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Review

The role of abnormalities in the distal pathway of cholesterol synthesis in the Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects (CHILD) syndrome ☆

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ABSTRACT

CHILD syndrome (*C*ongenital *H*emidysplasia with *I*chthyosiform erythroderma and *L*imb *D*efects) is a rare X-linked dominant ichthyotic disorder. CHILD syndrome results from loss of function mutations in the *NSDHL* gene, which leads to inhibition of cholesterol synthesis and accumulation of toxic metabolic intermediates in affected tissues. The CHILD syndrome skin is characterized by plaques topped by waxy scales and a variety of developmental defects in extracutaneous tissues, particularly limb hypoplasia or aplasia. Strikingly, these alterations are commonly segregated to either the right or left side of the body midline with little to no manifestations on the ipsilateral side. By understanding the underlying disease mechanism of CHILD syndrome, a pathogenesis-based therapy has been developed that successfully reverses the CHILD syndrome skin phenotype and has potential applications to the treatment of other ichthyoses. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier. Guest Editors: Kenneth R. Feingold and Peter Elias.

1. Introduction

The human skin forms an essential immunological, mechanical, and structural barrier between the organism and its environment. Genetic mutations that induce molecular changes in epidermal barrier permeability can have profound effects on the quality of life and survival of the affected individual. The ichthyoses are a diverse family of inherited skin disorders broadly characterized by areas of thickened and scaly skin [1]. The degree to which skin permeability is impaired in ichthyoses is directly proportional to the severity of the observed clinical phenotype [2–4], and consequently a detailed understanding of the genetic and molecular factors that contribute to the formation and maintenance of the architecture of the skin has proven to be critical to deciphering and reversing the pathology of certain ichthyoses.

2. CHILD syndrome

2.1. Clinical features

Congenital *H*emidysplasia with *I*chthyosiform erythroderma and *L*imb *D*efects (CHILD syndrome, OMIM #308050) is an exceedingly rare ichthyosis, with approximately 26 individual cases reported in the literature (Table 1). CHILD syndrome commonly presents at birth or in the first few months of life with features that may include unilateral ichthyosiform dermatitis, unilateral skeletal aplasia or hypoplasia, or occasionally defects in the cardiovascular, renal, central nervous system, genitourinary, pulmonary, or endocrine systems [5,6]. The ichthyosiform (sometimes called psoriasiform) dermatitis of CHILD syndrome usually appears as circumscribed erythematous plaques topped by prominent waxy scales (Fig. 1A and B) [7]. A striking aspect of the CHILD syndrome phenotype is the mostly unilateral distribution of skin and skeletal defects segregated to either the right or left side of the body midline, with right sided involvement occurring more often than left [8]. The erythematous plaques may be relatively narrow and follow the lines of epidermal tissue development (Blaschko's lines), reflecting inactivation of the X-chromosome that carries the normal allele at those sites, but often show a wider distribution across larger body surface areas. Occasionally, skin lesions are bilaterally symmetric [5,9,10]. Ptychotropism, the localization of skin defects to the skin folds, is also commonly observed [11]. An interesting skin lesion associated with CHILD syndrome is the verruciform xanthoma. It often presents as an exophytic, fleshy mass

Abbreviations: CHILD, Congenital hemidysplasia, Ichthyosis and Limb Defects; EBP, emopamil binding protein; NSDHL, NAD(P)H steroid dehydrogenase-like; SC, stratum corneum; SG, stratum granulosum; SS, stratum spinosum

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(Fig. 2), although the histologic features of verruciform xanthoma have been described in skin from the ichthyosiform lesions [12]. Frequently observed additional features include nail dystrophy and unilateral punctate cartilage calcifications (epiphyseal stippling) [5,6].

CHILD syndrome is an X-linked dominant genetic disorder that is embryonic lethal for males, and is therefore virtually always observed in females [13]. Patients with CHILD syndrome exhibit loss of function mutations in the *NSDHL* gene located at chromosome Xq28, which encodes the NAD(P)H steroid dehydrogenase-like protein (NSDHL) [14,15]. Although both *NSDHL* alleles are equally represented in affected skin keratinocytes, keratinocytes from affected areas express only the mutant X-chromosome [16]. In contrast, unaffected area keratinocytes

Table 1
Genetic mutations observed to date (gene and protein change) in CHILD syndrome and their corresponding clinical phenotypes.

