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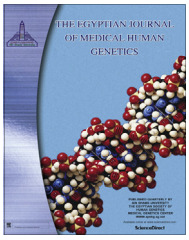

CASE REPORT

Autosomal recessive ichthyosis with limb reduction defect: A simple association and not CHILD syndrome

Rabah M. Shawky *, **Solaf M. Elsayed**, **Heba Amgad**

Genetics Unit, Children's Hospital, Ain Shams University, Cairo, Egypt

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KEYWORDS

Ichthyosis;
Limb reduction;
CHILD;
Autosomal recessive

Abstract Ichthyosis is a genetically and phenotypically heterogeneous disease that can be isolated and restricted to the skin manifestations or associated with extracutaneous symptoms. One of which is limb reduction defect known as CHILD syndrome; a rare inborn error of metabolism of cholesterol biosynthesis that is usually restricted to one side of the body. Here we describe an Egyptian child with generalized lamellar ichthyosis and limb reduction defect. Most probably this is a simple association and not a rare case of CHILD syndrome with bilateral skin involvement.

1. Introduction

The terms ichthyoses/Mendelian disorders of cornification (MeDOC) refer to conditions with visible scaling/hyperkeratosis of the skin which is clinically and genetically heterogeneous including autosomal dominant, autosomal recessive and X-linked inheritance [1,2]. Associated cutaneous and extracutaneous features, as well as disease onset and clinical course, provide important diagnostic clues. One example of extracutaneous manifestation is the limb anomaly characteristic of CHILD syndrome.

CHILD syndrome (Congenital hemidysplasia, Ichthyosiform nevus and Limb defect) is a rare X linked dominant disorder with male lethality first described by Otto Sachs in 1903 [3]. The second report was in 1948 by Zellweger and Uelinger, who described a patient with a "half-sided osteochondrodermatitis and nevus ichthyosiformis" [4]. It is considered one of the inborn errors of metabolism affecting cholesterol biosynthesis [5]. As the acronym states, the skin manifestations are usually unilateral with sharp midline delineation and bilateral affection is unusual.

Here we describe an Egyptian child with generalized ichthyosis and limb reduction defect which is most probably due to a simple association and not a rare case of CHILD syndrome with bilateral skin affection.

2. Case report

Our patient is a 13 year old girl, the first in birth order of first cousin parents, (Fig. 1). She was born at term by cesarean section of uncomplicated pregnancy. The patient was born in a yellow, tight and shiny sheath that started to desquamate after two to three weeks and replaced by rounded dark scaly lesions with continuous turn over and a tendency to get worse in winter. Also limb reduction deformities were noticed at birth affecting the left hand with complete cutaneous syndactyly of the right 4 fingers including the thumb and sparing the little

* Corresponding author.
E-mail addresses: shawkyrabah@yahoo.com, Prof.rabahshawky@gmail.com (R.M. Shawky).

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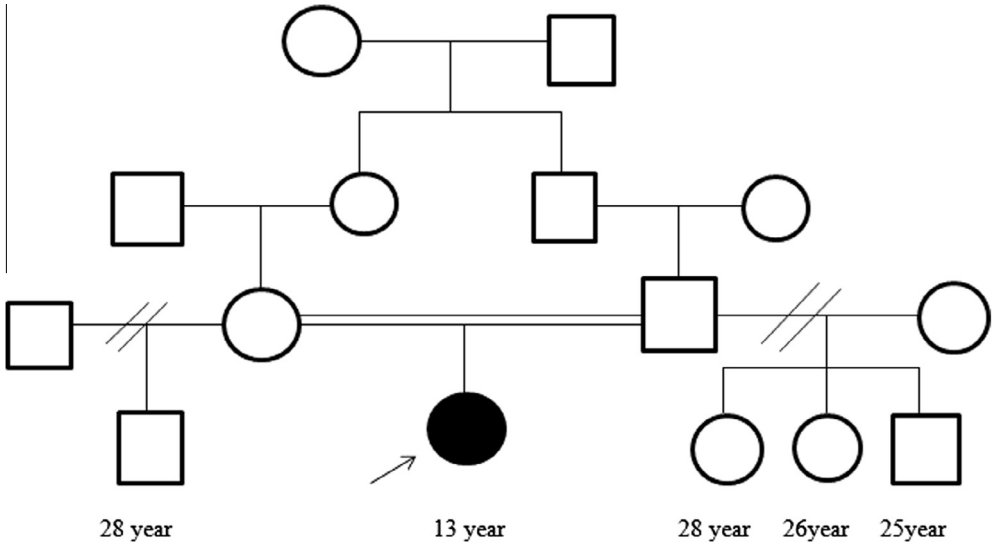

Figure 1 Family pedigree.

finger for which three corrective surgeries were done (first at the age of 2 years and the last at the age of 4 and half years). Family history revealed no similarly affected cases.

