International Journal of Clinical Dermatology
2026, Vol. 9, No. 1, pp. 72–75
https://doi.org/10.11648/j.ijcd.20260901.19

Case Report

A Malagasy Case Report of Harlequin Ichthyosis

Herin'Ny Fitiavana Princia Andriatahina[1, *], Louisebine Volasoa Jarison[2], Fenohasina Rakotonandrasana[3], Diane Angela Jaofeno[2], Lala Soavina Ramarozatovo[3], Fahafahantsoa Rapelanoro Rabenja[3], Irina Mamisoa Ranaivo[1]

[1]Department of Dermatology, Place Kabary Hospital, Antsiranana, Madagascar

[2]Department of Pediatry, Place Kabary Hospital, Antsiranana, Madagascar

[3]Department of Dermatology, Joseph Raseta Befelatanana Hospital, Antananarivo, Madagascar

Abstract

Introduction: Harlequin ichthyosis is the most severe form of autosomal recessive congenital ichthyosis. It is caused by mutations in the *ABCA12* gene, leading to a major defect in epidermal lipid transport and a profound impairment of the skin barrier. The estimated incidence ranges from 1 in 300,000 to 1 in 1,000,000 live births. Clinically, affected neonates present at birth with thick hyperkeratotic plates separated by deep fissures, associated with bilateral ectropion, eclabium, and limb contractures. Despite advances in neonatal intensive care and the introduction of systemic retinoids, mortality remains high. We report here a case of harlequin ichthyosis observed in Madagascar. Case presentation: We report the case of a full-term newborn, the first child of a 15-year-old mother, delivered vaginally with a birth weight of 2540 g. A first-trimester prenatal ultrasound was reported as normal. No parental consanguinity was known. At day 0 of life, physical examination revealed massive generalized hyperkeratosis with large thick plates separated by deep erythematous fissures, giving the skin an "armor-like" appearance. Marked bilateral ectropion, eclabium, nasal flattening, dysmorphic auricles, and limb contractures were also observed. The newborn was admitted to the neonatal intensive care unit. Supportive care including topical emollients, correction of hydro-electrolytic disturbances, and infection prevention was initiated. Systemic retinoids could not be introduced. By day 4 of life, increased skin rigidity, widening of the fissures, and distal dark discoloration of the extremities suggestive of ischemic compromise were observed. The clinical course was marked by death at day 6 of life. Discussion: Harlequin ichthyosis results from impaired lipid transport caused by *ABCA12* mutations, leading to severe disruption of the stratum corneum and skin barrier function. Prenatal diagnosis by ultrasound is possible but remains difficult and is often made late in pregnancy. The unfavorable outcome in our case highlights the challenges in managing this condition in resource-limited settings. Conclusion: Harlequin ichthyosis remains a severe neonatal emergency. Early recognition, prompt supportive care, and specialized multidisciplinary management are essential to improve prognosis.

Keywords

Harlequin Ichthyosis, Congenital Ichthyosis, ABCA12 Gene

*Correspondence: Herin'Ny Fitiavana Princia Andriatahina (andriaprincia@gmail.com)

Received: 1 April 2026; **Accepted:** 10 April 2026; **Published:** 23 April 2026

1. Introduction

Harlequin ichthyosis (HI) represents the most severe form within the spectrum of autosomal recessive congenital ichthyosis (ARCI) [1]. It is caused by mutations in the *ABCA12* gene, which encodes a lipid transporter essential for the proper function of lamellar bodies in keratinocytes and for maintaining the integrity of the skin barrier [2]. Dysfunction of this mechanism leads to a major disruption of the stratum corneum, resulting in massive hyperkeratosis and increased transepidermal water loss [3]. The incidence of this rare condition is estimated to range from 1 in 300,000 to 1 in 1,000,000 live births according to published series [4].

