CASE REPORT

Successful experimental treatment of congenital ichthyosis in an infant

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SUMMARY

Ichthyosis is a rare genetic disease that causes defects in skin keratinisation. Infants born with this disease have tight shiny skin that inhibits limb and ear mobilities, eyelid and lip deformities and poor hair and nail growths. In addition, the barrier properties of the skin are disrupted, which leads to dehydration, body temperature regulation difficulties and increased susceptibility to infection. The treatments currently available include topical keratolytics, emollients, and for severe disease systemic retinoids. Given the increased permeability of the skin and increased body surface area infants are particularly susceptible to accidental overdose from the topical keratolytic treatments currently available. An experimental emollient of 10% *N*-acetylcysteine (NAC) and 5% urea was recently used with success in Argentina. A newborn with congenital ichthyosis cared for in our clinic failed his initial treatment of topical emollients. He was subsequently treated successfully with off-label use of a topical 5% NAC and 5% urea emollient.

BACKGROUND

Lamellar ichthyosis is a rare genetic disease that is a part of the non-syndromic subgroup of autosomal recessive congenital ichthyoses. This disease is characterised by a defect in keratinisation that leads to non-bullous hyperkeratosis of the skin and presents as thick hyperkeratotic scales, tight skin, severe dryness and erythema. Owing to the defective keratinisation, the skin of patients with ichthyosis has increased permeability leading to increased insensible fluid and calorie losses, difficulty in temperature regulation and decreased elasticity which leads to limited limb mobility, development of ectropion (eversion of the lower eyelid), eclabium (eversion of the lips) and ear and nail deformities.[1] There is no cure for this genetic disease, but palliative treatments such as topical keratolytic agents and emollients may be helpful. These agents include lactic acid, salicylic acid and 5% urea, which can improve the appearance and symptoms in patients affected with ichthyosis.[2] Given the increased permeability of the skin, accidental poisoning and toxicity owing to absorption of the chemicals in these topical treatments has spurred the investigation of non-toxic alternatives for treatment. An earlier case report discussed the use of a compounded emulsion of 10% *N*-acetylcysteine (NAC) and 5% urea that led to significant decrease in the hyperkeratotic scales and improvement and resolution of ectropion in five children.[3] The emulsion was generally well tolerated, with the exception of two patients who developed mild skin irritation that resolved with decreased potency and continued use of the emulsion. A male infant delivered by our inpatient team was affected by congenital ichthyosis. After he failed to improve with the initial treatment of topical emollients, the off-label compounded NAC and the urea emollient were initiated, which resulted in significant improvement in his hyperkeratotic plaques, ectropion and nail growth.

CASE PRESENTATION

A male infant was born via spontaneous vaginal delivery at 35 weeks and 6 days after an uncomplicated pregnancy to a 25-year-old woman who had one prior healthy uncomplicated pregnancy and had received normal prenatal care. Upon delivery, he was noted to have physical findings consistent with collodion, a taut translucent shiny membrane overlying generalised erythroderma, and ectropion and eclabium. The infant was transferred to the neonatal intensive care unit (NICU) for further evaluation and treatment of his skin condition. Upon a more in-depth physical examination the patient was noted to have decreased limb movements and an inability to close his eyes secondary to a tight inelastic skin, thickened skin around nails and upper eyelids, and a tight skin over his ears restricting movements of the auricles. He was discharged home from the NICU at day 5 of life with a likely diagnosis of congenital ichthyosis lamellar subtype. The parents were instructed about skin care that included moisturising emollient application every 3 h and use of lubricating eye ointment every 3 h.

There was no family history of congenital skin disorders, and the parents' first child was unaffected.

TREATMENT

In consultation with a paediatric dermatologist the infant was continued on frequent applications of emollients/moisturisers, mupirocin ointment as needed for pustules and lubricating eye ointment. No improvement was seen at 6 weeks. He continued to have hyperkeratotic plaques, tight skin, ectropion, eclabium, restricted nail and hair growths, and limited limb and ear mobilities. The parents were referred to the Foundation for Ichthyosis and Related Skin Types where the mother connected with other parents of children with ichthyosis. Through this foundation and these connections, the mother learnt about an experimental off-label treatment—10% NAC and 5% urea compounded in a moisturising skin cream—being used in Argentina

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for children affected by ichthyosis. This experimental treatment was discussed with the infant's family physician, and after discussion with the attending dermatologist, a compounded prescription of 10% NAC in a moisturising skin cream was initiated. After 3 days of once daily use, the mother noted some decreased thickness of scales, but also noted increased skin sensitivity and erythema. On day 4 of treatment, the infant was evaluated in the local emergency department because of the increased erythema. It was felt that the 10% NAC cream was responsible for the increased erythema and irritation and therefore was discontinued. The patient was re-evaluated in the dermatology department 2 days after discontinuation of the topical treatment and it was noted that the skin was less tight and the scales were less thick than that the month before. Given the improvement in skin tightness and scale, it was agreed to try a less-potent mixture with 5% NAC and 5% urea compounded in a moisturising skin cream in addition to the continued frequent use of emollients/moisturisers. One month later, the infant was able to close his eyes while sleeping and had significant improvement with only mild erythema and superficial fissuring on his chest and around his mouth and eyes, and thick plaques noted only on his legs. He was seen again at 7 and 12 months with continued improvement in the amount and thickness of scaling and a decreased amount of involvement of the trunk and extremities.

