CASE REPORT

Not lost to follow-up: A rare case of CHILD syndrome in a boy reappears

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INTRODUCTION

Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome is an exceedingly rare, X-linked dominant genetic disorder of lipid metabolism that arises from mutations in NAD(P) dependent steroid dehydrogenase-like gene (NSDHL), which encodes 3β-hydroxysteroid-dehydrogenase, an enzyme essential to cholesterol synthesis. Cholesterol plays a crucial role in hedgehog signaling during normal mammalian development, thus explaining the striking right-to-left unilateralism of both cutaneous and visceral manifestations typified by this condition. Presenting at birth or in the neonatal period, cutaneous findings are unilateral erythema and scaling that progress to increasingly hyperkeratotic, verrucous plaques or bands, sometimes Blaschkoid; partial spontaneous regression may occur over time. Skeletal defects, ranging from hypoplasia to complete amelia, and organ hypoplasia are likewise ipsilateral. CHILD syndrome is predominantly seen in females, as it is generally lethal in affected male embryos. In fact, there are currently only 2 reported cases in the literature of this disorder in males, one of whom we saw for follow-up nearly 20 years after his original description in 1996. Here we provide an update on his clinical status and disease progression, as well as advances in the current understanding of disease pathogenesis and management of this rare condition.

CASE REPORT

A 24-year-old man with CHILD syndrome (NSDHL mutation c.262C>T, p.R88X) 1,2 presented for follow-up of right-sided, mildly pruritic, erythematous ichthyosiform nevus sparing the face. The overall area and distribution of involvement remained relatively stable over the years without much spread aside from slight expansion proportional to growth. He was treated in the past with topical corticosteroids, emollients, retinoids, and azole antifungals with minimal improvement. Dermabrasion of the affected areas on the trunk was gratifying initially but was ultimately nonsustained, with complete recurrence to original thickness within 8 months. The patient is currently undergoing treatment with a 2% simvastatin, 2% cholesterol compounded ointment applied twice daily to existing lesions with significant, sustained improvement.

The patient was born with a hypoplastic right leg lacking a fibula. Correctional attempts were made to salvage the lower leg, but he ultimately required...
above-the-knee amputation with no further complications. Otherwise, no organ hypoplasia was found at the time of initial description in 1996, with normalized heart, brain, eyes, and kidneys noted. Nearly 20 years later, the patient remained in good health overall without any chronic comorbid conditions or medications.

On examination, there was a well-marginated nevus involving the right thigh, groin, abdomen and chest extending down the right anteromedial arm along Blaschko lines (Fig 1). The affected areas on the thigh and groin were erythematous and thickened with waxy, yellowish scale, especially overlying the thigh. The affected areas on the abdomen and trunk were relatively clear in comparison, with faintly red-brown pigmentation and without significant hyperkeratosis or thickening. Periumbilically, to the right of midline, was a

![Fig 1](image_url)
geometric atrophic scar-like plaque, and around the right superior axillary fold was a curvilinear hyperkeratotic band with erythematous and verruciform accentuation centrally.

**DISCUSSION**

**CHILD** syndrome is an X-linked dominant disorder of lipid metabolism that is usually lethal in males. As such, the prevalence of this disorder in males is exceedingly rare, as is the case in other X-linked dominant disorders, such as incontinentia pigmenti. For our patient, with normal 46, XY karyotype identified on peripheral blood mononuclear cell cytogenetic analysis, the proposed mechanism is an acquired, postzygotic mutation in **NSDHL** with subsequent mosaicism. Depending on the timing of this mutation, this may account for the complete lack of ipsilateral hemidysplasia of his internal organs, which tend to develop at earlier Carnegie stages relative to skeletal structures. Furthermore, the postzygotic mutation in our patient may have occurred between days 22 and 55 of development, allowing for initiation of central nervous system (CNS) and kidney embryogenesis but not fibula development. Interestingly, of the 33 reported cases of **CHILD** syndrome in the literature, only 5 had internal organ involvement beyond ipsilateral musculoskeletal hypoplasias. The most common organs involved were the kidneys (3) and CNS (2), although lung, vocal cord, and auditory nerve involvement were also reported.

Specifically, a loss of function mutation in **NSDHL** (encoding 3β-hydroxysteroid-dehydrogenase) on Xq28 impairs cholesterol biosynthesis in the endoplasmic reticulum of keratinocytes. Deficits in cholesterol cause a decrease in lamellar granules in the stratum corneum of the epidermis, leading to altered permeability of the skin characteristic of ichthyosis. Buildup of cholesterol precursors lead to reduced oxysterols and degeneration of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, further exacerbating the decrease in cholesterol production and subsequent epidermal disruption. Impaired cholesterol biosynthesis also disrupts the functioning of sonic hedgehog hormone (SHH) in embryos, particularly in the development of the appendicular skeleton and central nervous system. Furthermore, signaling molecules in the SHH pathway are involved in dorsoventral axial patterning and left-right asymmetry. Buildup of harmful precursors of cholesterol synthesis contributes more to SHH dysfunction than does the lack of cholesterol itself, although both do contribute. This impairment explains the unilateral hypoplasias sometimes seen in the CNS and limbs of patients with **CHILD** syndrome.

Historical therapies for the cutaneous symptoms of **CHILD** syndrome include topical ointments (corticosteroids, emollients, retinoids, and azole antifungals such as ketoconazole), oral agents (ketoconazole, retinoids, and methotrexate), and surgical approaches (dermabrasion and skin grafting). These treatments have varying degrees of efficacy but do not address the underlying defect in cholesterol. Skin grafting had been rather unsuccessful because the unaffected donor graft does not express the mutated allele and exhibits donor dominance. However, this invasive approach can be costly and is not feasible in patients with nevi that take up large portions of their body surface. Today, treatment with topical 2% statin (lovastatin or simvastatin) and 2% cholesterol compounded ointment was found to be effective in 8 patients treated over 6 case reports. Twice-daily application for 6 months followed by 1 to 2 times weekly for maintenance produced marked improvement, with clinical improvement seen as early as 3 weeks into treatment. This new pathogenesis-directed therapy is a cost-effective and noninvasive approach to treating the cutaneous manifestations of **CHILD** syndrome.

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