







Case Report

Harlequin Ichthyosis: Experience with a short-course Oral Vitamin A as a potential adjunct therapy in low-resource settings

Harlequin İktiyozisi: Bir olgu sunumu ve düşük kaynaklı ortamlarda sistemik retinoidlere alternatif olarak kısa süreli Oral Vitamin A'nın potansiyeli

Abraham Kwadzo Ahiakpa¹, Elorm Kwaku Kpofo-Tetteh², Gerald Amprofi², Precious Akosua Raphaelson³,
Magdalene Dede Appiah³, Dorothy Sackey³

¹Catholic Hospital, Battor, Internal Medicine And Pediatrics, Battor, Ghana

²Catholic Hospital, Battor, Obstetrics And Gynecology, Battor, Ghana

³Catholic Hospital, Battor, Pediatrics, Battor, Ghana

ABSTRACT

Harlequin Ichthyosis (HI), the most severe form of congenital ichthyosis, has evolved in management, leading to improved outcomes. However, these outcomes may be impacted by resource availability. Based on published reports, we report, the first case of HI in Ghana, our management challenges and the potential benefit of short-course vitamin A as a potential adjunct therapy in resource-constrained settings. We report a male neonate delivered at 35weeks+3days gestation to a 20-year-old primiparous mother. Physical examination revealed generalized thick, grey scaly skin with diamond shapes interspersed with deep fissures, accompanied by facial and limb dysmorphic features. Supportive care was provided in the Neonatal Intensive Care Unit (NICU), including skin care, a 7-day course of low-dose oral vitamin A, and antibiotics. The infant was discharged in a stable state to parents upon a request of discharge against medical advice from parents. However, the infant died at home, of unclear cause, on day 12 of life. Systemic retinoids have considerably improved HI management outcomes in high resource settings. We propose that vitamin A could be a potential adjunct therapy in low-resource settings. This case lays a platform for more robust studies in the future to explore this finding.

Keywords: *Harlequin ichthyosis, Ichthyosis, Vitamin A, Retinoid, low-resource.*

ÖZET

Harlequin İhtiyozis (HI), doğumsal ihtiyozisin en şiddetli formu, yönetiminde gelişmelerle birlikte daha iyi sonuçlar elde edilmesini sağlamıştır. Ancak bu sonuçlar, kaynakların mevcudiyeti tarafından etkilenebilir. Yayımlanmış raporlara dayanarak, Gana'daki HI'nin ilk olgusunu, yönetim zorluklarımızı ve kaynak kısıtlı ortamda potansiyel ek tedavi olarak kısa süreli A vitamini kullanımının olası faydasını bildiriyoruz. 35 hafta + 3 gün gestasyonla doğmuş, 20 yaşında primipar anneden doğan erkek bir yenidoğanı bildiriyoruz. Fizik muayenede, derin çatlaklarla karışık elmas şekilleri olan genel olarak kalın, gri pullu cilt ve yüz ile ekstremitelerde dismorfik özellikler görüldü. Yenidoğan Yoğun Bakım Ünitesi'nde (NICU) destekleyici bakım sağlandı; buna cilt bakımı, 7 günlük düşük doz oral A vitamini tedavisi ve antibiyotikler dahildi. Bebek, ebeveynlerin taburculuk isteğine istinaden stabil durumda ebeveynlerine teslim edildi. Ancak, bebek hayatının 12. gününde evde, nedeni belirsiz bir şekilde öldü. Sistemik retinoidler, HI yönetim sonuçlarını yüksek kaynaklı

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Correspondence / Yazışma: Abraham Kwadzo Ahiakpa · Catholic Hospital, Battor, Internal Medicine And Pediatrics, Battor, Ghana · lincolnabrahamahiakpa@gmail.com

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ortamlarda önemli ölçüde iyileştirmiştir. A vitamininin düşük kaynaklı ortamlarda potansiyel ek tedavi olabileceğini öneriyoruz. Bu olgu, gelecekte bu bulguyu araştırmak için daha sağlam çalışmalar için bir platform oluşturmaktadır.

