Case report

Harlequin ichthyosis from birth to 12 years

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SUMMARY

A neonate was born with generalised, erythrodermic, thick, fissured skin, severe ectropion, hypoplastic auricles and limb abnormalities. A clinical diagnosis of harlequin ichthyosis was made, allowing supportive therapies to be commenced promptly. Oral acitretin was initiated on day 3 of life, complemented by an intensive skin care regimen. Rehydration, prevention and treatment of infection, temperature control and nutritional support were all essential to see him through the neonatal period. Nearly 12 years later, this child continues to receive multidisciplinary input and enjoys a good quality of life.

BACKGROUND

Harlequin ichthyosis is a rare (incidence 1:300 000 births)[1] and potentially fatal congenital dermatological disorder of keratinisation.[1] As the most severe of the autosomal recessive congenital ichthyosis, it is associated with a high mortality rate.[1] However, with early initiation of oral acitretin and intensive supportive care this child has survived and thrived, and has a good quality of life (QOL). There is some concern as to the long term risks of ongoing acitretin treatment but, in this case, it has been well tolerated.[1]

CASE PRESENTATION

A male neonate was born at 35+4 weeks gestation with an unusual and distinctive appearance (figure 1). His skin was extremely thick and taut (hyperkeratotic), yellow and split by deep fissures into plates, resembling a harlequin jester costume. The digits of his hands and feet were fused and flexed, encased in thick shiny skin. The sclera was occluded by severe ectropion and chemosis. He had marked eversion of the lips, eclabium. The pinnae and nostrils were rudimentary and bound down. He was pink and well perfused and required no resuscitative intervention. The paediatric team reviewed and transferred him to the neonatal unit.

There was no family history of ichthyosis. His parents are consanguineous, second cousins, originally from Pakistan. His mother had gestational diabetes requiring insulin. The couple has two older boys who are healthy.

On the neonatal unit, the diagnosis of congenital harlequin ichthyosis was suspected and confirmed by a Paediatric Dermatologist on reviewing photographs. Full supportive care, which included an intensive emollient and skin care regime and protein supplements, was initiated. Oral acitretin was commenced on day 3 of life and continues to this day. After a 29-day stay on the unit, he was discharged to the care of his family and community healthcare team, with ongoing multidisciplinary team (MDT) support.

Now 12 years old, his skin remains intensely erythematous with generalised scaling but his eyes and ears are much improved. He has persistent ectropion, epiphora (tear spillage) and myopia. However, despite his hypoplasticpinnae, his hearing is normal. His digits remain flexed and he has lost the tips of two fingers. He has extensive scarring alopecia and minimal sweating ability which leads to heat intolerance. He attends mainstream school with the help of a classroom assistant and retains the support of an MDT, including paediatrics, dermatology, ophthalmology, ear, nose and throat (ENT), physiotherapy, dietetics and children's community nursing.

INVESTIGATIONS

Karyotyping and DNA studies were undertaken in 2010 to identify the known pathogenic mutations underlying the spectrum of autosomal recessive congenital erythrodermic ichthyosis. The purpose of genetic clarification was to confirm the diagnosis of harlequin ichthyosis and guide preconception counselling in future pregnancies for the parents. The karyotype was 46XY and the ABCA 12 exon 42 mutation, the most common mutation underlying harlequin ichthyosis was not isolated. Other investigations were largely to guide supportive management.

DIFFERENTIAL DIAGNOSIS

The final diagnosis was reached by recognition of the characteristic clinical appearance in consultation with paediatric dermatology. It is well recognised that harlequin ichthyosis is the rarest and most extreme form of autosomal recessive congenital ichthyosis, a genetically heterogeneous group. A neonatal skin biopsy does not contribute additional information and, as the current best available treatment is supportive rather than curative, further genetic testing has been deferred. His parents have completed their family.

