Severe Ectropion in Harlequin Ichthyosis Managed Nonsurgical: Case Report

Abordagem Não Cirúrgica da Ictiose de Arlequim com Ectropion Grave: Caso Clínico

João Vaz [1], Mariana Vaz [1], Ana Cardoso [1], Audrey Sampaio [1], Nuno Campos [1], Ana Vide-Escada [1]

[1] Integrated Responsibility Center of Ophthalmology, Unidade Local de Saúde Almada-Seixal, Almada, Portugal

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ABSTRACT

Harlequin ichthyosis (HI) is the most severe form of autosomal recessive congenital ichthyosis, caused by pathogenic variants in *ABCA12*. Ocular manifestations, particularly cicatricial ectropion and exposure keratopathy, may threaten corneal integrity. Reports detailing successful nonsurgical ophthalmic management remain scarce.

A full-term female neonate presented at birth with generalized hyperkeratosis, skin fissuring, severe bilateral ectropion, and superficial punctate keratopathy. Genetic testing confirmed biallelic *ABCA12* variants. Systemic acitretin therapy was initiated, complemented by topical tazarotene and emollients. Ocular management consisted of daily eyelid massage, protective moisture chambers, preservative-free artificial tears, and vitamin A-based ointment.

Progressive regression of ectropion and complete resolution of keratopathy were observed. At 18 months, the patient showed a stable skin condition, clear corneas, and normal visual development, without surgical intervention.

Early multidisciplinary medical management can effectively stabilize ocular and systemic manifestations of HI, avoiding high-risk reconstructive surgery and preserving long-term visual outcomes.

KEYWORDS: Corneal Diseases/etiology; Corneal Diseases/therapy; Ectropion/etiology; Ectropion/therapy; Ichthyosis, Lamellar/therapy; Infant.

RESUMO

A ictiose arlequim (IA) é a forma mais grave de ictiose congénita autossómica recessiva, decorrente de variantes patogénicas no *ABCA12*. As manifestações oculares, nomeadamente o ectropion cicatricial e a queratopatia de exposição, podem comprometer a integridade corneana. Os relatos de sucesso com abordagem oftalmológica não cirúrgica permanecem limitados.

Recém-nascida de termo apresentou, ao nascimento, hiperqueratose generalizada, ectropion grave bilateral e queratopatia punctata superficial. O estudo genético confirmou variantes bialélicas no *ABCA12*. Instituiu-se acitretina sistémica e tazaroteno tópico. A abordagem oftalmológica incluiu lágrimas artificiais, pomada oftálmica à base de vitamina A e câmaras de hidratação ocular protetoras.

Verificou-se regressão progressiva do ectropion e resolução da queratopatia. Aos 18 meses, pele estabilizada, córneas transparentes e desenvolvimento visual adequado, sem cirurgia.

A gestão médica multidisciplinar precoce pode estabilizar as manifestações oculares da IA, evitar cirurgia reconstrutiva de alto risco e preservar o prognóstico visual a longo prazo.

PALAVRAS-CHAVE: Doenças da Córnea/etiologia; Doenças da Córnea/tratamento; Ectrópio/etiologia; Ectrópio/tratamento; Ictiose Lamelar/tratamento; Lactente.

INTRODUCTION

Harlequin ichthyosis (HI) is a severe yet extremely rare genodermatosis classified within the spectrum of autosomal recessive congenital ichthyoses (ARCI).[1] The disorder primarily affects the process of keratinization, during which the epidermis differentiates to form the stratum corneum between the twentieth and twenty-fourth week of gestation.[2] HI is caused by truncating mutations in the *ABCA12* gene, which encodes a transmembrane lipid transporter responsible for the regulation of epidermal lipid homeostasis.[3] Pathogenic variants result in defective lamellar granule secretion, altered lipid composition of the stratum corneum, and subsequent disruption of the epidermal barrier. This dysfunction leads to extreme hyperkeratosis, with thickened, plate-like scales separated by deep fissures and severe impairment of cutaneous elasticity.[2] The facial features may include eclabium, ectropion, a distinct flattened nose, and dysplastic ears, often accompanied by nasal hypoplasia, absence of eyebrows and eyelashes, and sparse scalp hair. Other systemic manifestations include respiratory distress secondary to thoracic restriction, dehydration, feeding difficulties, and electrolyte imbalance. Neurological symptoms such as seizures and metabolic dysregulation have also been described.[3]

The estimated prevalence of HI is approximately 1 in 300 000 live births, with no significant association with sex or ethnicity. Historically, the condition was almost uniformly fatal in the neonatal period, primarily due to sepsis and respiratory failure. However, since the introduction of neonatal intensive care and systemic retinoid therapy, survival has markedly improved, with some reports documenting long-term survivors reaching adulthood.[3,4]

