Conradi–Hünermann–Happle syndrome: report of a novel heterozygous mutation on the *emopamil-binding protein* gene, c.333delC

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Abstract

Conradi-Hünermann-Happle Syndrome, also called X-linked rhizomelic chondrodysplasia punctata, is a rare genodermatosis that presents with cutaneous, skeletal, and ophthalmological abnormalities. Herein, we report a full-term newborn that presented at birth with scattered blaschkolinear bands of adherent scales and scalp erosions in a spiral distribution. Genetic analysis of emopamil-binding protein gene revealed a previously undescribed heterozygous mutation of c.333delC.

Keywords: genodermatosis, Conradi-Hünermann-Happle syndrome, mutation, EBP

Introduction

Conradi-Hünermann-Happle syndrome (CHH syndrome), also called X-linked rhizomelic chondrodysplasia punctata (Online Mendelian Inheritance in Man no. 302960), is a rare genodermatosis caused by a mutation in the *emopamil-binding protein* (*EBP*) gene that leads to abnormal cholesterol synthesis. This syndrome is associated with cutaneous, skeletal, and ophthalmological manifestations; less frequently, cardiac defects, sensorineural deafness, and neurologic impairment are identified.

Case Synopsis

A full-term newborn girl, 49cm long and weighing 3350g (50th percentile), presented at birth with scattered Blaschkolinear bands of adherent scales involving virtually the entire integument and scalp

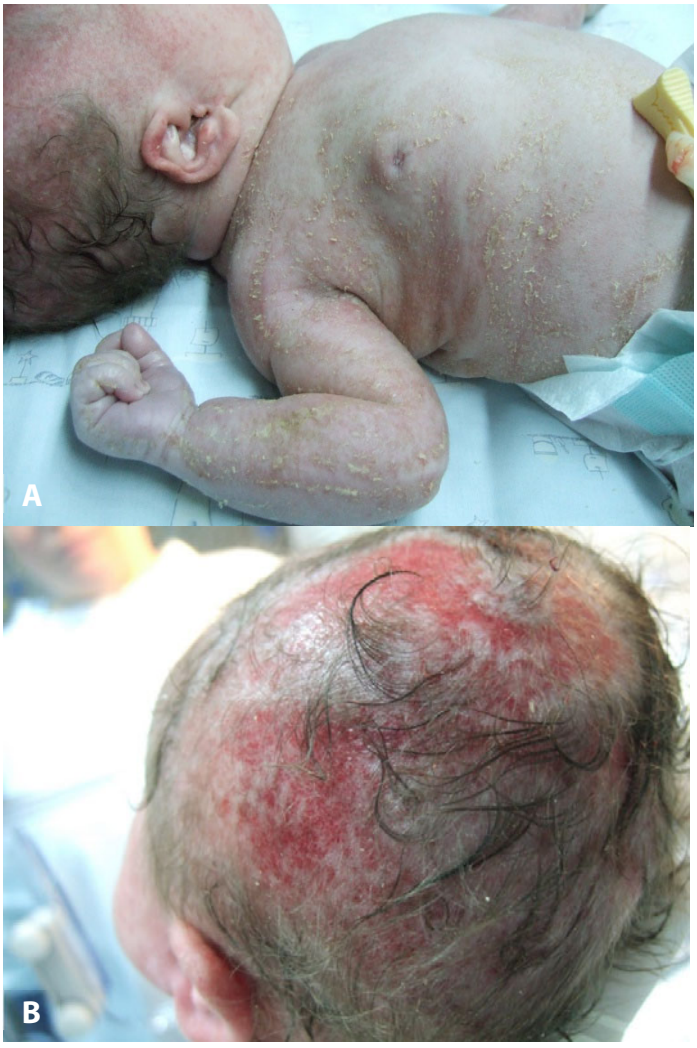

Figure 1. ***A)*** *The patient at birth. Hyperkeratotic scaling erythematous skin lesions following the lines of Blaschko.* ***B)*** *The patient at birth. Patchy alopecia and scalp erosions in a spiral distribution.*

