CASE REPORT

Harlequin ichthyosis: a case report of prolonged survival

Anwar A Mithwani,¹ Asif Hashmi,² Shahid Shahnawaz,² Yasser Al Ghamdi³

¹Department of Pediatrics, Armed Forces Hospital, Jubail, Eastern, Saudi Arabia

²Department of Medicine, Armed Forces Hospital, Jubail, Eastern, Saudi Arabia

³Department of Family Community Medicine, Armed Forces Hospital, Jubail, Eastern, Saudi Arabia

Correspondence to

Dr Anwar Adil Mithwani, dmithwani@hotmail.com

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SUMMARY

Harlequin ichthyosis (HI) is a rare type of congenital ichthyosis associated with poor survival. We report, with photographic record, a male baby born with HI. To the best of our knowledge, this is the first reported case of HI in Saudi Arabia, where the child has survived beyond 7 years. The baby was born at 37 weeks of gestation from consanguineous parents with no inherited skin disorder in the family. The mother was 28 years old with three normal previous pregnancies and healthy babies. At birth, the baby's skin had thick scales separated by deep fissuring. He was managed in intensive care with supportive treatment and frequent application of lubricants, emollients and urea cream. The skin gradually became softened, and began to shed after 6 weeks. After 8 months of inpatient management, he was discharged. He is currently 7 years old and is still being treated for non-bullous congenital ichthyosiform erythroderma.

BACKGROUND

Harlequin ichthyosis (HI) is the most severe form of rare, autosomal recessive congenital ichthyoses (ARCI), characterised by profound hyperkeratosis, widespread fissuring and a variable degree of cutaneous malformations. The neonates born with this disorder have hard, keratinised skin covering most of their body. The large diamond-shaped, dense skin plates are separated by deep, erythematous fissures. The skin anomalies affect the shape of eyes, ears, nose and mouth.

The underlying genetic abnormality in HI has been identified as a mutation in the lipid-transporter gene adenosine triphosphate-binding cassette transporter A12 (ABCA12) on chromosome 2. Histological examination of the skin reveals characteristic abnormalities in the structure of lamellar granules and in the expression of epidermal keratin.

At the beginning, HI was invariably fatal in the neonatal period; abnormal skin interfering with normal fluid and temperature balance and forming a poor barrier against infection are found. Intense supportive care and early use of systemic retinoids have been linked with improved survival. Cases surviving beyond infancy live with life-long ichthyosis resembling lamellar ichthyosis (LI) or non-bullous congenital ichthyosiform erythroderma (NBCIE), producing considerable physical and psychological stress.

CASE PRESENTATION

A male baby, weighing 2400 g, was born at 37 weeks of gestation to a 28-year-old mother. The

Apgar score was 8 and 9 at 1 and 5 min, respectively. The patient was born vaginally after induction of labour for intrauterine growth retardation and diminished fetal movements. The pregnancy was uneventful and the mother had received regular prenatal care. The baby was fourth and the last child of consanguineous Saudi parents, the couple being paternal first cousins. The previous three pregnancies resulted in healthy babies after normal vaginal deliveries. The parents had no family history of any inherited skin disorder.

At birth, the baby was covered with armour-plate-like, thick yellowish scales, split by extensive deep fissuring extending into the dermis. The scales and fissuring covered most of the body in a diamond-like configuration but was highly marked in the flexures. The limbs were held in rigid semiflexion. Other features included eclabion with a fixed, open mouth, flattened nose with keratin plugging the nostrils, small and rudimentary external ears, severe ectropion, absent eyebrow, eyelashes and scalp hair, oedema of the limbs and inflexible digits due to taut skin, dystrophic and ischaemic nails and coronal hypospadias with bilateral cryptorchidism (figure 1). Other systems were unremarkable. Any attempts at movement, for example, during crying, readily caused oozing of fresh blood from the fissures.

The baby was nursed in neonatal intensive care unit and placed in a humidified incubator with cardiorespiratory monitoring. Parenteral nutrition was initiated on the first day of life as the baby was unable to suck and a nasogastric tube could not be inserted through blocked nostrils. Severe electrolyte disturbances, hyperbilirubinaemia and neonatal

Figure 1 The patient soon after birth showing extensive areas of diamond-like skin plates and fissuring characteristic of harlequin ichthyosis.

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sepsis were successfully treated during initial 4 weeks of life. He required supplemental oxygen during this period. Nasogastric feedings were started on fourth day of life. There was initially mild feeding intolerance which subsequently improved.

INVESTIGATIONS

An ultrasound of the abdomen and a CT of the brain were reported as normal.

Skin biopsy performed at ninth day of life showed thickened stratum corneum with focal papillomatosis and acanthocytosis. Apparent follicular plugging was also noted. The dermal-epidermal junction and dermal tissue were unremarkable.

Mutation analysis was not performed due to non-availability of facilities.