On examination, patient's weight was 29.5 kg, her height was 127 cm (both were below the 5th centile), and her skull circumference was 51 cm (on the 10th centile). Her mentality was average. The whole body was covered by brownish scaly lesions also involving the flexural areas, (Fig. 2). She had normal motor and mental development with good school achievement. She had a prominent forehead, receding anterior hair line, hypertelorism, narrow palpebral fissures and bulbous nose.

The right hand showed clinodactyly of the little finger, adducted misplaced thumb with hyperextension of its distal interphalangeal joint and skin contracture of the distal phalanges of the index finger, (Fig. 3). The left hand was absent and was replaced by a soft boneless bulbous bud, (Fig. 4). Her feet showed medial deviation of the big toes, partial cutaneous syndactyly between the second and third toes and short right fourth toe (Figs. 5 and 6). Chest, heart and abdominal examinations showed no abnormality.

Radiological examination revealed dislocated metacarpophalangeal joint of the thumb, fragmented dislocated distal phalange of the index finger and very short second phalanx of the little finger of the right hand and absent left hand bones, (Figs. 7 and 8). Echocardiography and abdominal ultrasound revealed no abnormalities. Audiometry revealed bilateral

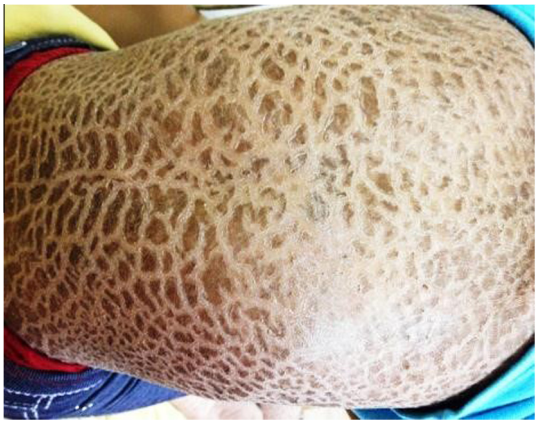

Figure 2 Patient's back showing brownish scaly lesions (lamellar ichthyosis).

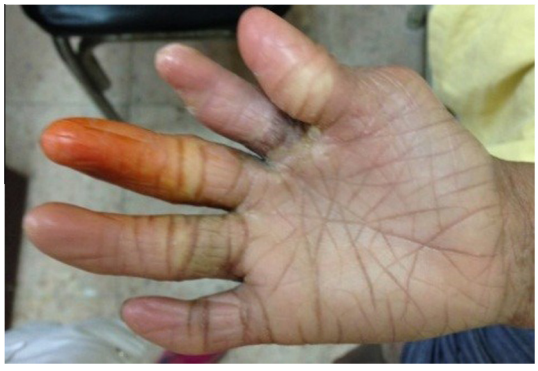

Figure 3 Patients right hand showing clinodactyly of the little finger, adducted misplaced thumb with hyperextention of its distal interphalangeal joints and skin contracture of the distal phalanges of the index finger.

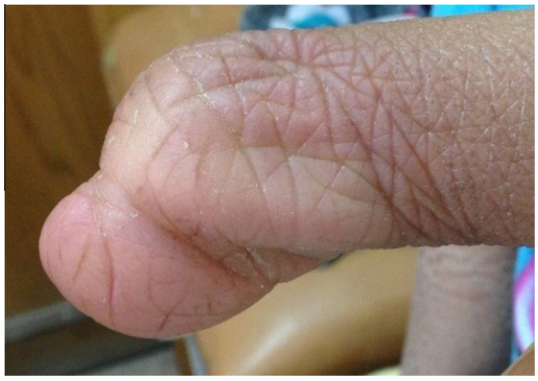

Figure 4 Left hand is absent and replaced by a soft boneless bulbous bud.

