Autosomal Recessive Congenital Ichthyosis Due to Heterozygote Variants in the ALOX12B gene Presenting as Mild Nonbullous Congenital Ichthyosiform Erythroderma

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ABSTRACT
Autosomal recessive congenital ichthyosis (ARCI) comprises a group of rare, clinically heterogeneous disorders of keratinization, characterized by hyperkeratosis, abnormal skin scaling, and a variable degree of erythroderma. Affected infants are most often born encased in a collodion membrane, which is usually shed within 2-4 weeks, revealing the underlying skin condition. To date, at least 14 genes have been identified as causative for ARCI, and phenotypes associated with mutation of different genes may overlap. Herein we report the case of an infant with ARCI due to heterozygous pathogenic mutations in the 12(R)-lipoxygenase (ALOX12B) gene.

KEY WORDS: ichthyosis, nonbullous congenital ichthyosiform erythroderma, collodion baby, genetic diseases, neonatal desquamation

INTRODUCTION

Autosomal recessive congenital ichthyosis (ARCI) represents a phenotypically and genetically heterogeneous group of disorders of keratinization, classified as non-syndromic forms of ichthyosis. This group comprises three major forms of non-syndromic ichthyoses, lamellar ichthyosis, nonbullous congenital ichthyosiform erythroderma, and Harlequin ichthyosis. In addition, three minor ARCI variants can be distinguished, including self-healing collodion baby, acral self-healing collodion baby, and bathing suit ichthyosis (1). We report the case of a female infant who was born with a collodion membrane and later exhibited mild nonbullous congenital ichthyosiform erythroderma.

CASE REPORT

A female infant was delivered at 39 weeks of gestation by caesarean section due to slow progress in labor. Birth weight was 3030 g, birth length was 49 cm, and the Apgar score was 10 and 10 at the first and fifth minutes, respectively. There was no history of maternal complications or any drug exposure during pregnancy. The patient's parents were nonconsanguineous and there was no family history of ichthyosis. At birth, the newborn was found to have a partial collodion membrane covering her face, extremities, and partially covering the trunk. The patient presented with white, hyperkeratotic scales covering the whole body. The underlying skin was erythematous, with areas of superficial erosions and macerations

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Figure 1.

around the axillary and inguinal folds and on the abdomen. The patient also had severe ectropion of both the eyelids with lid edema, and her lips were everted, showing eclabion. The earlobes were deformed by tension of the skin (Figure 1). Thorough systemic examination revealed no other associated anomalies. Within the first 14 hours after birth, the newborn was transferred from the city hospital Maternity ward to our tertiary care pediatric facility for further management. She was placed in a highly humidified incubator (80% humidity) and received empiric antibiotic therapy with ampicillin and gentamicin for 7 days. As advised by the dermatologist, soft white paraffin was applied frequently to keep the skin moisturized. Mild localized erosions were treated topically, with mupirocin ointment applied twice daily. As advised by the ophthalmologist, the ectropion was covered with eye pads soaked in saline solution, and the eyes were treated with tobramycin ophthalmic solution and ointment. In order to avoid hyperthermia, hypothermia, and dehydration, proper monitoring of body temperature was performed. In the first week after birth, the earlobes assumed a normal shape, and the ectropion and eclabium resolved. The collodion membrane was shed during the second week after birth. After shedding of the collodion membrane, the

Figure 2.

skin appeared erythematous, with localized areas of desquamation. The patient was moved to an open-air crib at the 12th day after birth, with a gradually improvement in the appearance of the skin. During further hospital stay, the newborn was in good general condition, had normal vital signs, and adequately tolerated oral food intake. Laboratory tests showed transient leukocytosis with normal serum levels of procalcitonin (PCT) and C-reactive protein (CRP). Other laboratory findings were within normal ranges. Ultrasound of the abdomen and echocardiogram results were unremarkable. The patient was discharged on the 21st day after birth, with a significantly improved skin condition. Her parents were educated about the disease and thoroughly instructed about skin care. The patient was referred to the Department of Genetics, where clinical exome sequencing (CES) was performed. Genetic testing revealed heterozygous variants in the ALOX12B gene, c.1562A>G and c.2036G>A. Both variants lead to the missense mutations p.Tyr521Cys and p.Arg679His, respectively. Therefore, on the basis of clinical features and genetic test results, the patient was diagnosed with ARCI type 2 (ARCI 2), presenting with the nonbullous congenital ichthyosiform erythroderma (NCIE) phenotype at the time. The patient continued to attend follow-up with the dermatologist, ophthalmologist, and otorhinolaryngologist in our hospital. After 2.5 months of follow-up, the patient's skin was slightly dry and erythematous on the scalp, neck, chest, and in the diaper area. She developed two superficial hemangiomas, one in the groin area and the other on the forehead, and topical treatment with timolol was started (Figure 2). Eye examinations were normal, and a hearing test (auditory brainstem response) showed hearing sensitivity within the physiological range. At the most recent follow-up visit at the age of 9 months, the patient was in excellent general condition. She continued to grow and develop normally and has been meeting developmental milestones. Her skin continued to improve, showing mild local erythema and desquamation, mostly on the face, eyelids, scalp, and in the retroauricular region. The palmoplantar skin was dry and slightly hyperkeratotic. The patient's hair, nails, and teeth were normal.

DISCUSSION

Children with ARCI often present as collodion babies at birth. The collodion baby is a descriptive term used for the appearance of neonates who are born encased in a tight, parchment-like membrane. The term was introduced by Hallopeau and Watelet in 1982 (2). The collodion membrane is usually shed within the first 2-4 weeks after birth, revealing the underlying ichthyosis phenotype (3). To date, at least fourteen genes have been identified as causative for ARCI: ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, CSTA, LIPN, NIPAL4, PNPLA1, POMP, SLC27A4, ST14, SULT2B1, and TGM1 (4). ALOX12B is the third most common gene affected in ARCI, with mutations occurring in approximately 12% of patients with ARCI (5). Homozygous or compound heterozygous mutation in the ALOX12B gene cause ARCI2 (MIM#242100) and are associated with nonbullous congenital ichthyosiform erythroderma (6-8). Additionally, some patients present the self-healing collodion baby phenotype, whereby the newborns are born with a collodion membrane, but the skin appears normal or shows very mild ichthyosis after shedding of the membrane (9). Our patient was born with collodion membrane, later exhibiting palmoplantar hyperkeratosis and only mild erythroderma with fine scaling on the face, scalp, and retroauricularly. Genetic analysis showed that our patient had compound heterozygosity for two variants in the ALOX12B gene, c.1562A>G (p.Tyr521Cys) and c.2036G>A (p.Arg679His). The first variant, c.1562A>G (p.Tyr521Cys), has been previously reported, either in the homozygous state or in combination with another ALOX12B variant, in multiple patients with ARCI (9,10,11). For this variant, functional analysis in HEK-293 cells was performed and showed complete loss of enzyme activity, while the protein expression level was similar to the wild type (11,12). The second variant, c.2036G>A (p.Arg679His), was submitted to ClinVar in January 2021 by the Institute for Human Genetics, University Clinic Freiburg, as a pathogenic variant causing ARCI. However, to date there are no assertion criteria available for that variant (13). Additional functional studies will define the pathogenic role of this variant.

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Written informed consent for publication of clinical details and clinical images was obtained from the parents of the patient.

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