# FINDINGS IN A CASE OF HARLEQUIN ICHTHYOSIS IN A NEONATE: A CASE REPORT AND REVIEW OF DIAGNOSTIC CRITERIA

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## ABSTRACT:

**Introduction:** Harlequin ichthyosis (HI) is a rare autosomal recessive congenital disorder caused by mutations in the ABCA12 gene, which is crucial for lipid transport and skin barrier function. The estimated incidence is approximately 1 in 300,000 births. HI is characterized by severe hyperkeratosis, leading to thick, plate-like scales separated by deep fissures. Infants with HI are at high risk for complications such as dehydration, infection, and respiratory distress.

**Case presentation:** This case report describes a newborn female with multiple congenital anomalies, including natal teeth, lustrous skin, left anophthalmia, right ectropion, eclabium, absence of eyebrows and eyelashes, and rudimentary nose and ears. She passed away two hours after birth. An autopsy and dental examination were performed at the Al-Khartoum morgue in Sudan to determine the cause of death and confirm the clinical diagnosis. External examination confirmed the findings and internal examination revealed mainly lung edema. The rarity of HI, with only 300 cases reported in the medical literature, combined with the presence of natal teeth, makes this case particularly unique.

**Conclusion:** this case highlights the presence of multiple congenital anomalies, including natal teeth and severe skin changes and pulmonary hypoplasia, which contributed to the infant's poor prognosis and death due to acute respiratory failure. The diagnosis of HI is primarily based on physical examination and histological evaluations, with confirmation through genetic testing for loss-of-function mutations in the ABCA12 gene. Although genetic testing was not feasible in this case due to limitations caused by the ongoing war, the severity of the findings strongly supported an HI diagnosis, even in the absence of genetic testing.

**Keywords:** Harlequin ichthyosis, natal teeth, congenital anomalies, newborn, ABCA12 gene, genetic testing

## INTRODUCTION

Harlequin ichthyosis (HI) is a rare autosomal recessive congenital disorder caused by mutations in the ABCA12 gene, which plays a crucial role in lipid transport and skin barrier function. The exact number of cases worldwide is difficult to determine due to its rarity, but it is estimated that fewer than 300 cases have been reported in medical literature globally occurring in approximately 1 in 300,000 births. Due to advances in neonatal care and genetic testing, the number of reported cases has increased

slightly in recent years, but it remains a very rare condition. **(Elkhatib et al 2024)**

HI is a severe congenital disorder characterized by distinct clinical features, histopathological findings, and genetic mutations. The diagnosis of HI is primarily based on several key criteria. Clinically, infants with HI are born with thick, plate-like scales that cover their skin and are separated by deep fissures. This condition causes the skin to appear tight, leading to notable facial deformities such as ectropion (outward-turning eyelids), eclabium (outward-turning lips), a flattened nose, and rudimentary ears. These severe skin abnormalities often restrict movement, complicated feeding, and increase susceptibility to infections due to the compromised skin barrier. Newborns with HI struggle to balance water loss, maintain body temperature, and combat infections. **(Jilumudi UB 2012 and Glick et al 2017)**

Histopathologically, while a skin biopsy is not always required due to the distinctive clinical appearance, it can reveal significant hyperkeratosis (thickening of the outer skin layer) and the absence of the granular layer, which supports the clinical diagnosis of HI. For definitive diagnosis, genetic testing is crucial as it identifies mutations in the ABCA12 gene. This gene is essential for skin barrier formation, and mutations lead to severe skin abnormalities characteristic of HI. Genetic testing is particularly important for prenatal diagnosis and genetic counseling, providing essential information for managing the condition and planning care. (**Akiyama et al 2008 and Vahlquist et al 2008 and Glick et al 2017 )**

In instances of neonatal demise, performing a thorough post-mortem examination is essential not only for understanding the pathological basis of death but also for providing critical information to the parents regarding the risk of recurrence in subsequent pregnancies. This information aids in genetic counseling and informs prenatal care strategies in future gestations special in rare diseases.

Ethical approval was obtained from the Research Ethics Committee of the faculty (Serial Protocol Number0306825). The data obtained after parent's consent and was maintained anonymously and confidentially.

## CASE PRESENTATION

### 1- Family History:

A 2-day-old deceased full term newborn female was brought to the mortuary for dissection. Her body weigh 2100 gm . She was born alive and had severe respiratory distress, with cyanosis. They put her on ventilator but she died two hours later according to the hospital records. The family with consanguineous parents have three healthy daughters. There was no prenatal history provided.