Mutation	Familial case	Side affected	Ipsilateral cutaneous defects	Contralateral cutaneous defects	Ipsilateral extracutaneous defects	Reference
c:108 + 2T → G; splice site	No	R	Diffuse involvement of trunk, linear lesions on thigh	No	Hypoplasia of leg and foot	[47]
c: 208C → T; p: Q70X	No	R	Widespread linear lesions on trunk and leg, diffuse involvement of groin	Minor linear lesions on hand	Hypoplasia of pelvis and femur, 6th finger at birth	[48]
c: 262C → T; p: R88X	No	R, male	Extensive linear lesions on trunk and limbs	No	Hypoplasia of leg	[10,30]
c: 314C → T; p: A105V	No	L	Groin	Minor lesions on scalp, neck, soles	Aplasia of one finger	[49]
c: 314C → T; p: A105V	Yes	L	Diffuse widespread involvement of leg, trunk, and hand	Linear lesions on fingers and toes	Hypoplasia of pelvis and foot	[50]
c: 314C → T; p: A105V	Yes	R	Patchy widespread involvement with partial resolution	Small linear lesions on face and arm	Absence of kidney, dilated cerebral ventricles, hypoplasia of limbs and vertebral column	[10,30]
c: 314C → T; p: A105V	No	R	Diffuse widespread involvement with partial resolution	Linear lesions on hand and thigh	Absence of kidney, hypoplasia of limbs, mandible, ribs, and vertebrae	[10,30]
c: 314C → T; p: A105V	No	R	Lesions in the axilla and groin	No	Hypoplasia of hand, alopecia of the occipital area	[31]
c: 370G → A; p: G124S	Yes	L	Patchy lesions on thigh, groin and vulva, linear lesions on hand and foot	Nail dystrophy on one finger and two toes	Hypoplasia of leg, foot, and skull	[14]
c: 396C → G; p: C132W	No	R	Diffuse involvement of trunk, upper arm and thigh, linear lesions on forearm and lower leg	Minor patchy and linear lesions on leg and foot	Hypoplasia of arm, dysplasia of hip and knee	[51]
c: 441 T → A; p: S147R	No	R	Involvement of axilla, breast, trunk, upper and lower limb, vulva and perineum	No	Hemidysplasia of palm, valgity of coxofemural joint	[52]
c: 451G → T; p: E151X	No	L	Erythemathous rash with minimal scaling over chest wall, linear lesions on leg	No	Hypoplasia of arm, leg and foot, absence of ribs and hypoplasia of vertebrae, hypoplastic left lung with right shift of cardiac structures, absence of kidney	[8]
c: 451G → T; p: E151X	No	R + L	Almost symmetrical involvement of body folds, right side involvement of neck	Almost symmetrical involvement of body folds	Hypoplasia of leg and vertebral column, absence of facial muscles	[10]
c: 613G → A; p: G205S	No	L	Trunk and arm	No	Hypoplasia of upper arm	[53]
c: 613G → A; p: G205S	No	L	Patchy widespread involvement	No	Hearing loss, absence of arm, hypoplasia of leg	[10,30]
c: 628C → T; p: Q210X	No	R	Large patch on back, linear lesions on limbs	Linear lesions on hand	Hearing loss, hypoplasia of vertebral column and foot	[10,30]
c: 894G → A; p: W298X	Yes	R	Linear lesions on hand, foot, scalp and forehead	Linear lesion on one finger	Hypoplasia of leg and vertebral column	[14]
c: 906C → A; p: Y302X	No	L	Diffuse and patchy involvement of neck and trunk, linear lesions on extremities	Small patches on hand	Hypoplasia of leg and vertebral column, syndactyly of index and middle finger	[54]
c: 1018T → C; p: C340R	No	R	Patchy and linear lesions in body folds	Minor lesions in body folds	Hypoplasia of arm and leg	[49]
c: 1041–1042 insert CATG; p: 358X	No	R	Patchy widespread involvement	No	Elongation of leg, hypoplasia of vertebrae, verrucous involvement of vaginal and gastric mucosae	[55]
c: 1045T → C; p: Y349H; c: 306C → T; p: F102F	No	R	Diffuse involvement of leg, linear lesions on abdomen and arm	No	Hypoplasia of vertebral column and arm	[56]
c: 1046A → G; p: Y349C	No	R	Diffuse involvement of trunk, forearm and leg, extensive linear lesions on upper arm	No	Hypoplasia of arm and leg, liver lobe and spleen hypertrophy	[57]
c: 1046A → G; p: Y349C	No	L	Patchy involvement of neck, axillae, buttocks, lower back and abdomen	No	Shortening of toes 2, 3 and 4	[58]
Deletion of promoter and exon 1, and the *CETN2* gene	No	R	Extensive involvement from the neck to the buttocks	Linear hyperpigmented hyperkeratotic papules in the forehead and both ears, linear hyperkeratotic plaques in the elbow, wrist, hand and foot	Contralateral overfolding of ear, clubbing of thumb, genu varum, scoliosis, dolichocephaly, bilateral hearing loss, severe mental retardation	[33]
Deletion of exons 6–8	No	L	Patchy widespread involvement	No	Absence of 2 fingers and 4 toes	[32]
Complete deletion	No	L	Patchy and linear lesions on trunk and extremities	Patchy and linear lesions on groin and hand	Hypoplasia of foot and vertebral column, ipsilateral deafness and vocal cord paralysis	[14]

C = chromosome; P = protein: L = left; R = right.