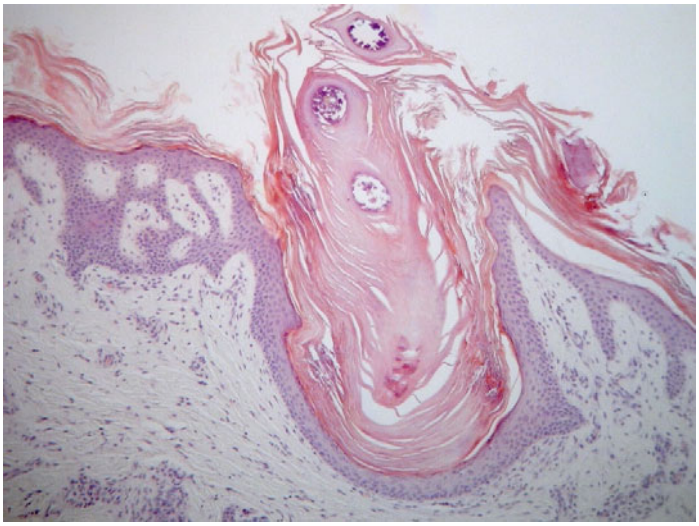

Figure 2. *Skin biopsy. Hyperkeratosis with intracorneal calcifications and dilated follicular ostia with keratotic plugging and calcification. H&E, 100×.*

erosions in a spiral distribution (**Figure 1**). Further physical examination revealed good general condition. The girl was the first child of nonconsanguineous parents with an uneventful pregnancy. Family history was negative for genetic skin diseases.

A skin biopsy revealed hyperkeratosis with focal parakeratosis and mild hypogranulosis (**Figure 2**). Additionally, vacuolated keratinocytes with calcium inclusions in a follicular distribution could be observed in the stratum corneum leading to the diagnostic suspicion of CHH Syndrome. Plasma mass spectrophotometry showed accumulation of 8(9)-cholesterol and 8-dihydrocholesterol and the diagnosis was confirmed by genetic analysis of the *EBP* gene that revealed previously undescribed heterozygous mutation of c.333delC.

By the age of 2, a right eye cataract and scoliosis were diagnosed. Nevertheless, the child has been developing normally, without neurological, cardiac, or otorhinolaryngological changes. Over the years there was a significant decrease in linear hyperkeratosis. Currently, at 10 years of age she exhibits linear and spiral depressed scars with follicular atrophoderma that have replaced the blaschkolinear bands of hyperkeratosis. Ichthyosiform desquamation with scattered brown adherent scales, especially on the legs and upper limbs, and spirally arranged cicatricial alopecia of the scalp with scarce, coarse hair can also be observed (**Figures 3, 4**).

Case Discussion

Ichthyoses are disorders of cornification whose common denominator is a defective epidermal barrier that leads to abnormal differentiation and desquamation of the epidermis. X-linked dominant chondrodysplasia punctata type 2, also known as CHH syndrome, is related to a defect in cholesterol biosynthesis that is caused by mutations in the *EBP* gene (or 3-β-hydroxysteroid-Δ8, Δ7-isomerase), located on the short arm of the X chromosome, which encodes emopamil-binding protein (EBP), [1]. The resulting deficiency of EBP, a widely expressed

