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## **Case Presentation**

### **A case of harlequin ichthyosis treated with isotretinoin**

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## **Abstract**

Harlequin ichthyosis is a rare congenital ichthyosis classified under the category of Autosomal Recessive Congenital Ichthyoses, which also include lamellar ichthyosis and congenital ichthyosiform erythroderma. It is caused by functional null mutations in the ABCA12 gene, a keratinocyte lipid transporter associated with lamellar granule formation. Patients have a classic clinical presentation at delivery and need neonatal intensive care treatment to maximize their chances of survival. Early oral retinoid therapy has been shown to increase survival in patients with harlequin ichthyosis[1], and we present a case of a 9-month-old male with this condition who has been treated with isotretinoin since day 7 of life.

## **Introduction**

Harlequin ichthyosis (HI) presents at birth with coarse, large plate-like scales with deep fissures, severe ectropion, eclabium, contractures of digits, and flattening of the ears and nose. Patients are usually born prematurely and do not have any brain or internal organ abnormalities. If patients survive the neonatal period, they continue with a persistent ichthyosiform erythroderma for life. We present a case of a 9-month-old male with HI who was started on treatment with isotretinoin on day 7 of life.

## **Case synopsis**

At birth, a male infant presented with thick, hyperkeratotic plate-like scales covering his trunk, extremities, and head with deep fissures, prominent eclabium, and bilateral ectropion. In addition, he exhibited poorly formed and flattened ears and nose (Figure 1). In the NICU the patient was placed in a humidified incubator at 80% humidity, started on IV antibiotics, fluids and electrolytes, morphine as needed for pain, and a topical emollient ointment was applied to the entire cutaneous surface every 2 hours. Ophthalmology was consulted, and he received lubricant ointment to the eyes every 3 hours. He was initially placed on total parenteral nutrition and then subsequently switched to orogastric tube feedings with breast milk. After discussion with the parents, he was started on oral isotretinoin compounded in medium chain triglyceride (MCT) oil at 1mg/kg/day on day 7 of life (10mg isotretinoin capsule compounded in 5mL MCT oil for final concentration of 2mg/mL).



**Figure 1.** At day one of life, the patient had thick, hyperkeratotic plate-like scales covering his trunk, extremities, and head with deep fissures, prominent eclabium, and bilateral ectropion. He exhibited poorly formed and flattened ears and nose.

He tolerated the medication well and the scales softened and began to desquamate. The ectropion and eclabium improved and the finger and toe contractures nearly resolved (Figure 2). The humidity in the incubator was decreased slowly to room air humidity, whereas oral isotretinoin and topical emollients were continued.



**Figure 2.** After two weeks of daily oral isotretinoin, the fissures in the skin had healed, the plate-like scales nearly resolved, and the eclabium and ectropion were much improved.

After discharge from the NICU, the patient required regular debridement of hyperkeratosis in the ear canals. He was regularly monitored by an ophthalmologist and had a few episodes of conjunctivitis treated with topical gentamicin. He was found to have a mild rise of his triglycerides to 157mg/dL (baseline 87mg/dL) as well as a decrease in his hemoglobin to 8.4gm/dL (baseline 12.6gm/dL) at 3.5 months. His isotretinoin dose was subsequently decreased to 0.3mg/kg/day and he was supplemented with iron. His lab abnormalities resolved and he has been continued on the lower dose of isotretinoin.



**Figure 3A,B.** At 9 months, the patient has a persistent ichthyosis with fine scale and erythroderma with resolution of the ectropion and eclabium.

At 9 months, he continues with scaly erythematous skin on his trunk, face and extremities (Figure 3A,B) as well as thick hyperkeratotic plaques on the frontal scalp which have almost resolved with daily topical application of tazarotene 0.1% cream [2]. He has been diagnosed with hyperopia and anisometropia and now wears glasses. He continues to require frequent debridement of his ears, and he has mild contractures of his bilateral thumbs for which he receives physical therapy.

