

East African Journal Vol. 87 No. 9 September 2010

HARLEQUIN ICHTHYOSIS IN AN AFRICAN CHILD: CASE REPORT

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SUMMARY

Severe congenital skin abnormalities are a rare event. This case is unique in that it is a case of harlequin ichthyosis in sub-sahara Africa in a child of African origin and elaborates the challenges faced in its management. We present a neonate who was managed for this condition at Chogoria Mission Hospital. In presenting this case, we aim to sensitise healthcare providers to promptly recognise and manage this rare skin condition.

INTRODUCTION

Harlequin ichthyosis is the most severe form of congenital ichthyosis, a congenital defect involving skin keratinisation. The incidence is estimated to be 1 in 300,000 (1). It is characterised by a profound thickening of the keratin layer in foetal skin. The affected neonate is born with a massive, horny shell of dense, plaquelike skin and contraction abnormalities of the eyes, ears, mouth, and appendages. This armor limits movement and compromises the functions of the skin leaving the newborn susceptible to metabolic abnormalities and infection. The term harlequin derives from the newborn's facial expression and the triangular and diamond-shaped pattern of hyperkeratosis. The newborn's mouth is pulled wide open, mimicking a clown's smile. Most affected infants die during the first several weeks of life, although longer-term survivors have been reported.

CASE REPORT

Baby P.M., term infant born at home by spontaneous vertex delivery to a now para 2+0 was brought to the hospital due to his unusual appearance. The mother had one living child who was normal but of different paternity. There was no family history of chronic or genetic disorders.

Physical examination revealed a newborn weighing 2.3 kilograms with moderate tachypnoea (64 breaths Per minute) and good bilateral air entry. The cardiovascular system was essentially normal with a heart rate of 120 per minute with the first and second heart sounds heard and no additional murmurs

Abdominal examination was normal with no organomegaly and a patent anus. The external male genitalia revealed a small penile shaft and scrotal sac with descended testicles. The main clinical findings were on the skin as shown in the accompanying pre-and post mortem photographs of the infant (fig 1-5).

Figure 1

On arrival at nursery



Figure 2

Characteristic facial features



Figure 3(a)
Poorly formed limbs

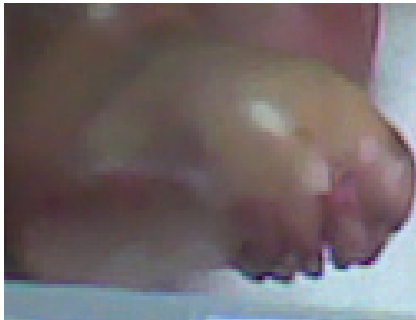


Figure 3(b)

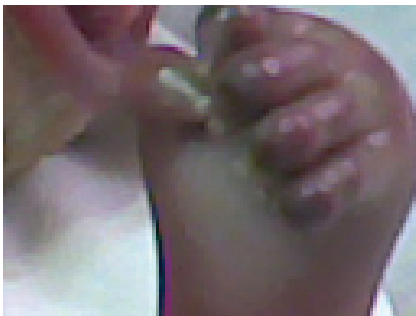


Figure 4
Characteristic facial features



Figure 5
Limbs with gangrenous extremities



The baby was covered in a thick "leathery" skin interspersed with erythematous fissures more prominent in the areas of skin folds. The eyes were cherry red masses with eversion of the eyelids (ectropion). In addition, the pinnae of the ears were

poorly formed and plastered with flaky skin. The infant had anterior nares without an external nose. The mouth was taut and maintained in a persistently open position similar to a "fish mouth" with eversion of the lips (eclabion). Both upper and lower limbs were in fixed flexion and the hairline was unusually high. A diagnosis of harlequin ichthyosis was made and the baby admitted to the newborn unit where he was nursed in a humidified incubator and fed on formula by cup with a target of 160kcal/kg/day as the mother was unable to express breast milk due to psychological stress and the baby was unable to suckle. Feeds were gradually increased as tolerated.

