonatal care was started and treated as per previous two cases. Despite this intensive care, the newborn died on fourth day of life due to respiratory failure.

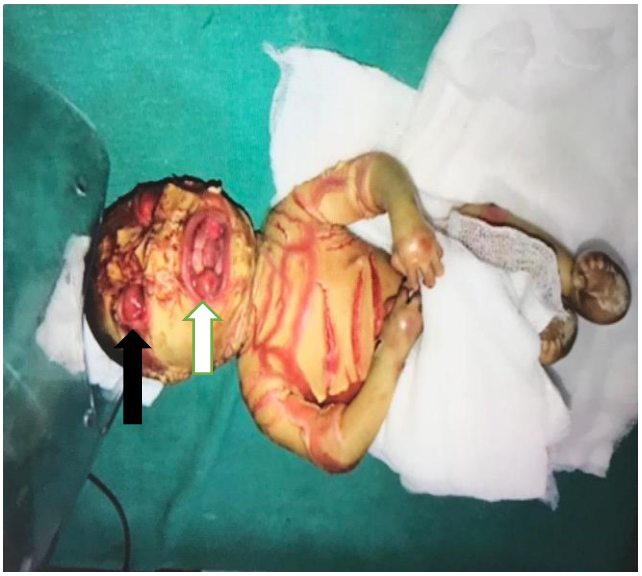

Figure-3 (Case-3): Case of Harlequin Ichthyosis with characteristic clinical features. Ectropion with conjunctival protrusion with chemosis (black arrow), eclabium with oral mucosa protrusion (white arrow)

DISCUSSION

Harlequin Ichthyosis is an autosomal recessive keratinization disorder. The first case of HI was reported in 1750.[4] Three major types of autosomal recessive congenital ichthyosis (ARCI) are harlequin ichthyosis, lamellar ichthyosis and congenital icthyosiform erythroderma. HI represents most severe form of ARCI and presents at the time of birth, while autosomal dominant and X-linked recessive ichthyosis are less severe forms and rarely present at birth.[5]

In majority of the cases with HI, there is mutation in adenosine triphosphate-binding cassette transporter A12 (ABCA-12) gene on chromosome 2q34 which encodes keratinocyte lipid transporter protein. This protein is responsible for formation and function of lamellar granules, it's major role in transporting lipids to cells that form epidermis.[6]

Patients present with thick, large armor-plate like, yellowish or creamish scales with deep erythematous fissures with marked facial disfigurement at the time of birth. All our

three cases had hard, large thickened hyperkeratotic plate like skin lesions at the time of birth. Multiple erythematous deep fissures were present over these skin lesions. They also had ectropion, eclabium, open and wide mouth, hypoplastic flat nose, rudimentary ear appendages, hypoplastic fingers and toes and anonychia. In our first case, conjunctival protrusion with severe chemosis and oral mucosa protrusion was present, which is a rare finding of HI. Contracture of joints leads to limited mobility and 'coat of armor' appearance. Digital contracture leads to clenched fist and incurved toes in HI. The extremities are swollen due to constriction by massive thickened skin. In all our three cases, joint contractures, digital contracture and swollen extremities were present. HI patients are at the risk of various complications such as respiratory failure, hypo/hyperthermia, infections, electrolyte imbalance and dehydration and feeding difficulty.[7]

Diagnosis mainly depends on characteristic clinical findings which we had done in all our cases. For confirmation, genetic testing is required to see the mutation in ABCA-12 gene by single nucleotide polymorphism array technology and skin biopsy is also diagnostic. In histological examination of skin lesions, characteristic abnormality in structure of lamellar granules and in expression of epidermal keratin is seen. Prenatal diagnosis by chorionic villous sampling, amniocentesis for genetic analysis, fetal skin biopsy and three-dimensional ultrasonography can be done as early as 18th weeks of pregnancy if the previous family history of similar disorder is present.[8]

Treatment is mainly supportive and includes maintaining temperature, fluid and electrolyte balance and preventing infections. The newborn should be kept in high humidity environment. Non-occlusive dressing or saline compresses with lubricants should be done which facilitates shedding of hyperkeratotic scales and keeps the skin soft. Keratolytic agents and emollient should also be applied to the skin to smoothen the skin, decreasing scale and hyperkeratosis. Topical retinoids should be applied as it increases shedding of grossly thickened scale. Oral retinoids as isotretinoin or acitretin 0.5-2.5 mg/kg/day should be started early after birth.[9] Survival rate increases more than 50% with early prescription of oral retinoid. Rajpopat et al reported 45 cases of HI, with 56 % survival from 10 months to 25 years. Survival also depends on type of mutation, as patients with homozygote mutation have less chances of survivability as compared to heterozygote mutation.[3] Protective devices and lubricants should be used to protect eyes. Sometimes fasciotomy for limb swelling due to constriction and plastic surgeries for digital contractures or necrosis is done.

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