OUTCOME AND FOLLOW-UP

At 15 months, though below 5% for weight, he continues to grow normally and is meeting developmental milestones. His skin continues to improve with only mild erythema and general xerosis. He has since developed a small patch of alopecia on the vertex of his scalp, but has had normal hearing screening examinations and normal eye examinations with almost complete resolution of ectropion without the need for surgical intervention.

DISCUSSION

There is no cure for congenital ichthyosis. The skin in patients with ichthyosis has increased permeability and decreased barrier function which puts the affected children at risk for heat stroke or exhaustion, dehydration and infection. The main goal of the therapy is to improve the barrier function of skin by enhancing hydration to minimise dryness and scaling. When scaling is minimal, topical keratolytic agents such as salicylic acid, urea, propylene glycol and agents with α-hydroxy acid (lactic acid, glycolic acid, etc) can be used and have met with some success.[1] When using topical agents, one must always consider the increased permeability of the skin in patients with ichthyosis as this can lead to increased absorption of topical therapies. This is especially important when treating infants with ichthyosis given the larger surface area per unit weight than adults which increases the risk of transcutaneous intoxication or accidental overdose.[1] When dryness and scaling is significant, the therapy must also focus on reducing the hyperkeratotic plaques, which historically has been achieved in severe cases with topical and systemic retinoids. Systemic retinoids have been shown to be effective in improving skin barrier function, decreasing scale, improving heat tolerance and sweating. However, retinoids can have considerable adverse effects including teratogenicity, hepatotoxicity, lipid abnormalities, and therefore patients must have frequent laboratory testing and women who are of childbearing age must be monitored with monthly pregnancy tests and counselled on the risks.[4] Given the adverse effects of retinoids, they are not typically used in the treatment of neonates or infants with ichthyosis. Recently, another topical therapy of tazarotene, a more selective retinoid, has been used successfully in the treatment of congenital ichthyosis in patients ranging from 5–57 years of age[4] and a neonate with severe contracture and digital ischaemia of limbs owing to collodion membrane that is characteristic of congenital ichythosis.[5] While the patients in these studies did not show any laboratory abnormalities, tazarotene is still a retinoid with potential for adverse effects.

In 2003, Sarici *et al*[2] successfully used a topical 10% NAC oil emulsion for the treatment of a collodion neonate with severe eclabium and ectropion, and contractures owing to ichthyosis. The NAC emulsion was applied twice daily on the left side of his body and a 4% urea emulsion on the right half. After 9 days, the collodion membrane had sloughed and significant improvement of scaling was noted on the NAC side. At this point, the entire body was treated with the NAC emulsion and a complete resolution of ectropion and eclabium by the 16th day of treatment was noted.

In 2011, a case series of five patients reported the efficacy of a 10% NAC and a 5% urea topical emollient in the treatment of congenital lamellar ichthyosis.[3] The 10% NAC and a 5% urea topical emollient was applied to the skin of the face, neck and torso, while a 5% urea oil emulsion (placebo) was applied to the lower limbs and buttocks. These therapies were applied twice daily for 6 weeks and then reduced to once daily for a further 4 months. The patients were evaluated after each week of therapy for the first 6 weeks and then again after 4 months. In addition, complete blood counts, liver function tests and urine tests were assessed regularly. Partial improvement with decreased scaling was noted after 7 days of treatment in all the five children. The scaling continued to decrease over time. No systemic side effects were reported and no changes in lab results were recorded. Localised skin irritation was noted in two patients, which improved with continued emollient use in one patient and a decrease in NAC to 5% in the second.

NAC is a non-toxic, hypoallergenic amino acid derivative that has been used systemically as a mucolytic, an antioxidant, a nephroprotective agent and an antidote of acetaminophen toxicity. The side effects seen with systemic use of NAC include nausea, vomiting, anaphylactoid reactions, urticaria and angio-oedema. These side effects are rare but are more common in asthmatic or atopic patients. When applied topically NAC has been shown to prevent cutaneous irritation from radiotherapy and to reduce solar erythema.[3] The side effects seen with topical use include mild pruritus, irritation and a burning sensation. Topical NAC has less than 3% bioavailability and is metabolised by the liver with renal excretion.[3] Studies have shown that NAC inhibits keratinocyte and fibroblast proliferation.[6 7] Given these characteristics, the NAC therapy is likely a safe, non-toxic therapy that can be used in neonates or infants with congenital ichthyosis.[2 3]

Learning points

- Congenital ichthyosis is a rare condition.
- A 5% *N*-acetylcysteine and a 5% urea cream compounded in a moisturising skin cream may be helpful in treating congenital ichthyosis.
- By listening to family members and related support groups when it comes to rare diseases, clinicians might learn about novel treatments being used in other situations and/or countries that may be beneficial.

Competing interests None.

Patient consent Obtained.

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