TREATMENT

Initial dermatological management comprised consultation with a tertiary dermatology centre, the frequent application of topical emollient ointment (50/50 paraffin mix, a fresh daily supply) to the entire body, daily antiseptic emollient baths, dry wraps (Tubifast garments) and the commencement on day 3 of acitretin solution at a dose of 0.5 mg/

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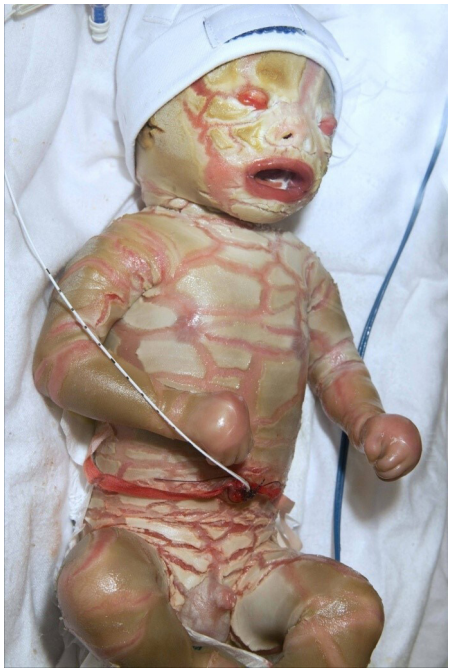

Figure 1 Our patient's appearance at birth.

kg/day. Acitretin is an oral second-generation retinoid, which modulates keratinocyte differentiation and allows shedding of the thick constricting skin plates.

The patient also required immediate supportive care due to his erythroderma and defective skin barrier function. This included intraumbilical fluids, daily blood tests (electrolytes, renal function, and full blood count and F) and correction of coagulopathy. He was treated for presumed sepsis with intravenous cefotaxime, gentamicin and flucloxacillin. However, these were stopped after 48 hours on clinical grounds and with a negative infection screen. He was isolated and nursed in a cot on a heated mattress as incubation was thought to pose a greater risk of infection due to humidity. He was able to bottle feed with expressed breast milk using a modified teat from day 1. However, it was noted on day 9 that he was losing weight and unable to meet the increased metabolic requirements caused by his condition. Therefore dietetic input was sought and nutritionally enhanced milk was commenced on day 11, allowing him to regain his birth weight by discharge. Ophthalmology recommended lubricating ointments and artificial tears until the ectropion and chemosis improved. On day 15, he was noted to have conjunctivitis, swabs grew *Serratia marcescens* and *Pseudomonas aeruginosa*, and he was treated with gentamicin drops. Physiotherapy input helped to reduce his limb contractures.

By discharge, his skin had markedly improved such that while still red and scaly, there were only a few plaques left on the scalp, ears and hands. The ectropion persisted and his fingers remained flexed. He was discharged on acitretin 0.5 mg/kg daily with the same skin care regimen and garments, and continued the nutritionally enhanced milk. Two weekly ward review was arranged, with ongoing paediatric, dermatological, ophthalmological, community audiology and community physiotherapy follow-up.

As an infant, he suffered from sleep disturbance due to skin irritation which responded to intermittent mild topical steroid and sedating antihistamine. Calcium and vitamin D supplements were started, in part to mitigate the skeletal risk of acitretin and also because of the need for long term sun avoidance. He suffers from intermittent leg pain of uncertain significance. He continues on a normal diet with protein supplements and currently his height and weight are on the 25th and 50th centiles, respectively.

OUTCOME AND FOLLOW-UP

Our patient is now 12 years old. The intense dermatological regimen continues and has allowed him a good QOL far beyond that expected at birth. This is only possible with the dedication of, and significant time and effort involved on the part of his family. He is thriving in mainstream school, has just transitioned to secondary school and has a statement of educational needs which affords him a full-time classroom assistant to aid with his demanding emollient regimen and general care. Ongoing acitretin therapy requires regular biochemical monitoring, including liver function tests, lipids and vitamin D. Theerythroderma, hypopigmentation, ectropion and scalp, eyebrow and lashes alopecia persist, but thick scaleis mainly confined to the hands and feet where it can cause fissures. Pustular lesions occur, particularly on the scalp and respond to topical fusidic acid. His finger and toenails grow thick and fast, requiring podiatry assistance. His inability to sweat properly can lead to overheating on exertion and he avoids direct sunlight. He continues under-regular paediatric, dietetic, dermatology and ophthalmological review, attending for physiotherapy and at the ENT clinic for aural toilet.