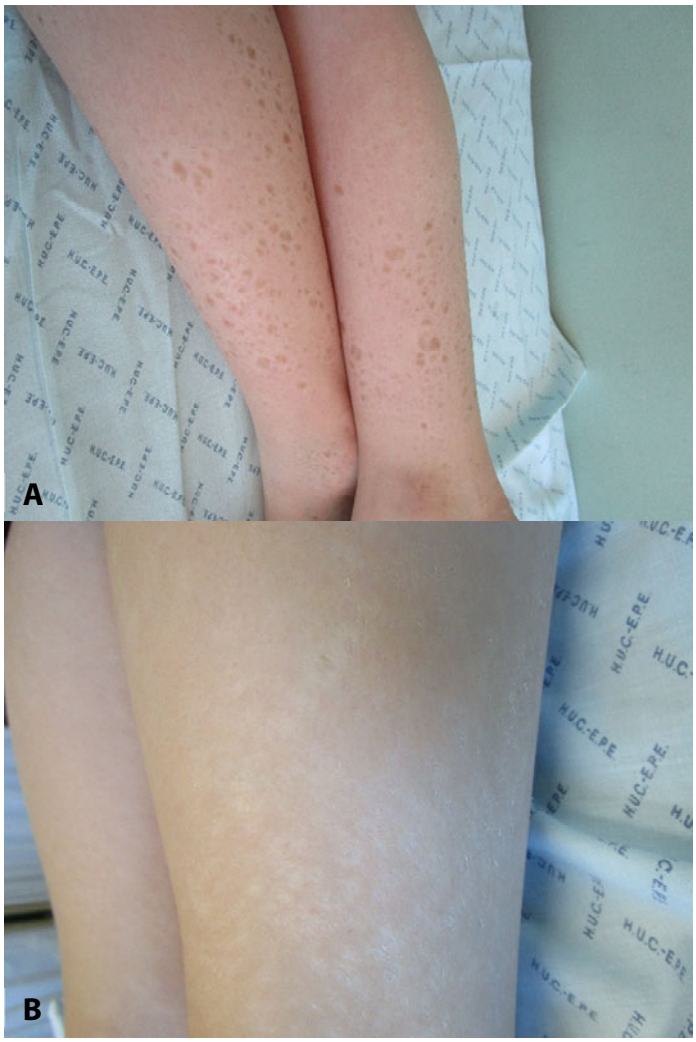

Figure 3. ***A)*** *Blaschkoid ichthyosis on the legs.* ***B)*** *Whorled blaschkolinear follicular atrophoderma and hypopigmentation.*

integral membrane protein with Δ8-Δ7-sterol isomerase activity, leads to accumulation of 8-dehydrocholesterol and 8(9)-cholesterol and cholesterol deficiency in the cell membranes with consequent barrier function alteration [2,3]. Measures of sterol levels have been reported as an effective aid to diagnosis [4]. Thus far no mutations have been definitively linked to a particular presentation.

Conradi-Hünermann-Happle syndrome is a rare condition affecting approximately 1:400 000 births [5]. Since it is an X-linked dominantly inherited disease, the condition is normally lethal for males and females are affected in 95% of the cases. Complete loss of protein function presumably accounts for the significant lethality in hemizygous males and rare survival in this population has been attributed to the presence of an additional X chromosome or a postzygotic somatic mosaicism [6,7]. In females, the phenotype demonstrates great variability, from stillbirth or early lethality to nearly undetectable manifestations, as reports of asymptomatic mothers with abnormal sterol profiles who harbor the same *EBP* mutation as their severely affected offspring demonstrate [8,9]. This is likely secondary to random X-chromosome inactivation, which is supported by the presence of Blaschkoid cutaneous findings [10]. Conradi-Hünermann-Happle syndrome is a genodermatosis that mostly affects the skin, skeletal system and eyes [11].