## Discussion

Harlequin ichthyosis presents at birth with coarse and large plate-like scales with deep fissures, severe ectropion, eclabium, contractures of the digits, and flattening of the ears and nose. Patients are usually born prematurely and do not have any brain or internal organ abnormalities. Pain from the fissures can discourage patients from taking deep breaths and lead to respiratory complications [2,3]. In fact, respiratory infections can be a major cause of death in the neonatal period [1]. Over time, the thick scale is shed leading to a persistent scaly erythroderma very similar to that in non-bullous congenital ichthyosiform erythroderma (CIE).

Harlequin ichthyosis is now classified under the category of Autosomal Recessive Congenital Ichthyoses, which also includes lamellar ichthyosis (LI) and CIE. HI was included in the classification with these disorders because functional null mutations in the ABCA12 gene leads to HI; missense mutations in this same gene can lead to collodion membrane formation and development of either LI or CIE [4]. Abnormalities in other genes and known to cause CIE and these include transglutaminase 1 (TGM1), 12R-lipoxygenase (ALOX12B), lipoxygenase-3 (ALOXE3), cytochrome P450 4F22 (CYP4F22), ichthyin (NIPAL4), and patatin-like phospholipase (PNPLA1). Individuals who have focal linear epidermolytic hyperkeratosis, which is indistinguishable clinically from epidermal nevi, may produce offspring with CIE.

Other disorders that can present with very tight skin include lethal restrictive dermopathy (OMIM #275210), Neu-Laxova syndrome (OMIM# 256520) [3], and LI and CIE, which present with collodion membrane at birth. Patients with Neu-Laxova syndrome present with ichthyosis at birth that can range in severity. In the most severe form, patients can have HI characteristics. Patients also may have severe intrauterine growth retardation, edema, microcephaly, and brain abnormalities [5].

Harlequin ichthyosis is caused by mutations in both ABCA12 alleles. ABCA12 is a keratinocyte lipid transporter associated with lamellar granule formation. Loss of normal ABCA12 function leads to defective lipid transport by lamellar granules in the upper epidermis and malformation of the stratum corneum lipid layers [6].

Management of the neonate with HI includes the use of a humidified incubator, temperature regulation, nutrition replacement, pain control, and monitoring for infections [2]. Emollients should be applied liberally to the skin and bathing and soaking can reduce the risk of skin infection and promote shedding of the thickened skin. Eye care is critical and at least artificial tears should be initiated. If patients have contractures, surgical treatment may be necessary to prevent necrosis and gangrene formation of the distal fingers [2,3].

In a recent review of 45 patients with HI, early systemic retinoid therapy (the majority starting treatment within the first week of life) leads to an increased survival rate (83%) compared to the survival rate without retinoid use (24%). The majority received acitretin but some also received isotretinoin or etretinate. Mutation analysis found ABCA12 mutations in 38 of the 45 patients; they were classified as homozygous (both alleles with the same mutation) or compound heterozygous (each allele with a different mutation). All the patients that died in the cohort had homozygous mutations, whereas only 48% of the survivors had homozygous mutations [1].

Beyond the neonatal period, patients suffer from temperature dysregulation and may have heat and cold intolerance [1,4]. Patients can also have generalized poor hair growth, scarring alopecia, contractures of digits, arthralgias, failure to thrive, and short stature. Some patients may even develop a rheumatoid factor-positive polyarthritis [3,7]. Patients are prone to skin infections with *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Klebsiella* [1]. Eye abnormalities such as persistent or recurrent ectropion, epiphora, recurrent conjunctivitis, keratitis, and nystagmus are also common [1]; thus patients need frequent evaluation by an ophthalmologist. Recurrent blockage of the ear canal may occur and frequent debridement is often needed. Patients are at risk of developmental delay, with one series reporting a 32% rate of developmental delay including not meeting developmental milestones and delay in motor skill development. Some patients, though, were able to attend higher education [1].

In conclusion, although HI was previously thought to be a fatal condition, more intensive care in the neonatal period and early use of retinoid therapy may increase survival of these patients. Unfortunately, the condition persists throughout life and can cause multiple medical complications after the neonatal period.

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