Keywords: Harlequin İhtiyozis, İhtiyozis, A Vitamini, Retinoid, düşük kaynaklı ortam

INTRODUCTION

Harlequin Ichthyosis (HI) is a rare, yet the most severe form of congenital ichthyosis. It is a congenital skin disorder that affects 1 in 300,000 to 500,000 newborns globally every year [1]. HI is inherited in an autosomal recessive pattern, and characterized by thickened, scaly, diamond/rectangular/trapezoid shapes separated by deep fissures on the skin nearly all over the body [2]. It may also be associated with defects of other body parts, including the face and limbs. Mutation in the Adenosine Triphosphate-Binding Cassette Transporter Protein A12 (ABCA12) gene, has been the most reported culprit [2-4]. This disrupts the normal intracellular lipid deposition of the stratum corneum of the skin, predisposing the infant's skin to cracks, serving as a nidus for infections as well as dehydration and hypothermia [1].

HI has been historically associated with a very high mortality rate, mainly from other complications including respiratory failure, infections and dehydration [5]. However, recent advances in management modalities, including early intubation, topical or systemic retinoids and multidisciplinary supportive care, have reduced mortality [1, 6].

Systemic retinoids, analogues of Vitamin A, have been shown to be the 'game changer' in the prognosis of HI, significantly improving survival [1]. However, access to these therapies may be limited by geographical disparities in resource allocation. Although systemic retinoids may be readily available in certain parts of the world, it is unavailable to clinicians in other settings. There is a paucity of research on HI, and its management in low-resource settings like Sub-Saharan Africa as well as the use of Vitamin A in such cases. We present the first case of HI in Ghana, delivered in a district facility. Specifically, we shared our management experiences with oral vitamin A, as a potential adjunct therapy in low-resource settings.

CASE REPORT

Clinical history

A male neonate was delivered to a 20-year-old primigravida at gestation of 35 weeks and 3 days (by first trimester ultrasound scan), via an emergency caesarean section due to breech presentation and severe oligohydramnios. APGAR scores were 0/10 and 1/10 in the 1st and 5th minutes, respectively. Birth weight was 2.2kg. The infant was resuscitated and sent to the Neonatal Intensive Care Unit (NICU) for intensive supportive care. Of note, the mother was a poor Antenatal Care (ANC) attendant, hence had no anomaly scan. There was no history of consanguinity or previous similar babies in the family. Antenatal records of the mother are documented below (Table 1).

Table 1. Mother's Antenatal Records

Parameter	Outcome
Blood Group	O-Positive
HBsAG	Negative
Sickling	Negative
VDRL	Negative
HIV	Negative
Booking Hemoglobin	11.4g/dl
HBsAG-Hepatitis B surface antigen, HIV-Human Immunodeficiency Virus, VDRL-Venereal Disease Research Laboratory (Rapid test for Syphilis)	

Physical Examination

A male neonate with thick, grey, scaly skin, with diamond shapes, interspersed with deep fissures all over the body. There was a flat nasal bridge, outwardly-turned eyelids with no visible eyeball (ectropion), lips pulled back (eclabium), and very small ears (microtia) (Please see **Figure 1**). Also noticed was hypoplastic and webbed digits with clubbed feet and fixed flexion deformities at elbows and knees (**Figure 1** and **Figure 2**). Anus was patent and there was micropenis with empty scrotum (undescended testes).



Figure 1. Clinical Features of the infant with Harlequin ichthyosis



Figure 2. X-Ray picture of the Harlequin ichthyosis infant showing digital hypoplasia

Management

The infant was resuscitated via chest compressions and ventilation with bag-valve mask (connected to oxygen) for about 8mins, after which he began to make sounds, with APGAR score 6/10 in 10mins. He was then rushed to the NICU. At NICU, infant was nursed in cot, put on supplemental intranasal oxygen, nasogastric tube passed for feeding, and umbilical venous access obtained. Empiric antibiotic therapy was started with IV ampicillin 50mg/kg 12hourly and IV Cefotaxime 50mg/kg 12hourly for 5days, oral Vitamin A 4000IU daily (started on day 2 of life) for seven days. Infant had savlon bath twice daily with lukewarm water, and twice daily skin care with Vaseline gel. He was fed three hourly with expressed breastmilk via nasogastric tube for the first six days and put to breast afterwards since suck was strong and sustained at this time. There was about 90% exfoliation of the skin covering by day 6 of admission, and infant was doing well off supplemental oxygen, breastfeeding,

with stable vitals throughout the stay at NICU. He was discharged home on day 10 of admission, following a request of discharge against medical advice from the family, and scheduled for review in 1week time

Follow up

Upon a follow up phone call on day 3 post-discharge, mother reported that the infant was seen foaming from the mouth, and died few hours later on day 2 of arrival at home (day 12 of life). Possible cause of death was however unclear, given the generally stable state of infant before discharge and the sudden change in general state shortly post-discharge.