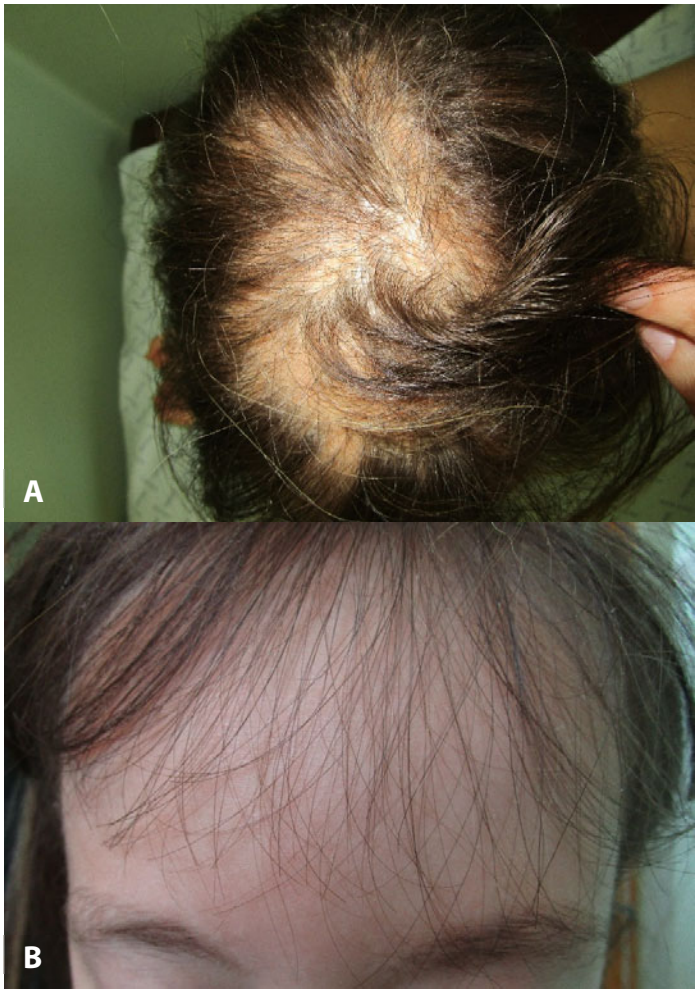

Figure 4. ***A)*** *Stable patchy cicatricial alopecia.* ***B)*** *Diffusely thinned, coarse hair.*

The skin is affected in 95% of the cases with congenital ichthyosiform erythroderma along with thick, adherent and feathery scale being the typical neonatal manifestation. Erythema is usually generalized whereas hyperkeratotic scales generally follow the lines of Blaschko. The blaschkolinear ichthyosis tends to fade during a period of weeks to months and is largely replaced by linear or patchy follicular atrophoderma with dilated follicular openings, hypopigmentation, and mild residual scaling [12,13]. The atrophoderma is most pronounced on the forearms and dorsal hands, whereas the palms and soles are usually spared. Scalp involvement results in patchy scarring alopecia although hair shaft abnormalities are nonspecific [14]. Typically hair is sparse, coarse, or lusterless. Nail changes include onychoschizia and flattening of the nail plate.

Skeletal involvement starts soon after birth and is characterized by chondrodysplasia punctata, a radiological finding evident on X-ray examination, that corresponds to stippling of the epiphyses of long bones [11,15]. Although it commonly affects the epiphyses of long bones, scapulae, clavicles, sternum, ribs, spinal column, and cartilage of the trachea may also be affected [6]. Patients can present with anomalies of the face (flattened nose bridge, frontal bossing, high-arched palate, and hypertelorism), [14], malformation of limbs (joint dysfunction, hexadactyly, and shortening of long bones), and scoliosis [3], as observed in our case. Asymmetric shortening of the limbs occurs in around 80% of the cases.

As in this case, the majority of the patients have cataracts (unilateral or bilateral), which are present at birth or develop within the first months of life [3]. Other eye findings including microphthalmia, microcornea, glaucoma, or atrophy of the optic nerve have been reported. Occasionally, other features may be associated and include congenital heart defects, sensorineural deafness, central nervous system malformations, and congenital renal anomalies [11]. Intellect is usually not impaired and life expectancy is normal.

The diagnosis is based on clinical suspicion in the case of ichthyosis following the lines of Blaschko and is confirmed by mutation analysis of the *EPB* gene [6]. However, histological findings on skin biopsy and increased plasma sterol levels point to the diagnosis of CHH syndrome.

Management of CHH is symptomatic. Persistent residual scaling may benefit from application of emollients and products containing urea or other keratolytic agents. Orthopedic and ophthalmologic care are mandatory. Thus, a multidisciplinary team approach is required for the proper diagnosis and management of this rare syndrome. Dermatologists play a central role in recognizing the distinctive feathery ichthyosis.

Conclusion

We report a female child with a typical clinical presentation of CHH syndrome in whom subsequent mass spectrophotometry showed accumulation of 8(9)-cholesterol and 8-dihydrocholesterol. Genetic analysis identified a heterozygous mutation in the *EBP* gene (c.333delC) that, to the best of our knowledge, has not been previously described.

Our case emphasizes the need to be aware of this rare genodermatosis. The increasing accessibility to genetic analysis will allow the establishment of an early correct diagnosis

Potential conflicts of interest

The authors declare no conflicts of interest. All authors approved the manuscript and agree with the publication.

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