

## SHORT COMMUNICATION

## Skin Abnormalities in CHILD Syndrome Successfully Treated with Pathogenesis-based Therapy

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CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects) is a rare X-linked dominant disorder first described in 1903 (1) and recently reviewed (2). The syndrome results from mutations in the *NSDHL* (NAD (P) H steroid dehydrogenase-like protein) gene leading to inhibition of cholesterol synthesis (3–5). The characteristic skin changes are unilateral, waxy, scaling, ichthyosiform erythematous plaques with a sharp midline demarcation present at birth or shortly thereafter. Most frequently affected areas are the vulva, axillae, and gluteal folds (6, 7). Ipsilateral hypoplasia or aplasia of skeletal or visceral structures such as the heart, kidney, brain and lungs may be seen (3, 8). The variation in symptoms seen from patient to patient are thought to be a consequence of skewed post-zygotic X-inactivation (9, 10).

Treatment has until recently been purely symptomatic using emollients and retinoids to reduce scaling. Recently, a pathogenesis-based therapy aiming at the disrupted cholesterol metabolism has proven successful (2, 5, 11). These studies suggest that topical application of cholesterol in combination with a cholesterol-synthesis inhibiting agent (statin) has the potential to reverse skin symptoms in CHILD by providing functional cholesterol while at the same time inhibiting the accumulation of toxic metabolites.

## CASE REPORT

The patient, a 33-year-old woman, was born with ichthyosiform skin lesions covering the left side of her body (Fig. 1). She also presented with syndactyli of the 4<sup>th</sup> and 5<sup>th</sup> finger on the left hand and hypoplasia and shortening of her left foot and leg, necessitating lower leg prosthesis. Moreover, the patient was found with deafness on her left ear. She had no abnormalities of her right side. The patient's parents and sister had no skin or limb abnormalities. Diagnosis was made in early childhood by the clinical manifestations in combination with skin biopsy. Genetic analysis performed in 2009 confirmed the diagnosis and revealed a missense mutation (c.1046A>G; p.Y349C) of exon 8 of the *NSDHL* gene. This mutation has been reported in CHILD syndrome previously (4). Genetic analysis was carried out at the "Zentrum für Humangenetik", Universität Marburg, Germany and the analysis was performed as previously reported (4).

The cutaneous changes diminished during childhood and as an adult the patient's ichthyosiform skin lesions are mainly located in the left axillary region, both groins and to smaller elements on her left leg, foot and hand. Clinically, the skin lesions are seen as circumscribed erythematous and yellowish crusty lesions with maceration, inflammation and waxy scaling. Skin lesions, especially in the groins, are often complicated by recurrent infections, exudation and odour.



Fig. 1. Our patient, 2 years old, showing classic unilateral manifestations of CHILD.

The treatment from childhood until adulthood included different regimens of topical keratolytics, emollients, corticosteroids, calcipotriol and calcineurin inhibitors as well as systemic treatment with retinoids and intermittent antibiotics. There was only limited effect of these treatments. In 2011, after Paller and colleagues (5) introduced the new pathogenesis-based therapy combining statin and cholesterol, the patient was treated with a 2% Lovastatin (Stada Arzneimittel AG, Bad, Germany), 2% cholesterol lotion (Pharmacin NL, Zwijndrecht, the Netherlands) (Lovastatin 2 g, cholesterol 2 g, polysorbate 80, 450 mg, cetylan 4.5 g, paraffin oil 10 g, glycerol monostearate 40–55, 5.4 g, glycerol 85%, 3.6 g, sorbitol 6.3 g, disodium edetate 45 mg, purified water up to 100 g. The lotion was produced at Glostrup Pharmacy (Denmark) and will be referred to as LC lotion.). The formulation was applied daily in the left axilla and left groin. After only 1–2 weeks of treatment there was a marked improvement with significant reduction of scaling, erythema and fissures of the skin (Fig. 2). A discrete post-inflammatory hyperpigmentation remained. The LC lotion was initially used daily, but after approximately 6–8 weeks, it was only necessary to apply the lotion every other day to maintain the full effect. Further reduction of the application frequency was not possible without losing effect.