Ethical considerations

A written and signed informed consent was obtained from infant's mother and family to publish information and clinical images of infant for educative purposes. We tried as much as possible to anonymize our patient and family and to de-identify all confidential patient information attached.

DISCUSSION

Babies born with HI may survive to adulthood with appropriate supportive and multidisciplinary care with current advancements in management [1]. Our infant had the typical dermatologic features of HI as have been well-established by literature [7,8]. Hence, although we could not do a genetic testing due to lack of resources, we based our diagnosis on the typical clinical features.

A significant challenge we faced was the need to battle with sociocultural beliefs of the family. A discussion with the family revealed their belief that the infant was an 'abnormal human' and signified a misfortune to the family. This made them reluctant to allocate limited resources on the infant throughout the period of admission. To address this misconception, a pediatrician, Neonatal nurse and a Palliative care nurse were involved in counseling the family to demystify their misconception. However, extensive counseling did not result in a significant change in attitude of the family to the care of the infant. This notwithstanding, we provided the minimum standard of care, which yielded significant results.

Systemic retinoids, though essential in managing HI, are not readily available in low-resource settings. Several cases of HI, reported from such settings, were not administered retinoids due to their unavailability

[9,10]. We faced a similar challenge whereby all attempts to get systemic retinoids from major pharmacies across the country failed. Meanwhile, vitamin A (retinol), a fat-soluble vitamin, is a natural analogue of these synthetic retinoids. Vitamin A has not been routinely given to infants fewer than six months because the breastmilk contains an adequate amount within this period. Also, long-term use of high doses of Vitamin A raises concerns of adverse effects, including bulging fontanelle, which are, however rare, mild and self-limiting [11]. However, some studies have demonstrated safety and improved outcomes with vitamin A supplementation in neonates, especially those from regions endemic for vitamin A deficiency [11,12].

Based on the above premise, we decided to do a short course (7 days) of daily low-dose (4000IU) oral vitamin A for our infant, upon failed attempts to get the retinoids. Since limited data exist on the vitamin A use in HI, the optimum dosing was a challenge. Based on this, we calculated the dose using a surrogate of the dose of 800-1000mcg/kg/d (2700-3300IU/kg/d) synthetic retinoids for neonates with HI, recommended in an earlier study [13]. We did a short of seven [7] days because we did not have the facilities to monitor serum levels, to trace and mitigate any toxicity. Moreover, no local or national guideline existed at the time of this case, since this was the first case recorded in Ghana, to our knowledge. Interestingly, we noticed that the infant's general condition improved significantly after few days of initiation of oral Vitamin A 4000IU daily, combined with other recommended components of the supportive care [1,6,14]. We did not find any reported side effects of Vitamin A, including irritability and bulging fontanelles. In contrast to most HI cases reported from similar settings, who survived for 3-5 days with similar management excluding retinoids, our infant survived for 12 days. He was discharged home in a stable state on day 10 of life, at the request of discharge against medical advice from the family. At this point, he had about 95% exfoliation, breastfeeding normally, and stable vitals. He died at home of unclear cause two days post-discharge. Although the actual cause of death was not ascertained, and an autopsy was not done due to resource unavailability, we believe

the outcome could have been better if he had stayed on admission for a few more days.

STUDY LIMITATIONS

Due to socio-economic constraints, we could not perform genetic testing for molecular confirmation of diagnosis. However, clinical features were outstandingly typical of Harlequin Ichthyosis. Also, this is a single case, with no comparison with babies receiving standard treatment, and hence, may not be sufficient for treatment recommendations; hence, more robust studies are needed to explore this finding. The infant's survival till day 12 may be influenced by other factors, including antibiotic therapy, skin care and other interventions aside Vitamin A. Finally, we could not tell the actual cause of death of the infant at home, and could also not tell if the infant would have survived beyond the 12days if he was on admission.

CONCLUSION

To our knowledge, this is the first documented case of HI in Ghana, a country facing sociocultural and resource limitations. We propose that careful attention should be given to sociocultural components of care when managing infants with similar anomalies. Importantly, based on our incidental finding, we suggest that a short course of low-dose oral vitamin A may serve as a potential adjunct therapy in low-resource settings. However, this finding was just an early observation in a single case, and is therefore subject to further exploration with more robust studies in the future, probably in the context of a control with babies receiving standard therapy.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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