### 2-External Examination:

The examination revealed that the umbilical cord was clamped 4 cm from the abdominal wall. The newborn's length was 46 cm, head circumference was 32 cm, and weight was 2100 grams. The skin was smooth and lustrous, with desquamation observed over the chin and nose (Fig. 1). The left eyeball was absent, and ectropion was present in the right eye. Other notable features included eclabium, loss of eyebrows and eyelashes, a flattened and rudimentary nose and ears, and an absent nasal septum (Fig. 2). Absence of the Nasal Septum (Hyporhynia) was diagnosed by physical inspection and autopsy .Clinically it can be diagnosed by looking for a single nostril, absent columella, and hypoplastic mid-face. In addition, there was dysmorphic features (e.g., left anophthalmia, right ectropion, eclabium, absence of eyebrows and eyelashe). By compressing the nasal tip the deformity worsens, this is usually associated with other craniofacial anomalies if additional features (e.g., growth retardation, organ malformations) are present**.(**

**Abdulkadir et al 2020,and Erdoğdu S 2024)**

The teeth were large and white, occupying the entire upper jaw (Fig. 3). Edematous hands and feet with finger hypoplasia were also observed. A diamond-shaped area of colored skin was noticed on the forehead. To determine the cause of death, an autopsy was performed.

3-Internal Examination:

All organs appeared normal upon gross inspection, except for the lungs, which were edematous and hypoplastic. The gingiva and teeth were dissected for histological examination and a DNA sample was taken for genetic analysis, but the analysis could not be completed.

4-Odonatological Examination:

The oral examination revealed a few large white teeth set in the upper jaw (Fig. 4)

Absence of Tooth Roots was diagnosed clinically where the teeth was loose due to minimal root formation. In addition ,there was open apical foramina (visible at the tooth base). And it is associated with several anomalies**. (Meade et al 2023)**

## DISCUSSION

The role of the ABCA12 gene is to transport lipids across extracellular membranes via lamellar granules, which are crucial components of the stratum corneum. When there is a mutation in the ABCA12 gene, lipids are not properly transported to the stratum corneum. This malfunction leads to hyperkeratosis, an excessive buildup of keratin in the epidermal keratinocytes, resulting from the impaired lipid barrier. The distinctive features of Harlequin ichthyosis (HI) are caused by the accumulation of lipids within the epidermal keratinocytes. **(Akiyama et al 2005 and Akiyama M 2014 )**

In the current case, there were many features that support the congenital anomaly of Harlequin ichthyosis. These included abnormal skin, bilateral ectropion, eclabium, flattened and malformed ears, a malformed nose with an absent septum, and semi-flexed extremities, along with the absence of eyebrows and eyelashes. Additional features such as an absent left eyeball, edematous hands and feet with finger hypoplasia, and a colored skin patch on the forehead were also observed. These features have been described in the literature as indicative of Harlequin ichthyosis. **.( Rajpopat et al 2011 , Jilumudi UB 2012 and Dacaj-Elshani et al 2022)**

The observation that the scales and fissures are only present on the face, while the rest of the body shows a different presentation, suggests that the neonate may not have the full-blown, severe form of HI. There are different forms of ichthyosis with varying presentations, and some may have more localized or milder features than HI. **(Maritska,et al 2024)**

What had not been previously mentioned in cases of Harlequin ichthyosis is the presence of natal teeth, as observed in this infant girl. Photo 4 showed large, white teeth in the upper jaw, which appeared to have no roots upon visual examination. This contrasts with the findings of Khandelwal et al. who reported that natal teeth are typically smaller, conical, yellowish, and exhibit hypoplastic enamel and dentin, with poor or absent root formation. **(Khandelwal et al 2013)**

If the child had survived, a dentist would have been needed to evaluate the condition and determine whether the teeth should be removed or retained. Roa et al. described the histological features of these teeth, noting a thin enamel layer with varying degrees of mineralization, and in some cases, hypoplastic or completely absent enamel in certain regions. The presence of tubular osteodentin, as observed in the occlusal central fossa, is similar to irregular tertiary dentin that forms in response to stimuli such as caries or attrition. **(Rao et al 2009, , Štamfelj et al 2010 and Mhaske et al 2013)**

Natal teeth, which are teeth present at birth, are relatively uncommon but have been observed in cases of HI. The incidence of natal and neonatal teeth ranges from 1 : 2,000 to 1 : 3,500. **(Yamamoto et al 2010)** Their occurrence in HI can be a significant clinical finding that supports the diagnosis, particularly when seen alongside other hallmark features of the condition such as severe skin abnormalities and facial deformities. Their presence can complicate feeding and oral care due to severe skin involvement and associated systemic issues. While there is no direct genetic link between the ABCA12 mutations that cause HI and the presence of natal teeth, the severe nature of HI can contribute to a broader spectrum of congenital anomalies, including natal teeth. **(Fischer et al 2008 and Hsu et al 2016 )**

A theory was proposed that these natal teeth are due to the inheritance of autosomal characteristics. Endocrine dysfunction caused by the pituitary, thyroid, and gonads could also be a significant factor. Another theory proposed is that the premature emergence of natal or neonatal teeth is caused by excessive or heightened absorption of the surrounding bone. Several factors such as maternal health issues, hormonal imbalances, fevers during pregnancy, intoxication by polyhalogenated aromatic hydrocarbons and congenital syphilis can contribute to the occurrence of natal and neonatal teeth. Lastly, it may be due to a fast or early dental growth pattern instead of the tooth germs being positioned near the surface. **( McDonald et al 2004 and DeSeta et al 2022)**