The family have received social support throughout: his parents were deeply distressed by the alarming appearance of their baby at birth and needed significant reassurance and support in the neonatal unit and in the community before they felt confident in managing his condition at home. In addition, they were signposted to the ichthyosis support group for practical and emotional support. He receives government financial support (disability living allowance), and grants for improved facilities at home and school have contributed to the quality of his care.

DISCUSSION

Fortunately rare, harlequin ichthyosis represents the most profound and severe of the autosomal recessive congenital ichthyosis, a heterogeneous group of dermatological disorders of keratinisation.[1] Harlequin ichthyosis is due to a loss of function mutation in the ABCA12 gene.[1] This gene codes for an ATP binding cassette involved in lipid transport within and between skin keratinocytes, and its absence or improper function leads to a defective epidermal barrier resulting in a 'leaky skin', epidermal hyperplasia, abnormal desquamation and secondary inflammation that produce the characteristic appearance of harlequin ichthyosis.[2] While harlequin ichthyosis is not syndromic,[1] the severity of the dermatological manifestations leads to early complications that previously accounted for the high mortality in the neonatal period: the constrictive skin may cause respiratory distress and cardiac failure, the defective epidermal barrier function cannot regulate transepidermal water loss leading to dehydration, electrolyte abnormalities (especially hypernatraemia) and renal failure,[1–3] skin fissures predispose to infection, inadequate intake and erythroderma contribute to hypothermia and malnutrition. Severe ectropion can lead to keratitis.

In the absence of an evidenced-based consensual approach, oral retinoids are currently held to be necessary in the management of harlequin ichthyosis and in combination with emollients and the supportive measures outlined were used successfully in this case. However, their long term use is not without potential side effects,[4] including skeletal, hepatic, dermatological and

embryonic toxicity.[5] At 6 months of age, a trial without acitretin was attempted, but it was reinstated within 4 months as our patient suffered increasingly thick restrictive scaling, crusting and itch.

While harlequin ichthyosis is still associated with significant neonatal mortality and long term morbidity, and there are many reports of survivors now ranging in age from 10 months to 35 years.[6] Most have been treated with long term oral retinoids, and it is accepted that though they carry a risk of skeletal toxicity and teratogenicity, the risks are outweighed by the significant benefits in terms of improved survival and QOL.[5] Notably, there has been a case report in the American literature of the first patient with harlequin ichthyosis to survive to childbearing age and deliver a healthy child.[7]

It has been argued that since systemic retinoids are usually commenced on day 3 of life when most case fatalities will have already occurred,[3] they are not essential to early survival. Rather, the observed clinical and genetic heterogeneity[8 9] and developments in neonatal supportive care may be behind clinically favourable outcomes. However, the beneficial effects of retinoids may reduce long term complications and thus enhance QOL in patients who have survived the neonatal period.

Essential neonatal measures involve vigilant detection and correction of the consequences of inadequate dermatological function, including respiratory distress, dehydration, electrolyte disturbance, hypothermia, nutritional support and not forgetting sepsis.[1–3]

Early diagnosis is critical for the patient and family and institution of a management plan drawn up by an MDT is essential to improving survival and QOL for patients with harlequin ichthyosis. Active involvement of the family from the start as well as scrupulous attention to detail in the management ensure the best positive outcome. The quotidien regimen is onerous; but healthy eyes, ears, mouth and hands represent vital tools for the survivor's growth and development beyond the neonatal period. Hence the multidisiplinary team approach and ongoing intensive support is essential in the management of this dramatic condition and ensures the optimal outcome.

Patient's perspective

I am very happy and grateful that I have a great family, friends and doctors who are always there to support me whenever I need them. This year I have started secondary school where I am enjoying my experience doing the various subjects. The support for my caring and medical needs from the teachers is fantastic. When not in school, I enjoy listening to music, my iPad, watching movies at the cinema, visiting friends, eating out and going out to theme parks.

Learning points

- Neonatal intensive care and early oral retinoid therapy have improved survival and clinical outcomes in harlequin ichthyosis.
- The role of long term oral retinoid therapy in targeted care guidelines needs to be assessed in individual cases, in light of the clinical and genetic heterogeneity of harlequin ichthyosis and predicted long term outcomes.
- Early consultation with dermatology is essential to guide early and ongoing management, in order to reduce neonatal mortality and morbidity and ensure best care and outcomes in the long term.

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