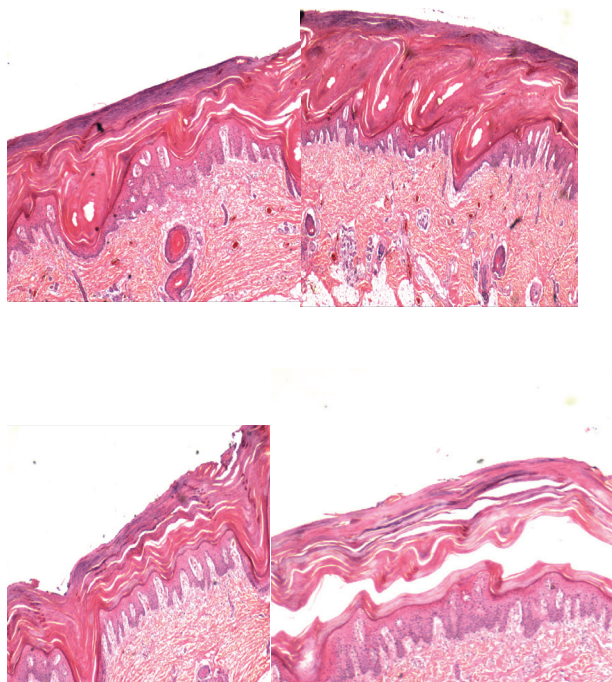
Emollients were applied to keep the skin moist. Broad spectrum antibiotics were initiated and a stat dose of vitamin A at 50,000 IU given. A cranial and abdominal ultra-sound carried out to evaluate for additional abnormalities were reported to be normal. On day four, the baby developed gangrene of the toes and fingers and finally succumbed on the 8th day of life.

POST-MORTEM AND HISTOLOGY RESULTS

Gross post-mortem examination revealed that the entire skin was thickened and shiny with fissuring more marked at the skin folds and sloughing over the right anterior thigh, knee, neck and back. The hands and feet were poorly formed with presence of contractures and digital gangrene. The facial dysmorphic features described earlier were still present. Examination of the chest cavity revealed fragile ribs that fractured easily on mild pressure with adhesions noted from the inner aspect of the ribs onto the liver and spleen. The right lung appeared normal with all three lobes visualised. However, the left lung appeared smaller and poorly formed. The pericardial sac was filled with straw coloured fluid. The coronary vessels appeared normal. The right atrium appeared enlarged compared to the left. On examination of the abdominal cavity, there was haemorrhagic fluid visualised over the splenic area with adhesions between the transverse colon and stomach. The liver was enlarged extending into the left hypochondrial region while other abdominal organs were grossly normal.

The cranial cavity had fibrinopurulent material in the subgaleal space and the skull bones appeared unusually thin. Gyri and sulci were visualised on the brain matter however the forebrain and hind brain appeared caseous and friable. The corpus callosum, cerebellum and brain stem were identified and appeared normal. Microscopic examination of the skin revealed marked hyperkeratosis with changes consistent with harlequin ichthyosis but no specific changes noted in the brain tissue (Fig 6). The cause of death was neonatal sepsis secondary to harlequin ichthyosis.

Figure 6



Examination of the skin biopsy specimens revealed marked hyperkeratosis (thickening of the stratum corneum) which extended into the hair follicles. There is pronounced parakeratosis (retention of nuclei in the stratum corneum), hypogranulosis and irregular acanthosis (epidermal thickening). Normal adnexal structures were present. The underlying dermis showed no obvious abnormalities.

DISCUSSION

Congenital defects involving skin keratinisation cause a unique dermatosis derived from the Greek word "ichthys" meaning fish. Harlequin ichthyosis is the most severe form of congenital ichthyosis and was first described by Rev. Oliver Hart in 1750 as follows:

"The skin was dry and hard and seemed to be cracked in many places, somewhat resembling the scales of a fish. The mouth was large and round and wide open. It has no external nose but two holes where the nose should have been. The eyes appeared to be lumps of coagulated blood, turned out about the bigness of a plum, ghastly to behold. It had no external ears but holes where the ears should be. The hands and feet appeared to be swollen, were crumpled up and felt hard. The back part of the head was much open. It made a strange kind of noise, very low, which I cannot describe. It lived about eight and forty hours and was alive when I saw it" (2).

The longest living survivor is "Nelly" born in 1984 and currently lives in the United Kingdom studying sports coaching and leadership (3). Forty five percent of patients die soon after birth while those

surviving beyond six months develop non-bullous congenital ichthyosiform erythroderma (4).

Harlequin ichthyosis is believed to be inherited in an autosomal recessive manner (5). Akiyama *et al* showed that abnormal keratinocyte lamellar granules are the hallmark of this condition and identified 5 mutations in the *ABCA12* (ATP binding cassette sub - class A) transporter on the lamellar membrane (6).