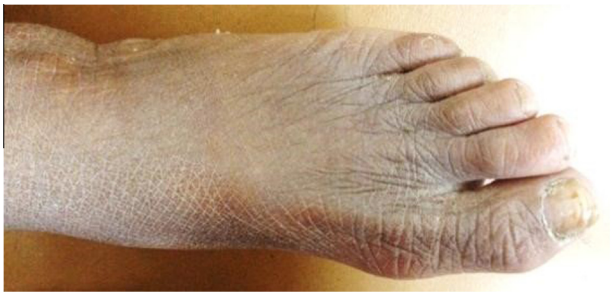

Figure 5 Left foot showing lateral deviation of big toe, partial cutaneous syndactyly between the 2nd and 3rd toes and short 4th toe.

normal hearing. Cytogenetic analysis revealed normal female 46, XX karyotype.

3. Discussion

Most neonates with autosomal recessive congenital ichthyosis (ARCI) are born as collodion babies as described in our case. However, the clinical presentation and severity may vary significantly from Harlequin ichthyosis which is the most severe and fatal form of lamellar ichthyosis (LI) and non-bullous congenital ichthyosiform erythroderma (CIE) [6].

LI is characterized by dark brown like scales with no erythroderma. Ectropion, eclabium, scarring alopecia and palmar and planter hyperkeratosis may be associated. CIE is characterized by finer white scales and underlying redness and often with palmoplantar hyperkeratosis. An intermediate form with same features of both CIE also exists [7].

Our patient has typical skin findings of generalized ARCI with large brown scales. The presence of limb reduction defect is a very unusual association suggesting a differential diagnosis of atypical form of CHILD syndrome in which the ichthyosis involves both sides of the body. CHILD syndrome is inherited in an X-linked manner with male lethality. Although bilateral involvement in CHILD syndrome is very rare, it was reported before [8,9] and was explained by the effect of random X inactivation in affected females [9] and can be also responsible for mild or minimal presentation [10].

The skin condition of CHILD syndrome is characterized by large patches of skin that is red and inflamed (erythroderma), which is covered with flaky scales (ichthyosis). This skin condition is delineated and respecting the middle line. It usually involves the skin folds and creases. This skin lesion is more

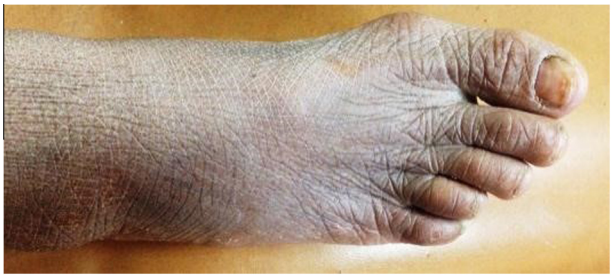

Figure 6 Right foot showing lateral deviation of big toe, partial cutaneous syndactyly between 2nd and 3rd toes and short 4th toe.

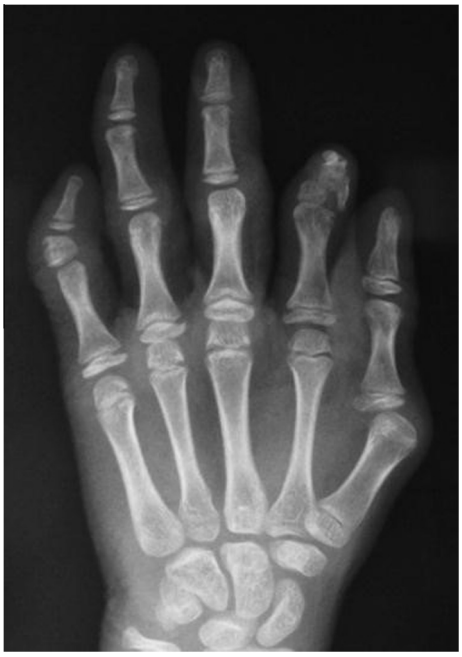

Figure 7 X ray right hand.

