Chapter 34
Child Syndrome

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Contents

Introduction

Otto Sachs in 1903 is attributed to having published the first case of an 8-year-old girl with *xanthoma-like naevus* involving the right axillary region and weakness in the ipsilateral upper arm [1]. The condition remained obscure until 1948, when the Swiss-American paediatrician Dr. Hans Zellweger and Üehlinger reported a patient with "half-sided osteochondrodermatitis and naevus ichthyosiformis" [2].

About hundred sporadic cases have been reported in the literature under a number of designations, including unilateral ichthyosiform erythroderma, unilateral erythrokeratoderma, unilateral epidermal naevus, unilateral ectromelia, inflammatory epidermal naevus and unilateral limb and skin deformities with congenital heart disease [3–5]. For unclear reasons, the right side of the body is twice more likely to be affected.

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CHILD syndrome (OMIM 308050) follows a dominant X-linked pattern with a female-to-male ratio of 19:1, invariably lethal to male trait [6]. All three types of mutations (missense, nonsense and stop mutations) in the *NSDHL* gene have been identified. The gene is located on the long arm of the X chromosome at position 28. It encodes for 3-β-hydroxysterol dehydrogenase (sterol-4-α-carboxylate 3-dehydrogenase) found in endoplasmic reticulum and intracellular lipid storage droplets, which catalyses the biosynthesis of steroid progesterone and androstenedione from dehydroepiandrosterone (Fig. 34.1). It is the only enzyme in the corticosteroid synthesis not belonging to the cytochrome P450 family [7, 8].

Pathogenesis

Peroxisomes play a key role in the pathogenesis of CHILD syndrome as they are intimately involved in the catabolism of prostaglandins and hydroxyeicosatetraenoic acid [9]. Skin fibroblasts from *CHILD* naevus exhibit a decrease in both the peroxisome number and the activity of two specific peroxisomal enzymes – catalase and dihydroxyacetone phosphate acyltransferase [10], specifically centred in the areas of cutaneous involvement without systemic manifestations. Peroxisomal deficiency in the involved naevus leads to the accumulation of *PGE2* and keratinocyte growth, which consequently may contribute to the epidermal hyperproliferation. Markers of keratinization possess the typical patterns of hyperproliferative skin diseases, defined by expansion of the basal layer keratins (*K5/K14*), thickening of filaggrin, involucrin-positive (the differential marker of human keratinocytes) upper epidermal layers and expression of hyperproliferative keratins (*K6/K16*) [11]. The genotype in *CHILD* naevus is explained by the *Lyon* hypothesis; i.e. random inactivation of one of the X chromosomes in female cells and daughter clonal populations results in mosaicism that manifests in *Blaschko* lines [12] (lines that represent dorsal-to-ventral migration tracks of precursor cells from the primitive streak). The lateralization of all associated abnormalities could be hypothesized by the hypothesis that the X chromosome inactivation coincides and interferes with a clone of organizer cells that control a large morphogenetic field [13, 14]. The NSDL protein product is a 3-β-hydroxysterol dehydrogenase, an oxidoreductase, that is involved in the removal of two C-4 methyl groups with $NAD(P)^+$ as acceptor in one of the end steps of cholesterol biosynthesis [15, 16]. There is absolute requirement for cholesterol synthesis in situ once the blood-brain barrier is formed in the foetus [17].

Clinical Characteristics

CHILD syndrome is an exceedingly rare disorder. It affects the ipsilateral skin, viscera, musculoskeletal and central nervous system. Cutaneous naevi are described as waxy, yellow scaly (*ichthyosiform*), erythematous plaques, having a sharp