In the current case, the internal examination revealed lung edema. Autopsy findings in Harlequin ichthyosis often demonstrate pulmonary complications, including lung immaturity, pulmonary hypoplasia, and interstitial thickening. These abnormalities contribute to respiratory distress, which is a common cause of death in affected neonates, as seen in this case. Additionally, the lungs may exhibit edema, hemorrhage, or infection, likely resulting from the compromised skin barrier and the infant's overall fragile condition. These findings emphasize the systemic impact of Harlequin ichthyosis and the significant challenges in managing respiratory function in these cases. **(Rajpopat et al 2011)**

Differential diagnosis is crucial in distinguishing Harlequin ichthyosis (HI) from other congenital ichthyosis, such as Lamellar ichthyosis or Congenital Ichthyosiform Erythroderma (CIE). These conditions exhibit less severe skin involvement and lack the characteristic plate-like scales and deep fissures seen in HI, making accurate differentiation essential for proper management. The severity of the findings in the current case strongly supported an HI diagnosis, even in the absence of genetic testing. **(Rajpopat et al 2011 and Jilumudi UB 2012 )**

## CONCLUSIONS

In conclusion, this case highlights a rare occurrence of Harlequin ichthyosis, marked by multiple congenital anomalies, including natal teeth, severe skin abnormalities, and pulmonary hypoplasia identified during autopsy. These complications contributed to the infant's poor prognosis and death two hours after birth due to acute respiratory failure. Diagnosing such cases requires a thorough case history, along with comprehensive clinical, histological, and genetic examinations of the infant. However, genetic testing was not feasible in this case due to the ongoing war. However, the severity of the findings strongly supports an HI diagnosis, even in the absence of genetic confirmation.

## ETHICAL CONSIDERATION

Ethical approval was obtained from the Research Ethics Committee of the faculty (Serial Protocol Number0306825). The personal data were maintained anonymously and confidentially.

## CONFLICT OF INTEREST

The authors declare no competing interests.

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## الملخص العربي

### النتائج في حالة إصابة طفل حديث الولادة بمرض السمكة الهارلكوين: تقرير حالة ومراجعة معايير التشخيص

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**المقدمة:** داء هارلكوين السمكي هو اضطراب خلقي نادر متنحي وراثيًا يحدث بسبب طفرات في جينABCA12 ، وهو أمر بالغ الأهمية لنقل الدهون ووظيفة حاجز الجلد. يقدر معدل الإصابة بحوالي 1 لكل 300000 ولادة. يتميز داء هارلكوين السمكي بفرط التقرن الشديد، مما يؤدي إلى ظهور قشور سميكة تشبه الصفيحة مفصولة بشقوق عميقة. الأطفال المصابون بداء هارلكوين السمكي معرضون لخطر كبير للإصابة بمضاعفات مثل الجفاف والعدوى وضيق التنفس.

**عرض الحالة:** يصف تقرير الحالة هذا أنثى حديثة الولادة تعاني من تشوهات خلقية متعددة، بما في ذلك الأسنان الولادية، والجلد اللامع، وانعدام العين اليسرى، وانقلاب الجفن الأيمن للخارج، وتشوه الشفة، وغياب الحاجبين والرموش، والأنف والأذنين البدائيين.

توفيت االمولودة بعد ساعتين من الولادة. تم إجراء تشريح الجثة وفحص الأسنان في مشرحة الخرطوم في السودان لتحديد سبب الوفاة وتأكيد التشخيص السريري.

وقد أكد الفحص الخارجي تشخيص الحالة ، وكشف الفحص الداخلي عن نقص نمو الرئتين ووذمة الرئة بشكل رئيسي. إن ندرة مرض هارلكوين السمكي ، مع وجود 300 حالة فقط في المراجع الطبية، إلى جانب وجود أسنان الولادة، يجعل هذه الحالة فريدة من نوعها بشكل خاص.

**الخلاصة:** تسلط هذه الحالة الضوء على وجود تشوهات خلقية متعددة، بما في ذلك أسنان الولادة وتغيرات جلدية شديدة ونقص نمو الرئتين ، والتي ساهمت في سرعة وفاة الرضيع بسبب الفشل التنفسي الحاد. يعتمد تشخيص داء هارلكوين السمكي I في المقام الأول على الفحص البدني والتقييمات النسيجية، مع التأكيد من خلال الاختبارات الجينية لطفرات و اختلال الوظيفة في جين ABCA12. وعلى الرغم من أن الاختبار الجيني لم يكن ممكنًا في هذه الحالة بسبب القيود الناجمة عن الحرب الجارية، إلا أن ، الا أن تعدد التشوهات الخلقية دعم التشخيص بقوة وإن كان بدون الإختبار الجينى) جين ABCA12، المسح الجينى ( اثناء و بعد الولادة )- بأخذ عينة من النسيج الجينى (الغيبات المشيمة) أو بسحب عينة من السائل الأمنيوسى. وذلك التحليل يساعد على التشخيص المبكر حتى يمكن إتخاذ القرار المناسب بخصوص الولادة والعناية بالمولود بعد الولادة.

**الكلمات المفتاحية:** داء السمكة الهارلكوين ، الأسنان المولود حديثا، التشوهات الخلقية، حديثي الولادة،