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Harlequin ichtyosis: A rare form of congenital ichthyosis- A case study

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Abstract
Harlequin ichthyosis is a severe genetic disorder that affects the skin. Infants with this condition are born prematurely with very hard, thick skin covering most of their bodies. The skin forms large, diamond-shaped plates that are separated by deep fissures. The disease might be lethal at birth and the affected babies are often premature. The present study reports a new case with harlequin ichthyosis and adds to the collective knowledge of this rare skin disorder. The purpose of this study is to show the interest of adequate and early management to improve the prognosis.

Keywords: ABCA12 gene mutation; autosomal recessive; skin abnormalities

Introduction
Congenital harlequin baby syndrome is a rare genetic severe skin disease with massive thickening of skin over the entire body [1]. The overall incidence is 1 in 300,000 births [2]. It is a transient neonatal condition but can be life-threatening in the short term due to complications. Its name comes from the Greek “ichthys” meaning "fish" and referring to the clinical appearance of scaly skin. It causes hyperkeratinization of the epidermis which is the mode of onset and revelation of ichthyosis transmitted in a recessive mode [3]. The long-term prognosis depends on the underlying keratinization disease,which is usually severe, but favourable outcomes exist. The prognosis of this condition depends on the management in the neonatal period, hence the need for early diagnosis and adequate management to optimise this prognosis.

Patient and observations
J.E, newborn female, third of three siblings, from the Casablanca region in Morocco, admitted to neonatal intensive care on the first day of life for congenital ichthyosis and prematurity. He has a history of first degree consanguinity, no similar cases in the family, healthy siblings. The pregnancy was followed at the health centre, carried out at 36 weeks of amenorrhea, negative infectious anamnesis. There is no drug or toxic intake in the mother during pregnancy. The mother received her first dose of the COVID19 vaccine during the first trimester of pregnancy and became infected with the COVID19 virus at 19 weeks of amenorrhea without complications. The delivery was by caesarean on premature rupture of the membranes and deceleration of the foetal heart rate. At birth APGAR was rated 10/10 with good adaptation to extrauterine life. The clinical examination on admission showed a weight of 1,940 kgs, a height of 46 cm, a cranial circumference of 35 cm, a eupneic at 50 c/min, a blood oxygen saturation at 99% in ambient air, normal cardiopulmonary auscultation, soft abdomen, and no palpable mass. On mucocutaneous examination, erythematous skin is noted with large, thick, yellowish scales separated by deep red cracks, eclabion and ectropion, and edematous extremities (cf. Figure 1). We also noted badly hemmed ears bilaterally, an absence of eyebrows and little hair (cf. Figure 2), difficulty in sucking, a normal echocardiogram, and an ophthalmological examination with normal fundus.
An initial assessment was performed, and it showed a normal blood count, correct ionogram, and negative C-reactive protein. The treatment consisted of placement in a high humidity incubator and local care based on daily chlorhexidine baths and petroleum jelly compresses on all skin surfaces and analgesic treatment as well as eye care (cf. Figure 3). The family refused the rest of the exploration assessments and the newborn came out on day 20 of life from hospitalisation at 2,200 kgs. He was seen again in consultation one week after discharge with good skin and weight evolution. A genetic counselling consultation is planned for the parents.

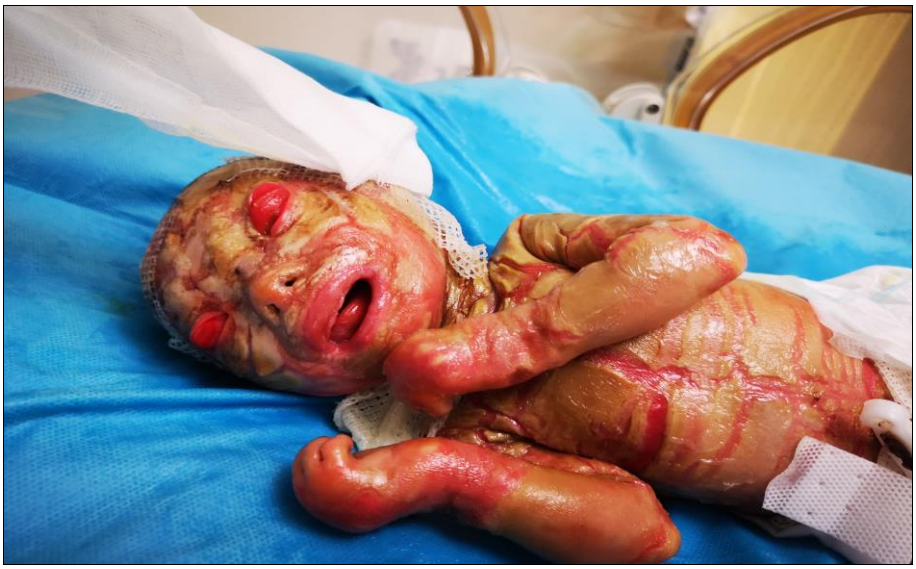

Fig 1: The patient exihibitng yellowish scales separated by deep red cracks

Fig 2: Patient with badly hemmed ears bilaterally and absence of eyebrows and little hair.