The patient has given birth to 2 children. A daughter who has inherited the mutation but so far shows no indication of CHILD skin lesions and neither the presence of limb defects. Prenatal diagnostics was offered to the family for the second child showing an unaffected boy. During pregnancy our patient stopped using

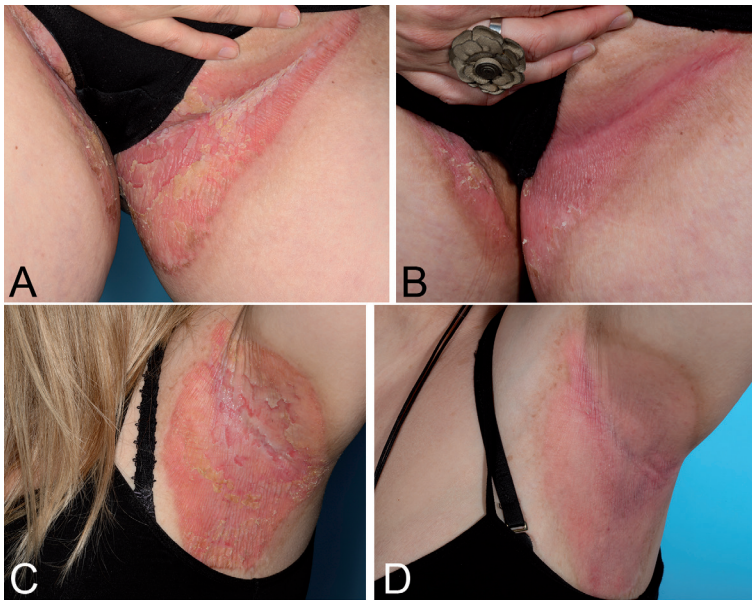


Fig. 2. The effect of the LC lotion. A and C are pre-treatment, B and D after 1 and 2 weeks of treatment, respectively. Please, confer text for details.

the LC lotion which resulted in the recurrence of ichthyosiform lesions within a short period of time. After birth and nursing she resumed the treatment and the same fast and efficient improvement was seen as before the pregnancy. The patient experienced no adverse effects to the treatment with the LC lotion.

## DISCUSSION

Many of the ichthyoses are associated with defects of skin lipid metabolism (12). The phenotypic changes seen in CHILD are assumed to arise from accumulation of toxic metabolites and/or deficiency of pathway end-products (3, 5, 13). A pathogenesis-based therapeutic approach seems therefore possible and recent studies using a statin-cholesterol lotion have shown promising results (2, 5, 11). Similarly, ketoconazole, which influences cholesterol biosynthesis via CYP51 inhibition, has been shown to improve CHILD lesions (14). The case reported here confirms a remarkable improvement of the skin lesions in CHILD as a response to treatment with a statin/cholesterol (2%/2%) ointment. The marked improvement was seen already after 1–2 weeks. The patient stopped treatment with the LC lotion during pregnancy due to the limited data on statin in relation to pregnancy. Existing data do not indicate a teratogenic effect of statin, however a potential risk of this drug in relation to pregnancy cannot be completely excluded (15). Furthermore, animal studies has suggested that transdermal application of lovastatin results in higher serum concentrations than seen with oral administration (16). The efficiency of the LC lotion on the skin lesions of the patient seemed similarly good after pregnancy as compared to before pregnancy. Furthermore, in the case presented here, the patient experienced that a reduction of the application frequency from daily to every second day was possible after a couple of month.

This case clearly illustrates that a pathogenesis-based therapy can reverse the ichthyosiform skin lesions in CHILD syndrome within a few weeks. This brings hope that further research and insight into lipid metabolism of the skin will lead to even more effective treatments of not only CHILD but also other types of ichthyoses.

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