Congenital heart disease in harlequin ichthyosis: Case series

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ABSTRACT

Harlequin ichthyosis (HI) is the most severe form of congenital ichthyosis and inherited in an autosomal recessive manner. The disease is marked by severe thickened and scaly skin on the entire body. It is a lethal disease, but patients can rarely survive for several months or years with treatment. We present here seven cases of HI, where cardiac evaluation was done by echocardiography. To our knowledge, this is the first study to report associated cardiac abnormalities in such patients.

Keywords: Atrial septal defect, cardiac abnormalities, echocardiography, patent ductus arteriosus, ventricular septal defect

Introduction

Harlequin ichthyosis (HI) is the most severe form of congenital ichthyosis, with the incidence of one in 300,000 births.¹ It is an autosomal recessive disorder associated with mutations in gene ABCA12.² Babies with HI are covered in thick, scaly, armor-like plates of highly keratinized skin separated by deep fissures. The rigid skin severely restricts movement and results in deformities of the face, head, and extremities.³ In addition, there cleft with a fixed, open mouth and thick lips, hypoplastic, hypoplastic ears with closed pinna, and severe ectropion (everted eyelids). The eyebrow, eyelashes, and nails are also absent.⁴ Antenatal diagnosis can be suspected by 3D or 4D ultrasound examination and can be confirmed using electron microscopy of fetal skin biopsy and DNA-based diagnosis with chorionic villus sampling or amniocentesis.⁴

HI is associated with preterm birth and often leads to death due to neonatal complications such as septicemia, respiratory distress, dehydration, electrolyte imbalance, temperature instability, and feeding problems.⁵,⁶,⁷ In the past few years, however, the prognosis of HI infants has improved because of advances in neonatal intensive care and targeted oral retinoids.⁷,⁸

The improved survival makes it imperative to better understand the complete phenotypic expression of the disease for better management. We present here seven cases of HI, where cardiac evaluation was done by echocardiography. Relevant clinical features and cardiac abnormalities are summarized in Table 1.

Case 1

A female baby weighing 2.1 Kg was born at 28 weeks of gestation to a 27 years primigravida woman, by cesarean section because of obstetrical indication. She had typical features diagnostic of HI [discussed in Figure 1]. Echocardiography showed a small patent ductus arteriosus (PDA) and a large ostium secundum type atrial septal defect (OsASD) measuring 6.9 mm both with left to right shunt [Figure 2]. She was placed in a humidified incubator and given intra-venous fluids, nasogastric feeding, intravenous antibiotics, emollients, and retinoids. However, the baby died on the 5th day.
Case 2
A 34-week preterm female baby of 1.8 Kg was born to 23 years old primigravida mother out of consanguineous marriage. There was no cardiac abnormality seen on echocardiography. The baby had to be discharged against medical advice on the same day.

Case 3
A 30-year-old multiparous woman in her fourth pregnancy gave birth to a preterm female baby of 2.1 Kg by vaginal delivery. Her first baby was also female who had similar features and was stillborn. Echocardiography did not reveal any significant cardiac abnormality. The parents self-discharged their daughter on the same day after birth.

Case 4
A primigravida woman aged 20 years underwent vaginal delivery at 33 weeks of gestation giving birth to a female baby of 1.9 Kg. A history of 2nd degree consanguinity was present. The echocardiography revealed a 4.5 mm OsASD and 1.5 m restrictive perimembranous VSD with left to right shunt. The baby died on the same day.

| Gravida | Gestational age | Mode of delivery | Sex | Cardiac abnormalities |
|---------|-----------------|------------------|-----|-----------------------|
| Case 1  | Primi           | Pre-term         | F   | OsASD, PDA            |
| Case 2  | Primi           | Pre-term         | F   | PFO                   |
| Case 3  | Multi           | Full-term        | F   | Nil                   |
| Case 4  | Primi           | Pre-term         | F   | OsASD, PM VSD         |
| Case 5  | Primi           | Full-term        | F   | OsASD                 |
| Case 6  | Primi           | Pre-term         | M   | OsASD                 |
| Case 7  | Multi           | Pre-term         | M   | OsASD, PDA            |

*Assessed by echocardiography. OsASD: Ostium secundum atrial septal defect; PDA: Patent ductus arteriosus; PFO: Patent foramen ovale; PM VSD: Peri-membranous ventricular septal defect; SVD, Spontaneous vaginal delivery; F, Female; M, Male

**Case 5**
A preterm female baby of 1.5 Kg was born to a 19-year-old primigravida at 35 weeks of gestation by spontaneous vaginal delivery. An antenatal fetal ultrasound had revealed facial and extremity abnormalities. The echocardiography revealed a 5.2 mm OsASD with left to right shunt. Conservative management was started, but the parents took the baby against medical advice.

Case 6
A male baby, referred from outside, was born out of spontaneous vaginal delivery at 33 weeks of gestation to a 25-year-old primigravida. The birth weight was 2.3 Kg, and a history of consanguinity was present. The echocardiography revealed 6.8 mm OsASD with left to right shunt. The parents refused treatment.

Case 7
A 27–year‑old multiparous lady underwent vaginal delivery at full‑term and gave birth to a male baby of 1.4 Kg. The echocardiography showed a 5.5 mm OsASD and small PDA with left to right shunt. Treatment was refused by the attendants.

**Discussion**
HI is recognized at birth by the typical clinical appearance. Although there was a female preponderance in our study (71%), an equal predilection has been reported earlier.6 Most babies were preterm (71%) as seen in this disease.6 Vaginal delivery is usually the norm, and cesarean section is reserved for obstetrical indications only. Consanguinity, a risk factor for the disease, was seen in three patients.10 Being an autosomal recessive disease recurrence in subsequent pregnancies is 25%. In fact, both multiparous patients had history of similar illness and death in a previous sibling.

At present, there is no cure for this condition. The mortality of HI is high, and most babies die within a few weeks of birth. However, the prognosis of HI infants has significantly improved because of advances in neonatal intensive care and targeted oral retinoids.7,8 A survival rate of 56% has been reported ranging from 10 months to 25 years.8 A baby born with HI poses great challenge for the whole family, and as such the role of family physicians in such cases cannot be understated. Treatment in most of babies in our study could not be done owing to refusal of treatment from the parents. This is because HI has...
huge social stigmata in our country further confounded by lack of awareness and knowledge of the disease. It is, therefore, extremely important for family and primary care physicians to educate and prepare families before discharge for the prognosis and prolonged care of such babies.\[11\]

Congenital heart disease, as determined by echocardiography, was seen in five babies (71%). The most common lesion was OsASD seen in all the babies with cardiac abnormalities [Table 1]. PDA and PM VSD were seen along with OsASD in one patient each. Previously also, we have reported a case of HI with the presence of OsASD.\[12\] Though OsASD appears to be a common cardiac abnormality in such babies, the exact incidence is not known. Although our study revealed a high prevalence of congenital heart disease in HI, there clinical significance is not known as the patients either died or refused treatment. Furthermore, all these defects have a high probability of spontaneous closure over due course of time. Larger and long-term studies focussing cardiac disorders would be required to shed light on clinical significance of these preliminary findings.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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