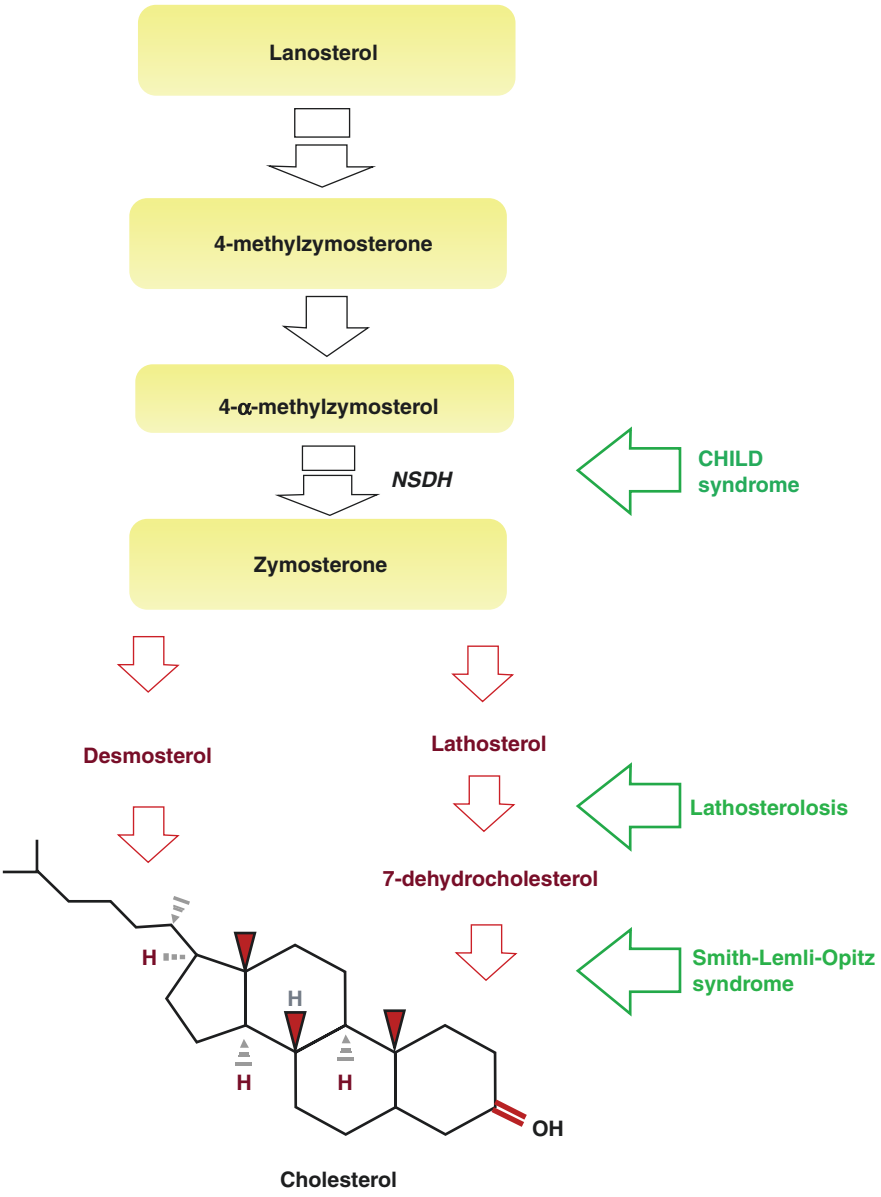

Fig. 34.1 3-β-Hydroxysterol dehydrogenase is involved in step 4 subpathway that synthesizes zymosterol. CHILD syndrome, shown in relation to other metabolic disorders, involves mutations in *NSDH* gene

unilateral midline demarcation [18]. About 80% of the cases occur on the right side. This distinct unilateral pattern may be diffuse and/or linear, with streaks following the *lines of Blaschko* within the diffuse erythema. On the other hand, partial

resolution or spread to uninvolved areas has been observed during the early years of life. There is impaired hair growth and streaks of alopecia on the ipsilateral side [19]. The nails often exhibit hyperkeratosis and dystrophic changes (*onychodystrophy*). Punctate calcifications of the cartilage are often evident on radiographs and may disappear during the early years of life [14]. Cognition is usually in the normal range.