Three clinical subtypes of HI have been described, distinguished mainly by the severity and pattern of epidermal abnormalities. Harlequin ichthyosis is the most severe phenotypic variant. Recent studies have identified additional novel *ABCA12* mutations (e.g., p.Gly1508Val and intronic variants) that may explain the phenotypic variability and differential survival outcomes observed among patients.[2]

Ocular involvement may be one of the earliest and most dramatic manifestations of HI. Cicatricial ectropion of both upper and lower eyelids can lead to lagophthalmos and exposure keratopathy, significantly increasing the risk of corneal ulceration, infection and blindness.[5,6] Reports advocating surgical correction using full-thickness skin grafts have inconsistent outcomes, with high recurrence rates and risk of infection.[3,4] Although scarce, more recent literature emphasizes conservative management with aggressive lubrication, protective measures, and multidisciplinary coordination as the safest and most effective initial approach.[4] The present report describes the case of a neonate with genetically confirmed HI managed exclusively through medical and multidisciplinary care, achieving full systemic and ocular stabilization without surgical intervention.

CASE REPORT

A full-term female neonate was born via spontaneous vaginal delivery at 39 + 3 weeks of gestation to non-consanguineous, healthy parents after an uneventful, regularly monitored pregnancy. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. At birth, the newborn presented with generalized thick, armor-like hyperkeratotic plaques separated by deep erythematous fissures, generalized desquamation, eclabium, a flattened nose, and dysplastic ears (Fig. 1 A). The systemic examination confirmed the classical phenotype of HI.

The patient was immediately admitted to the tertiary neonatal intensive care unit (NICU) under reverse isolation and a humidified incubator. Initial stabilization included heated humidified ventilation, continuous cardiorespiratory monitoring, sterile non-adherent petrolatum dressings covering the entire body, high ambient humidity and minimal handling. Strict input and output, daily weight monitoring, and serial electrolyte and renal function testing were maintained. Rigorous asepsis was ensured, with topical antibiotic initiated empirically. Analgesia was used to relieve discomfort associated with deep fissuring. Nutritional support was provided through nasogastric feeding due to jaw constriction and eclabium.

Dermatologic and genetic assessments were performed in collaboration with the multidisciplinary team at Hospital Niño Jesús, Madrid. Molecular testing identified biallelic pathogenic variants in *ABCA12*, confirming the diagnosis of ARCI type 4B.

Ophthalmologic evaluation within the first 24 hours revealed severe bilateral upper- and lower-eyelid ectropion, lagophthalmos, diffuse conjunctival hyperemia, and superficial punctate keratopathy, with otherwise clear corneas. A nonsurgical ocular regimen was initiated, consisting of preservative-free artificial tears containing trehalose 3% and sodium hyaluronate 0.15% every 1–2 hours; a vitamin-A (retinol palmitate) ophthalmic ointment at least every 2 hours and during sleep; gentle yet firm eyelid massage twice daily; and protective moisture chambers. Ophthalmology, dermatology, and neonatology coordinated care to ensure safe periocular management.

Figure 1. Neonatal intensive care management on the first day of life (A) and 1 month of life (B). NICU admission under reverse isolation and a humidified environment, with full-body sterile non-adherent dressings and continuous monitoring to ensure thermoregulation, hydration, and infection prevention.

Systemic therapy with acitretin (10 mg every 72 hours) was initiated on day 3 of life, combined with topical skin emollients (petrolatum and dexpanthenol), keratolytic agents (urea 10%–20%), and topical tazarotene 0.1%. Antimicrobial prophylaxis with topical fusidic acid for the skin was maintained as needed. Vitamin D supplementation and high-calorie nutrition were provided to prevent deficiency and ensure adequate growth.

Over the first month (Fig. 1 B), progressive regression of ectropion was observed, with improved eyelid mobility and reduced conjunctival hyperemia. By six weeks, superficial keratopathy had resolved and eyelid closure was nearly complete. At eight weeks, the patient was discharged with bi-weekly ophthalmic and dermatologic follow-up. At six months, the skin and ophthalmologic conditions had markedly improved, with minimal residual ectropion and intact corneal epithelium. At 18 months, she remained in good general health, with no ectropion or lagophthalmos, orthotropia, clear corneas, and age-appropriate visual development (Fig. 2). No surgical procedures were required.