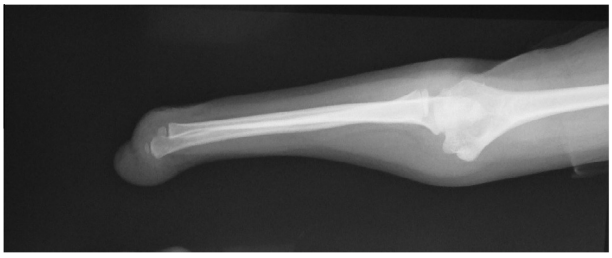

Figure 8 X ray left hand.

adequately classified as nevi and Happle et al. [10], replaced the term ichthyosiform erythroderma by ichthyosiform nevus [11].

Minimal presentation in CHILD syndrome was first observed in the sister of a severely affected patient who had only bilateral minor lesions on her fingers and toes [12] and also in a mother of a typical patient with CHILD syndrome having only some minor linear lesions on her hand [13]. CHILD syndrome was also reported in five members from a three generation family with minimal skin lesions without other extra cutaneous manifestations and the diagnosis of CHILD syndrome was confirmed by molecular testing [10].

These exceptions of ARCI or CHILD syndrome confirm the importance of molecular testing in proper management and proper genetic counseling: As for ARCI, inheritance is autosomal recessive disorder with 25% recurrence risk and 75% chance to have normal babies. Management will include treatment of skin lesions only with no current explanation for the presence of the associated limb reduction defect except probably amniotic band sequence.

On the other hand, CHILD syndrome phenotype is not restricted to skin and could be associated with ipsilateral defects involving all skeletal structures. Other organs including

lung, thyroid, psoas muscle, cranial nerves V, VII, VIII, IX and X, pons, medulla, cerebellum and spinal cord may be also involved [14]. Also cardiac septal defects [9], unilateral ventricle [15], and a single coronary artery may be associated [14]. Lung hypoplasia with respiratory distress [5], hearing loss, absence of facial muscles, and unilateral hypoplasia of the thyroid gland, adrenal glands, ovaries, and fallopian tubes [9] and progressive bilateral optic nerve atrophy may be associated [16].

Rarely bilateral presentation of CHILD syndrome has been reported. Fink-Puches et al. described a case with CHILD syndrome with almost symmetrical linear lesions on the extremities and body folds in a near symmetrical distribution [8]. Konig identified a missense mutation in the NSDHL gene in the previous patient [9]. More cases with bilateral CHILD syndrome presentation were also reported [10,17,18]. All these cases presented with erythematous xerotic plaques in a linear distribution in upper limbs, groin, thigh and sometimes diffusely bilaterally on the cheeks.

Also CHILD syndrome has a different pattern of inheritance with different genetic counseling.

It has X-linked dominant inheritance with male lethality and scarce reports of affected males [4,19] due to mosaicism for the mutation in the NSDHL gene [9].

The NSDHL gene is localized to Xq28 and encodes for a 3-betahydroxysterol dehydrogenase which catalyzes a step in the cholesterol biosynthesis pathway. The enzyme is located both within the membranes of the endoplasmic reticulum and on the surface of intracellular lipid storage droplets [5]. The striking laterality of the syndrome may arise from this impaired cholesterol processing causing abnormal sonic hedgehog signaling which is important in spatial patterning of the embryo [20,21] and on this basis topical application of 2% cholesterol and 2% lovastatin could reduce inflammation, skin thickening, scaling and lead to complete reversion of CHILD nevus [22]. Similar results were obtained with an ointment containing simvastatin and cholesterol. Oral and topical ketoconazole, which decreased the accumulation of toxic pathway metabolites and possibly the endogenous elevated levels of retinoic acid, resulted in an effective treatment of the nevus [23].

Our patient has dark brown scales with no erythroderma, covering the whole body with no linear distribution as reported in CHILD syndrome. So most probably our patient has LI.

The parents of our child are consanguineous as consanguinity is high in Egypt [24]. Also the mother as well as other female relatives does not exhibit any cutaneous involvement as reported in mothers of cases of CHILD syndrome due to random X inactivation [9]. So the inheritance in our patient is most probably autosomal recessive.

In conclusion, our patient is most probably a case of ARCI due to generalized body affection and a simple association of limb reduction defect.

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