Clinically, affected neonates present with thick hyperkeratotic plates arranged in large polygonal scales separated by deep erythematous fissures, associated with bilateral ectropion, eclabium, and characteristic facial abnormalities [3, 5]. Skin rigidity may lead to limb contractures as well as systemic complications related to the disruption of the skin barrier, including severe dehydration, hydro-electrolytic imbalance, infections, and respiratory distress [5].

Advances in neonatal intensive care and the early use of systemic retinoids have contributed to improved survival over recent decades [6]. However, mortality remains high, particularly in resource-limited settings where access to specialized treatments is restricted [7].

We report here a case of harlequin ichthyosis in a Malagasy newborn seen at the University Hospital of Place Kabary, Antsiranana.

2. Case Report

The patient was a newborn from northern Madagascar, born to a 15-year-old mother in her first pregnancy and a 19-year-old father. The delivery occurred vaginally in a primary healthcare center. Birth weight was 2540 g. A first-trimester prenatal ultrasound had been performed and was reported as normal. No similar family history or previous neonatal deaths were reported. There was no known parental consanguinity, although both parents originated from the same village in southern Madagascar.

At birth, clinical examination revealed massive generalized hyperkeratosis with thick yellowish plates arranged in large polygonal lamellae, associated with deep erythematous fissures involving the trunk and thighs, giving the skin a rigid armor-like appearance. Marked bilateral ectropion with conjunctival exposure, eclabium with persistent mouth opening, flattening of the nasal pyramid due to cutaneous tension, hypoplastic and dysmorphic auricles, and flexion contractures of the limbs were also observed (Figures 1 and 2). This presentation corresponds to the typical neonatal phenotype described in the literature [5, 8].

Figure 1. *Generalized hyperkeratosis with deep fissures at birth.*

Figure 2. *Bilateral ectropion and eclabium at birth.*

Management consisted of repeated application of emollients, nasogastric feeding and enteral hydration due to feeding difficulties related to eclabium, correction of hydro-electrolytic disturbances, and infection prevention. Due to the impossibility of obtaining peripheral or umbilical venous access, intravenous fluid therapy could not be initiated. Oral amoxicillin-clavulanic acid was administered empirically according to body weight because parenteral antibiotic therapy was not feasible. Lubrication with artificial tears was also initiated, as recommended in the literature [6]. Supplemental oxygen via nasal cannula was provided to support respiratory function. Systemic retinoid therapy could not be introduced due to limited resources.

By day 4 of life, worsening of the skin fissures and increased rigidity of the integument were noted, with persistence of the marked bilateral ectropion and eclabium (Figures 3 and 4), as well as distal dark discoloration of the extremities

suggestive of ischemic compromise (Figure 5).

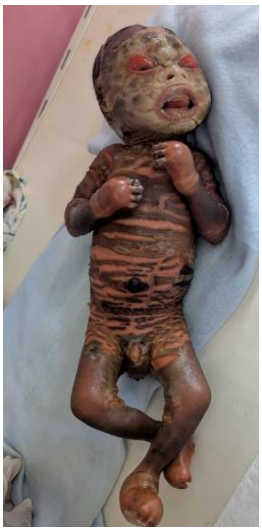

Figure 3. *Whole-body view of worsening skin fissures and rigidity at day 4 of life.*

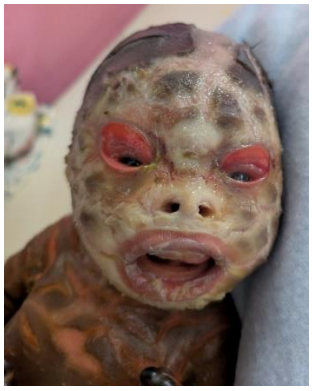

Figure 4. *Facial close-up showing worsening skin fissures and rigidity at day 4 of life.*

Figure 5. *Distal extremity discoloration suggestive of ischemia at day 4 of life.*

The clinical course was marked by death on day 6 of life due to multifactorial complications, including severe transepidermal fluid loss, suspected sepsis, and progressive respiratory compromise related to thoracic skin rigidity.

