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Pediatric Dermatology WILEY

Conradi–Hünermann–Happle syndrome associated with severe hypocalcemia in a newborn

Abstract

Conradi–Hünermann–Happle syndrome is rare X-linked dominant syndrome associated with stippled epiphyseal calcifications, congenital cataracts, Blaschkoid ichthyosiform scaling, and follicular atrophoderma. This case describes a novel finding of hypocalcemia and hypoparathyroidism in an infant with Conradi–Hünermann–Happle syndrome.

1 | CASE REPORT

A 10-day-old female presented to pediatric dermatology with ichthyosiform scaling in a Blaschkoid distribution associated with erythroderma and scattered pustules (Figure 1). Given the lack of pediatric subspecialty care in the patient's home state and concern for dehydration and infection, the infant was admitted for further evaluation and treatment. Other remarkable findings included irritability and eye-opening difficulty with moderate periorbital edema. Pregnancy was notable for hydronephrosis on fetal ultrasound, which had resolved postnatally. Family history was negative for ichthyosis. Upon admission, the baby's skin was treated with wet wraps, bleach baths, and petrolatum-based emollients. Ophthalmologic examination revealed bilateral cataracts. A skin biopsy was performed, which showed follicular hyperkeratosis and plugging, with intracorneal calcium deposition (Figure 2). Ultimately, Next-Generation Sequencing identified a heterozygous EBP c. 338 + 5 G>A mutation, confirming the suspected diagnosis of Conradi–Hünermann–Happle syndrome (CHHS), also known as X-linked chondrodysplasia punctata 2.

Initial laboratory studies, collected to assess for electrolyte abnormalities from elevated insensible fluid losses, were remarkable for critically low calcium (<5 mg/dl (normal 8.5–10.7)), low 25-OH Vitamin D (16 ug/L (normal 20–75)), and elevated phosphorus (8.0 mg/dl (normal 3.9–6.5)). Endocrine was consulted, and further workup demonstrated an inappropriately normal PTH (30 pg/ml (normal 18–80)), suggesting hypoparathyroidism. A skeletal survey showed several areas of abnormal calcific stippling in periarticular soft tissues. Ultimately, her calcium and phosphorus normalized on oral calcium and calcitriol supplementation and with the resolution of her cutaneous scaling. She now has atrophic patches in the same distribution as her past scaling. Her cataracts were surgically corrected.

2 | DISCUSSION

Conradi–Hünermann–Happle syndrome is a rare genodermatosis resulting from a mutation in the emopamil-binding protein (EBP) gene and subsequent defective cholesterol synthesis. Female fetuses are typically affected, as the condition is usually lethal for male fetuses.[1–3] Many of the classic clinical findings are the consequences of abnormal calcium deposition in the tissues. Histopathology of ichthyosiform scaling shows intracorneal calcification.[3] Congenital cataracts are the results of abnormal calcium deposition in the cornea, and the epiphyseal stippling seen on X-ray is caused by premature calcification of cartilage.[1] Genetics references and reviews do not, however, include hypocalcemia as an associated clinical feature.[1–3] Interestingly, severe hypocalcemia has been described in case reports of an infant with CHHS and in an infant with the more severe rhizomelic form of chondrodysplasia punctata, but these findings were not addressed specifically by the authors.[4,5] We postulate that the hypocalcemia noted in our infant was secondary to serum calcium depletion due to transient tissue deposition in conjunction with hypoparathyroidism, which was evidenced by elevated serum phosphorus and inappropriately normal PTH levels. Endocrinology hypothesized that neonatal stress and dehydration may have been triggers for the hypoparathyroidism given the lack of other potential culprits such as hypomagnesemia, or associated genetic syndromes such as DiGeorge. Our infant's calcium levels normalized in the first few weeks of