Fig 3: Treatment by compresses of petroleum jelly

Discussion

Ichthyoses are a heterogeneous group of diseases having as common characteristics the formation of an abnormal stratum corneum with hyperkeratotic skin lesions that result in generalised desquamation with, or without, epidermal hyperproliferation or inflammation of the dermis. Different classifications have been proposed based on the physiopathological characteristics, the mode of transmission or even the molecular and genetic bases [4]. The four main hereditary ichthyosis are [5]:

- ichthyosis vulgaris of autosomal dominant transmission;
- X-linked ichthyosis or X-linked recessive black ichthyosis;
- autosomal recessive lamellar ichthyosis;
- autosomal dominant congenital bullous ichthyosis form erythroderma.

Certain clinical presentations immediately allow the causative gene to be suspected and molecular analysis to be targeted. This is the case of the collodion baby with spontaneous healing: mutations of TGM1 or ALOX12B [7], of the harlequin foetus (mutations of ABCA12), of ichthyosis bullosa (mutations of keratins 1 or 10) [8]. Harlequin ichthyosis is the most severe form of ichthyosis. It is transmitted autosomally recessive. This syndrome is manifested clinically at birth by a newborn enclosed in large thick, yellowish scales, separated by deep red cracks. Extreme skin tension is responsible for eversion of the eyelids (ectropion), lips (eclabion), ears and nose. The extremities are edematous due to strictures by the massive thickening of the skin. Children alive at birth die rapidly within days of respiratory complications, infections or dehydration [7]. Akiyama *et al*. [9] demonstrate that harlequin ichthyosis is caused by loss-of-function mutations in ABCA12, which codes for a lamellar granule membrane protein involved in lipid transport. Together with the knowledge that mutations in ABCA1 and ABCA4 cause Tangier disease and Stargardt disease, respectively, this most recent discovery further supports a pivotal role for ABCA class lipid transporters in cellular homeostasis and sheds light on the importance of lipid processing in the development and maintenance of the epidermal barrier. The treatment is most often only symptomatic and consists of daily local care sometimes associated with systemic treatments. It is preferable to start it in the intensive care unit with local hydration by placing it in a 100% humid incubator and applying emollients.

Keratolytic treatments with many preparations are available on the market containing urea, -hydroxy acids (lactic acid, glycolic acid), salicylic acid or propylene glycol [10]. Treatment with emollients and retinoids in the early phase improved the survival of patients without MA for retinoids. This treatment requires close hepatic monitoring with the possibility of the appearance of cataracts or bone damage at doses greater than 1 mg/kg per day [7]. Etiological treatment is rarely possible but is the subject of much research. Multidisciplinary care within specialised teams, most often hospital, is necessary especially psychological for the entourage [9]. Rajpopat *et al*. [11] reported in a study of 45 harlequin baby cases in 2011 that the overall survival rate in this study was 56%. Death usually occurs within the first three months of life from sepsis or respiratory failure in 75% of cases. Early introduction of oral retinoids may improve survival, as 83% of those treated survived, while 76% who were not treated with retinoids died. Several complications have been described in living patients, such as mucocutaneous, gastric, ophthalmological, orthopaedic, neurological, respiratory, urological disorders and growth retardation. Akiyama *et al*. [9] also showed that genetic correction of ABCA12 deficiency by gene transfer in patients' keratinocytes restored normal glucosylceramide cell distribution and lamellar granule formation. This Result raises the possibility of harlequin ichthyosis treatment using systemic administration of functional peptides with ABCA12-like properties or ABCA12 gene delivery approaches undertaken either prior to or after birth.

Conclusion

Harlequin ichthyosis is a rare skin disorder. It follows an autosomal recessive mode of inheritance. Prenatal diagnosis should be offered to women with previously affected babies. It can be fatal through dehydration and infection. It requires multidisciplinary care from birth. Treatment with emollients and oral retinoids may improve patient survival but the prognosis remains poor with a high percentage of deaths.

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