Anomalies in *CHILD* syndrome consist of homolateral (*ipsilateral*) limb defects ranging from hypoplasia of the phalanges to defects of the long bones and absent extremity. Ipsilateral hypoplasia of the axial skeleton, including the calvarium, mandible, scapula, ribs and vertebrae, which can lead to scoliosis, is also present, along with cardiac malformations and ipsilateral hypoplasia of the brain, lungs, thyroid, kidney and reproductive tract [20, 21]. The cardiovascular malformations are the most common causes of early death [22]. Although *CHILD* syndrome is an ipsilateral condition, abnormalities on the contralateral side may be seen. A case of bilateral involvement has been described in a 16-year-old girl [13]. In familial cases with atypical or minimal findings, the importance of molecular analysis to confirm the diagnosis cannot be overstated [23].

An associated naevus, known as *CHILD* naevus, shows a marked preference for the body folds (*often by dermatomes*), which is defined as ptychotropism [24]. The expression is derived from the *Greek words* ptyche/πτυχή (fold) and trope/τροπή (*a turning*). The most frequently affected areas are the vulva, axilla and gluteal folds [6, 24]. Most often, the extent of skin involvement remains constant in the affected side, contrary to *Conradi-Hünermann* syndrome (or CDPX2) that has the characteristic ichthyosiform erythroderma (psoriasiform epidermis with hyperkeratosis), chondrodysplasia punctata and orthokeratosis [25]. Other features of the latter syndrome are waxy, yellowish naevi as well as scaly and microscopic changes within the verruciform xanthomas.

Diagnosis

Diagnosis of CHILD syndrome is based on clinical and radiological findings of the pelvis, ribs, vertebrae and extremities in infancy. Skin biopsy from the involved and uninvolved areas is necessary. Histologically, the epidermis shows acanthosis with alternating orthokeratosis, hyperkeratosis, parakeratosis and mild hyperplasia [21, 26]. Patchy hypergranulosis may also be observed, and the biopsy shows suggestive of an ichthyosiform dermatosis [7]. Radiographic examination of the head, trunk and extremities is essential in detecting skeletal abnormalities. Computerized tomography of the head and trunk may reveal progressive hypoplasia or aplasia of the cerebral cortex and hippocampal neurons [17].

Echoencephalography is needed to examine the size and flow of the ventricles. Sleep electroencephalography may elucidate the diagnosis of a predisposed seizure disorder. A distinctive phenomenon of verruciform xanthoma, which is characterized by enlarged papillae filled with foamy histiocytes, has been reported when

biopsy samples are obtained from the body folds. On electron microscopy, the parakeratotic corneocytes and basal cells contain lipid vacuoles and numerous intercellular vesicular structures.

Abnormal cementsomes (lamellar granules) with electron-dense bodies have also been reported. The papillary dermis is thickened and filled with histiocytes containing large lipid vacuoles. Fibroblasts are similarly filled with lamellated structures. In fact, combining clinical and molecular examination could determine the diagnosis of CHILD syndrome with milder features [23], and to distinguish CHILD from other conditions such as *Conradi-Hünermann-Happle* syndrome (*X-linked dominant*) caused by mutations in EBP. The latter harbours *ichthyosiform* erythroderma as well as linear or whorled pigmentary lesions, striated ichthyosiform hyperkeratosis and patchy cicatricial alopecia.

Therapy

No curative therapy exists, only symptomatic relief based on the severity of clinical presentation. A multidisciplinary approach of experts in the fields of dermatology, orthopaedics, cardiology, physiotherapy and psychology is imperative for effective management. Patients with milder forms carry a normal life.

The management of ichthyosiform erythroderma includes oral and/or topical steroids, such as 2% lovastatin emollients, or with lactate-based creams (topical retinoids and keratolytics). Alternative therapy with oral or topical ketoconazole is possible [5, 27]. The use of topical lovastatin leads to complete healing of the inflammatory CHILD naevus in a few cases [28, 29]. Scoliosis or other bone problems, e.g. contractures, are treated with orthopaedic braces and/or corrective surgery. Although the right side of the body is invariably affected, patients with left-sided symptoms harbour a more dire prognosis, usually succumbing to cardiovascular complications.

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