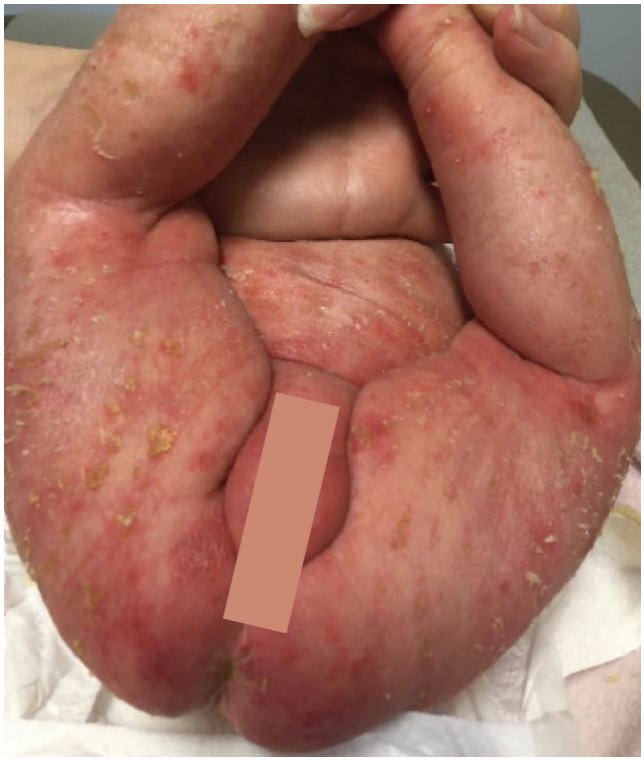

FIGURE 1 10-day-old patient with ichthyosiform scaling in a Blackschkoid distribution

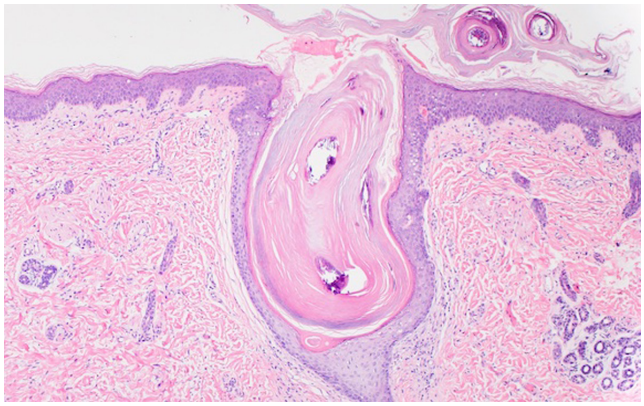

FIGURE 2 Follicular hyperkeratosis and plugging with intracorneal calcium deposition highlighted by H&E 100×

life, further suggesting that the etiology was transient. Based on these observations, further investigation into calcium metabolism in CHHS is needed.

KEYWORDS

genetic diseases/mechanisms, genodermatoses

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CONFLICT OF INTEREST

We have no conflicts of interests to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Morgan Dykman BA[1]
Lindsey Marie Voller MD[2]
Christina Boull MD[3]

[1]*Division of Pediatric Dermatology, Department of Dermatology, University of Minnesota, Minneapolis, Minnesota, USA*
[2]*Department of Internal Medicine, Santa Clara Valley Medical Center, San Jose, California, USA*
[3]*Division of Pediatric Dermatology, Department of Pediatric Dermatology, University of Minnesota, Minneapolis, Minnesota, USA*

Correspondence
Morgan Dykman, Division of Pediatric Dermatology, Department of Dermatology, University of Minnesota, 31 Arthur Ave. SE, Minneapolis, MN 55414, USA.
Email: dykma003@umn.edu

ORCID

Morgan Dykman https://orcid.org/0000-0002-9261-7483

REFERENCES

1. Cañueto J, Girós M, Ciria S, et al. Clinical, molecular and biochemical characterization of nine Spanish families with Conradi-Hünermann-Happle syndrome: new insights into X-linked dominant chondrodysplasia punctata with a comprehensive review of the literature. *Br J Dermatol*. 2012;166(4):830-838.
2. Hoang MP, Carder KR, Pandya AG, Bennett MJ. Ichthyosis and keratotic follicular plugs containing dystrophic calcification in newborns: distinctive histopathologic features of x-linked dominant chondrodysplasia punctata (Conradi-Hünermann-Happle syndrome). *Am J Dermatopathol*. 2004;26(1):53-58.
3. National Organization for Rare Disorders *Conradi Hünermann Syndrome*. NORD (National Organization for Rare Disorders). https://rarediseases.org/rare-diseases/conradi-hunermann-syndrome/ Published June 29, 2021 Accessed November 1, 2021
4. Martanová H, Krepelová A, Baxová A, et al. X-linked dominant chondrodysplasia punctata (CDPX2): multisystemic impact of the defect in cholesterol biosynthesis. *Prague Med Rep*. 2007;108(3):263-269.
5. Williams DW 3rd, Elster AD, Cox TD. Cranial MR imaging in rhizomelic chondrodysplasia punctata. *AJNR: Am J Neurorad*. 1991;12(2):363.

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