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PHOTOLETTER TO THE EDITOR

# Lamellar ichthyosis and arthrogryposis in a premature neonate

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## Abstract

Lamellar ichthyosis is a rare congenital disorder characterized by collodion membrane at birth and facial anomalies (eclabium and ectropion). The major underlying genetic defect is in TGM1, with mutations of this gene found in 50% of patients. An early diagnosis is fundamental in view of establishing a specific treatment due to the severity of the disease. We report a case of severe lamellar ichthyosis and arthrogryposis, without the typical facial presentation, negative for TGM1 mutations. The clinical improvement was achieved only after treatment with oral retinoids, highlighting the importance of early diagnosis and prompt administration of a specific therapy. (*J Dermatol Case Rep*. 2015; 9(2): 49-51)

### Key words:

autosomal recessive congenital ichthyoses, congenital ichthyoses, lamellar ichthyosis, oral acitretin, transglutaminase-1 gene mutations

Skin barrier function is fully developed at birth in healthy term infants. In some cases, congenital dermatological diseases may disrupt this function as in our patient presenting with ichthyosis, a broad spectrum of severe cornification disorders characterized by scaly, dry, fish-like skin.[1]

A 2-day-old male presented to the neonatal intensive care unit with brown plate-like scales covering the body. He was born prematurely at 35 weeks in a collodion membrane and his family history was unremarkable. The physical examination revealed generalized cracked hyperkeratosis without erythroderma, arthrogryposis and palmoplantar hyperkeratosis with curved and beaked nails (Fig. 1). Complete blood count, liver and renal function tests, CRP, urine analysis and aminoaciduria were normal. At admission, as he had high risk of infection due to the impairment of skin barrier function, he started broad-spectrum antibiotics suspended at 7 days of life after repeatedly negative CRP and cultures. The infant underwent a dermatological consult and an autosomal recessive lamellar ichthyosis was strongly suspected based on clinical findings, negative family history and collodion baby at birth. Genetic analysis revealed a normal karyotype and no mutation of the TGM1 gene (14q11.2). The newborn was treated with alkaline baths containing sodium bicarbonate and bath-oil followed by application of petrolatum-based ointment three times per day. As no improvement occurred after 2 days, systemic treatment with oral retinoids was added (acitretin at 1 mg/kg/day). A generalized cutaneous desquamation occurred after 20 days of acitretin with interruption of the treatment. For the elevated toxicity of retinoids, routine follow-up visits were performed during the treatment and no acute adverse effects were identified. Moreover, the arthrogryposis improved at the age of 5 months by manual joint mobilization.