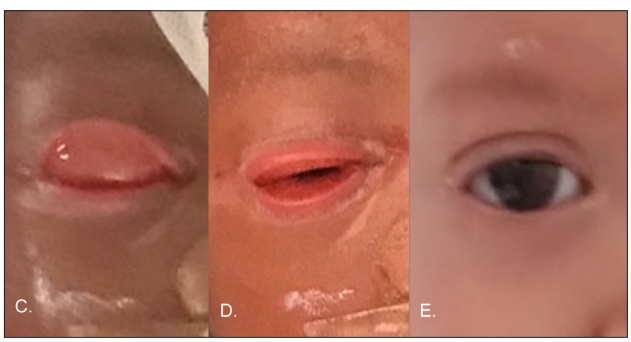

Figure 2. Sequential evolution of eyelid ectropion.
(C) At birth: severe bilateral upper and lower eyelid cicatricial ectropion
(D) At 1 month: progressive regression of ectropion with improved eyelid mobility and near-complete eyelid closure;
(E) At 18 months: full eyelid apposition without ectropion or lagophthalmos.

DISCUSSION

This case highlights the critical role of early, intensive, and multidisciplinary management in improving survival and functional outcomes in Harlequin ichthyosis, particularly regarding ocular involvement. Historically, HI was regarded as universally fatal; neonatal mortality rates exceeded 70% due to respiratory distress, dehydration, and sepsis. The introduction of advanced neonatal intensive care, including humidified incubators, infection control, and nutritional support, has increased survival to approximately 55%, with documented long-term survivors. Admission to a specialized NICU in collaboration with neonatology, dermatology, ophthalmology, plastic surgery, otorhinolaryngology, genetics, and nursing is fundamental to ensure optimal outcomes. Early airway management, respiratory support, strict fluid balance, and prevention of infection are cornerstones of care.

In the context of ocular management, severe ectropion and exposure keratopathy should always be excluded since these are real threats to vision and ocular development, and were evident in this clinical case. While surgical correction with full-thickness skin grafts or tarsorrhaphy has been reported, outcomes remain unpredictable, and recurrence is common. Surgical procedures in HI are technically challenging due to the fragile skin, poor graft adherence, and risk of secondary infection. Additional risks include iatrogenic injury, anesthetic complications, and delayed wound healing, particularly in neonates receiving systemic retinoids. Furthermore, although retinoids may theoretically aid in the reepithelialization of ectropion-related eyelid defects, clinical data remain inconsistent and their use (such as acitretin) may even impair wound healing in large graft sites, limiting the safety of early surgery.

Recent literature emphasizes that early and coordinated medical therapy should precede any consideration of surgery, which reinforces our clinical conduct. Topical retinoids and vitamin A–based ointments promote epithelial differentiation, while frequent lubrication prevents corneal desiccation. Non-adherent dressings and high humidity aid mechanical protection and skin flexibility.

One can still debate whether there is a surgical timing and indication. With respect to ocular disease, there is no evidence that early surgery prevents ectropion recurrence within the first year of life. In fact, recurrence rates remain high even after technically successful grafting. In our patient, a non-surgical approach resulted in a complete functional and aesthetic recovery, reinforcing that surgery should be reserved for refractory cases only, after full medical optimization.

Emerging research explores immunological and molecular pathways that may expand future treatment options. HI shares inflammatory signatures with other hyperkeratotic disorders such as psoriasis and atopic dermatitis, including IL-17 and IL-23 signaling dysregulation. Novel therapies targeting these pathways, as well as enzyme replacement with kallikrein proteases to restore physiological desquamation, are being investigated. Nevertheless, current evidence supports that comprehensive medical

management remains the standard of care, with early multidisciplinary coordination being the determinant of prognosis, as was demonstrated in the present clinical case.

CONCLUSION

In summary, Harlequin ichthyosis remains a rare and life and eventually sight-threatening disorder requiring immediate, coordinated, and individualized care. This case demonstrates that early and comprehensive medical management, including systemic acitretin therapy, ocular surface protection, and intensive neonatal care, can achieve complete recovery without surgical intervention. The avoidance of surgical ophthalmologic procedures, with their associated morbidity and recurrence risk, underscores the value of a multidisciplinary medical approach in optimizing both systemic and ocular outcomes. Prompt recognition, genetic confirmation, and close collaboration between dermatology, neonatology, and ophthalmology teams are essential to improving survival and preserving vision in these patients.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

V: Writing of the article, data collection and analysis.

MV, AC, AS, NC and AVE: Data collection, analysis, and discussion of results.

All authors approved the final version to be published.

JV Escrita do artigo, recolha e análise de dados.

MV, AC, AS, NC e AVE: Recolha de dados, análise e discussão dos resultados.

Todos os autores aprovaram a versão final a ser publicada.

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Corresponding Author/
Autor Correspondente:

João Vaz
Centro de Responsabilidade Integrada de Oftalmologia - Unidade Local de Saúde Almada-Seixal - Hospital Garcia de Orta, E.P.E
Av. Torrado da Silva,
2805-267 Almada, Portugal
E-mail: joaovazmedical@gmail.com

ORCID: 0000-0002-4518-3854