The *ABCA12* is a transporter that binds *ATP* (adenosine triphosphate) for active transport of lipids across cell membranes against a concentration gradient (5). Along with lipids, lamellar granules (LG) transport lipid processing enzymes, proteases and their inhibitors that play a role in barrier permeability and control of the desquamation process (5). Thus mutations in *ABCA12* that codes for lamellar granular protein means they are not properly formed so lipids abnormally processed are diffusely distributed and abnormally secreted or not at all. Corneocytes are then embedded in lamellar intercellular lipid complex of cholesterol, phospholipids and ceramides that are trafficked by lamella bodies (7). Skin biopsies typically show a thickened corneal layer and nuclei that are flattened early on in differentiation but retained in cornified layers (parakeratosis) (4). In addition, there is hyperkeratosis and hypergranulosis (4). The cytoplasm in the stratum corneum is congested with abnormal lipid containing droplets and vacuoles resembling immature LG like vesicles (6).

Management of babies with harlequin ichthyosis is a challenge because of the increased water loss, impaired thermal regulation, respiratory embarrassment and increased risk of infection (8). Retinoids such as etretinate, the current first line of therapy, were first used to treat harlequin ichthyosis in 1985 and were shown to improve the skin condition in some cases (9). Etretinate has been given at 1 mg thrice daily and gradually tapered until the skin symptoms improve (9). Additional recommended treatment includes application of topical retinoid cream (9) or 10% topical urea on the tight bands around the wrists and ankles and cerumol applied to the keratin plaques on the external auditory meatus (10). None of these therapies have been evaluated in a clinical trial setting, largely due to the rarity of the condition and therefore the dose and duration of therapy have not yet been standardised. The mode of action of the retinoids is unknown however it is hypothesised that they control the differentiation and proliferation of keratinising and non keratinising epithelia. Baby P.M. was successfully nursed in a humidified incubator to reduce water loss and maintain a warm environment. Broad spectrum antibiotics were given to treat the infection. Baby P.M. was treated with the only alternative to a retinoid available then, vitamin A, given as a stat dose of 50,000 IU.

Prenatal diagnosis can be done by amniocentesis with DNA testing between 15-18 weeks, chorionic villous sampling at 10-12 weeks, 3D ultrasound in second trimester (11) and ultrastructural examination of fetal skin biopsy samples at 19-23 weeks estimated gestational age (EGA) (12-14). Identification of the gene defects associated with this condition which include mutation IVS23-2A>G, truncation mutation R434X have facilitated DNA based prenatal diagnosis. *In vitro* studies have demonstrated that **ABCA12** corrective gene transfer in cultured harlequin ichthyosis keratinocytes can restore normal ability of cells to secrete lamella granular lipids (6). Babies born with harlequin ichthyosis present significant challenges to care providers that include unavailability of prenatal diagnostic tests, required drugs and counselling needs of the parents. Despite limited resources we were able to provide supportive care to the baby until its final moments. If resources allow, the parents were advised on close follow up upon the next pregnancy due to the likelihood of recurrence.

PROGNOSIS

Fulminant sepsis remains the most common cause of death in affected infants. With specialised medical treatment to control temperature, prevent fluid loss and infections, treat skin conditions and provide physical therapy, more babies are surviving into childhood and longer. Children who survive have skin changes that resemble non bullous congenital ichthyosiform erythroderma, with chronic erythroderma and a fine scale over the whole body thus requiring long term follow up. Severe ichthyosis with eclabium and ectropion can relapse. In general, intellectual development is thought to be normal. In patients who survive, growth and development must be closely monitored. Severe failure to thrive from excessive cutaneous protein loss may occur. The congenital ichthyoses can have devastating medical and social consequences. Thus the family should receive adequate social and psychological support.

In conclusion harlequin ichthyosis is the most severe form of congenital ichthyosis. The hallmark of this condition are mutations in the ABCA12 (ATP binding cassette subclass A) transporter on the lamellar membrane of the skin that binds ATP (adenosine triphosphate) for active transport of lipids across cell membranes against a concentration gradient. This presents as a unique scaly dermatosis similar to that of fish scales hence the name ichthyosis. Diagnosis is confirmed on histology of the skin that reveals hyperkeratosis and parakeratosis. Management is mainly supportive aiming at thermal control, infection control, adequate hydration, administration of retinoids and psychosocial support for the family. Early recognition, management and

understanding its potential complications can lead to better survival of these children.

ACKNOWLEDGEMENTS

To the parents of Baby P.M., Chogoria Mission Hospital for their co-operation and providing a written informed consent for publication of this case report and S. K. Ngichabe for his continuous support in preparation of this case report.

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