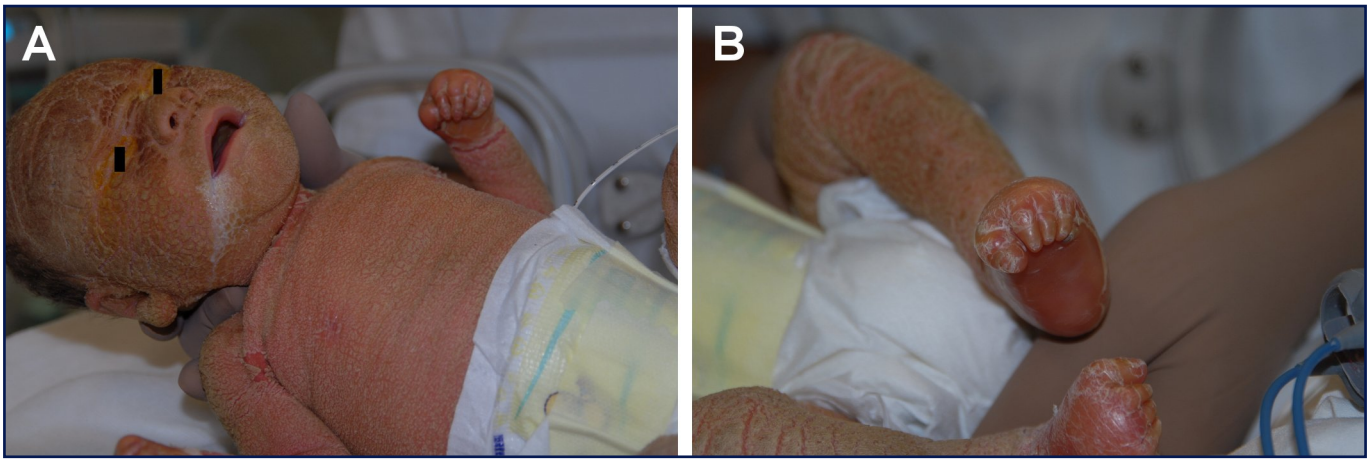


**Figure 1**

*(A) Brown, large plate-like scales covering the all body and arthrogryposis of hands, with rigidity in flexion of fingers and hyperadduct thumb. (B) Arthrogryposis and short phalanxes of toes. The fifth toe is cyanotic but without annular constriction of the digit (pseudoahinum).*

## Discussion

Ichthyoses encompass a clinically and genetically heterogeneous group of cornification disorders among which autosomal recessive congenital ichthyoses (ARCI) represent the most frequent among congenital forms.[1] Children with ARCI are often born prematurely with generalized scaling at birth and increased risk of hyperthermia and hypernatremic dehydration and sepsis.[1] The clinical presentation and severity vary significantly (Table 1), ranging from the most severe harlequin ichthyosis (HI) with diamond-shaped scales, to lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE) characterized by generalized erythroderma.[1-2]

The ARCI has an estimated prevalence of 1:200,000-300,000.[1] Most patients are born in a collodion membrane, which is replaced during the first weeks of life with plate-like scales, often associated with palmoplantar hyperkeratosis and beaked nails.[1] The diagnosis is argued on

**Table 1.** Differential diagnosis of the ARCI based on the clinical characteristics of the scales and the presence/absence of erythroderma.[1] Note the genetic testing that should be performed in the suspect of each form of ichthyosis. Specifically, HI has mutations in ABCA12 only, whereas LI and CIE can be associated with mutations in multiple genes, with TGM1 mutations as the most frequent forms.[1-3]

| Autosomal Recessive Congenital Ichthyoses (ARCI) | | |
|---|---|---|
| Ichthyosis | Clinical Characteristics | Mutations – Genetic Testing |
| Harlequin Ichthyosis (HI) | • Most severe form<br>• Large, thick and diamond-shaped scales<br>• Facial abnormalities (severe ectropion, eclabium and flattened ears) | ABCA12 |
| Lamellar Ichthyosis (LI) | • Large, thick and dark scales<br>• Absence of severe background erythroderma | TGM1<br>ABCA12<br>NIPAL4 (or ICHTHYIN)<br>CYP4F22<br>ALOX12B<br>ALOXE3<br>LIPN<br>CERS3 |
| Congenital Ichthyosiform Erythroderma (CIE) | • Fine, whitish scales<br>• Background of erythematous skin over the whole body | TGM1<br>ABCA12<br>NIPAL4 (or ICHTHYIN)<br>CYP4F22<br>ALOX12B<br>ALOXE3<br>PNPLA1<br>LIPN<br>CERS3 |

skin findings and can be confirmed by genetic testing. Genetic defects in at least eight diverse genes have been associated with ARCI.[1-3] About 40-50% of all ARCI patients has mutation of the TGM1 gene (OMIM *190195), which encodes keratinocyte transglutaminase-1 (TGase1).[3] The remaining patients may suffer mutation of ALOXE3, ALOX12B, NIPAL4 (known as ICHTHYIN), ABCA12, CYP4F22, PNPLA1, LIPN, and CERS3 at least (Table 1).[1-3] Deficiency of the proteins encoded by some of these genes affects intercellular lipid layers formation in the stratum corneum and causes abnormal hyperkeratosis.[3]

Treatment, based on hydration, lubrication and keratolysis, is directed at decreasing symptoms. Oral retinoids are generally recommended in neonates with severe skin involvement, but not in all cases.[4-5] The benefit/risk ratio must be carefully balanced, as systemic retinoid therapy has significant short and long-term adverse effects. These include development of ligamentous calcifications, skeletal hyperostosis, liver and mucocutaneous toxicity (cheilitis, epistaxis, and eye irritation).[5]

In our patient, clinical improvement was achieved only after treatment with oral acitretin and the incredibly quick resolution of such a destructive clinical picture highlights the importance of early administration of a specific therapy.

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