3. Discussion

Harlequin ichthyosis is a rare genodermatosis caused by mutations in the *ABCA12* gene, leading to a major defect in lipid transport within keratinocytes [2, 3]. This defect results in a profound disruption of the skin barrier and the characteristic massive hyperkeratosis [3].

The diagnosis is usually established at birth based on the typical clinical presentation characterized by thick hyperkeratotic plates, deep fissures, ectropion, and eclabium [5]. Several case series have reported similar clinical findings in newborns affected by harlequin ichthyosis [4, 8].

Prenatal diagnosis is possible but remains challenging. Ultrasound examination may reveal suggestive abnormalities such as ectropion, persistent open mouth, or abnormal ears, although these signs often appear late during pregnancy [10]. Diagnostic confirmation relies on the identification of *ABCA12* mutations through genetic analysis [2, 11]. This molecular diagnosis, based on DNA analysis, can be performed using chorionic villus sampling or amniocentesis. Fetal skin biopsy may also contribute to the diagnosis from the 18th week of gestation [2, 11]. In subsequent pregnancies at risk, when the familial mutation is known, targeted prenatal diagnosis can be performed by chorionic villus sampling between 11 and 13 weeks of gestation or by amniocentesis from 15 weeks of gestation to detect the specific mutation [2]. Genetic counseling is recommended for future pregnancies in order to assess the recurrence risk and discuss available prenatal diagnostic options [1].

Several studies have shown that management in neonatal intensive care units combined with early administration of systemic retinoids, particularly acitretin, may improve survival in patients with harlequin ichthyosis [6, 9, 12]. Early initiation of systemic retinoids has also been associated with faster desquamation of hyperkeratotic plaques and improved skin flexibility, which may reduce the risk of respiratory restriction and distal ischemic complications [6, 9].

Systemic complications observed in these patients are mainly related to disruption of the skin barrier, leading to excessive fluid loss, hydro-electrolytic imbalance, and increased susceptibility to infections [5].

Similar fatal outcomes have been reported in low-resource settings, where limited access to intensive care and invasive management significantly affects neonatal survival [13].

In our case, the absence of peripheral or umbilical venous access significantly limited optimal fluid and electrolyte management. Although enteral hydration, oral antibiotic therapy, and supplemental oxygen were provided, these measures were insufficient to prevent clinical deterioration. This highlights the challenges of managing harlequin ichthyosis in resource-

limited settings, where access to neonatal intensive care, vascular access, laboratory monitoring, and systemic retinoids remains restricted [5, 6, 14, 15].

4. Conclusion

Harlequin ichthyosis is a rare and severe genetic disorder of the newborn, characterized by massive hyperkeratosis and severe impairment of the skin barrier secondary to mutations in the *ABCA12* gene. The diagnosis is usually clinical at birth, although confirmation relies on genetic testing. Early management in neonatal intensive care units and the use of systemic retinoids may improve prognosis [6, 9, 12, 14]. Our observation highlights the severity of this condition and the challenges of its management in resource-limited settings.

Abbreviations

HI	Harlequin Ichthyosis
ARCI	Autosomal Recessive Congenital Ichthyosis
NICU	Neonatal Intensive Care Unit

Author Contributions

Herin'Ny Fitiavana Princia Andriatahina: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing

Louisebine Volasoa Jarison: Data curation, Investigation, Validation

Fenohasina Rakotonandrasana: Investigation, Resources, Validation

Diane Angela Jaofeno: Data curation, Investigation, Validation

Lala Soavina Ramarozatovo: Supervision, Validation, Writing – review & editing

Fahafahantsoa Rapelanoro Rabenja: Supervision, Resources, Validation, Writing – review & editing

Irina Mamisoa Ranaivo: Conceptualization, Supervision, Methodology, Validation, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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