TREATMENT

The skin management included daily bath and gentle debridement with an emulsifying ointment. Urea cream was applied to the whole body three times a day, with no increase noted in serum urea levels. Frequent and generous use of lubricants and emollients gradually resulted in softening of skin. The thick skin plaques turned yellowish brown, then became separated and shredded off gradually, leaving a red surface covered with whitish thin scaly skin. The eczabion improved with softening of the perioral skin and the baby was able to suck from the bottle by the 12th week of life ([figure 2](#)). Bacterial conjunctivitis was treated with gentamicin eye ointment. We did not use retinoids or propylene glycol for this neonate.

OUTCOME AND FOLLOW-UP

The baby was shifted to a high dependency unit at 45 days of age. He stayed in the hospital for 8 months during which skin infection, gastroenteritis and acute bronchiolitis were treated. He was last seen in our clinic at 30 months of age ([figure 3](#)). Currently, the baby is over 7 years old ([figure 4](#)), and is being treated for NBCIE in another hospital.

DISCUSSION

Ichthyoses (Greek *ichthys*, meaning 'fish') represent a heterogeneous group of skin disorders that are characterised clinically by generalised scaling of the skin due to defective keratinisation and desquamation, and histologically by hyperkeratosis.

Figure 2 The patient at the age of 3 months.

They are usually distinguishable on the basis of inheritance pattern, clinical features, associated defects and histological changes. The autosomal dominant and X linked recessive ichthyoses are clinically less severe and rarely ever present at birth.

ARCI represents severe form of the disease which is usually evident at birth. Using clinical, histological and molecular genetic criteria,^{1 2} ARCI is divided into several major subtypes, that is, LI, NBCIE and HI. The nature of the scaling and the intensity of the erythroderma are important clinical features that distinguish these forms. Generalised erythroderma with fine, white or grey scales of NBCIE are milder than large, dark scales seen in LI. Many patients with ACRI do not fit neatly into the definition of LI or NBCIE and have overlapping characteristics. HI is the most severe form with thick, armour-plate-like, yellowish scales, separated by deep fissuring and often accompanied by marked disfigurement of facial features.

The overall prevalence of HI is unknown; few cases have been reported in the literature. Al Zayir *et al*,³ from the survey conducted at dermatology clinic of a large university hospital in Saudi Arabia, estimated an occurrence rate for primary congenital ichthyoses of 7/1000 new dermatology cases. They, however, do not provide specific data on HI.

Children born with ARCI often present at birth with collodion membrane or ichthyosiform erythroderma. According to the findings of Van Gysel *et al*,⁴ the most common outcome of collodion babies is erythrodermic autosomal recessive IL in 7 of 17 children (41% of cases), followed by non-erythrodermic autosomal recessive IL in 3 of 17 children (17% of cases) and other forms in 3 of 17 children (17% of cases). In 4 of 17 children (24% of cases), they found that the skin eventually developed normally, thereby giving rise to a self-healing collodion phenotype.⁵

Diagnosis depends on clinical phenotype, histological findings and molecular genetics. Prenatal diagnosis can be made by three-dimensional ultrasound,⁶ fetal skin biopsy or amniotic fluid sampling for genetic analysis.⁷

Several genetic faults have been implicated in ARCI, with most commonly identified gene in HI being ABCA12.⁸ Until

Figure 3 The patient at the age of 30 months.

Figure 4 The patient at the age of 7 years.

recently, a total of 56 ABCA12 mutations had been reported in 66 ARCI families, including 48 HI, 10 LI and 8 NBCIE families of African, European, Pakistani/Indian and Japanese origin.^{9 10}

Treatment is symptomatic. High-humidity environment and non-occlusive dressings with lubricants facilitate shedding of collodion membrane. Frequent and generous application of emollients and keratolytic agents helps in reducing the scaling. Ectropion requires ophthalmological care.

Neonates born with HI carry a poor prospect. Neonatal morbidity and death may be caused by hypernatraemic dehydration, hypothermia, skin infections, aspiration pneumonia, conjunctivitis, sepsis, anaemia, malnutrition, dehydration and constrictive bands of the extremities resulting in vascular compromise and oedema.

In their review of clinical outcome in 45 cases of HI, Rajpopat *et al*¹¹ reported a survival rate of 56%; 16 of 45 HI cases surviving for 7 years or longer and the longest surviving case reaching 25 years. Improved outcome was linked to heterozygous mutations and early use (by day 7) of oral retinoids, whereas most neonatal deaths were attributed to sepsis and severe disease following homozygous mutations. The maximum reported survival of a baby with HI from Saudi Arabia is 22 months.¹²

Learning points

- ▶ The babies born with harlequin ichthyosis (HI) need intensive care management and persistent efforts from a team of neonatologist, dermatologist and neonatal intensive care unit nurses.
- ▶ Careful management and monitoring of patients for complications may improve outcome in neonates born with HI; patience is a virtue as long periods are required for significant recovery.
- ▶ Genetic counselling to the parents is of crucial importance to avoid situations such as rejections and child abuse.

Contributors AAM and SS were the primary treating physicians. AAM and AH contributed to the writing of the manuscript. SS provided the photographs. AA and YAG were involved in the literature search.

Competing interests None.

Patient consent Obtained.

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