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Ichthyotic Skin Disorders in the Neonate

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Case Report and Hospital Course

An ex-37-week Caucasian baby boy was born to a 32-year-old gravida 3, abortus 2, para 0- >1 mother and her 43-year-old husband via cesarean section due to breech presentation. During the prenatal period, no complications arose. The patient had Apgars of 9 and 9 at 1 and 5 minutes and was immediately noted to have a collodion membrane (a tight wax-like sheath encompassing the entire body) with eclabium (mouth forced open) and ectropion (everted eyelids) (Figure 1a). The patient was evaluated by Neonatology and promptly transferred to the NICU to institute preventative measures against fluid loss and sepsis.

The patient's pedigree revealed only a 53-year-old cousin on the father's side, who was identified as possibly having the same skin disorder as the patient, but the exact diagnosis was unknown to the family. The parents did state that the word "ichthyosis" was mentioned and that this case was written up in the past. This cousin was known to have skin findings at birth that improved with time but persisted throughout life; she had 3 healthy children, and it is unknown if genetic testing was ever performed. Both mother and father were of Western European/non-Jewish decent with no history of consanguinity.

Final Diagnosis and Follow up

As a neonate, the patient tested negative for mutations in transglutaminase 1, which accounts for 90% of patients with lamellar ichthyosis.¹ They chose not to pursue further testing at this time. Seventeen months later, a second child was born with a collodion membrane (Figure 2a), and the family chose to pursue further genetic testing. Both patients rapidly improved with appropriate NICU management and continue to do well with a regimen of topical hydrating creams (Figures 1b, 2b).

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Discussion

Ichthyosis is a term derived from *ichthy*, the Greek word for fish, and it is used to describe a group of disorders that present with scales on the skin.¹ Autosomal recessive congenital ichthyosis (ARCI), is a heterogeneous group of inherited keratinization disorders, characterized by widespread scaling of the skin and varying levels of erythema.² The spectrum of ARCI phenotypes ranges from the fatal harlequin ichthyosis to less severe disorders such as lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE).² Both LI and CIE affect males and females equally, and CIE is more common than LI with an incidence of 1:180,000 compared to 1:300,000 for LI.³

LI and CIE may be indistinguishable at birth, as both are associated with a collodion membrane, ectropion (eversion of eyelids), and eclabium (eversion of lips).³ Beaked, curved nails and crumpled ears are a common finding in neonatal LI and CIE, and while erythroderma can be present, it is never a predominant finding.²

LI and CIE develop into distinct phenotypes after infancy. LI is characterized by a brown, plate-like scale on a non-erythematous base, as well as persistent ectropion.² Alternatively, CIE presents with generalized erythroderma with an overlying fine, white scale, although extensor legs may exhibit a large, platelike, dark scale.² Both conditions may include palmoplantar keratoderma, decreased sweating with heat intolerance, and scarring alopecia.² While both LI and CIE patients have a normal life span, LI symptoms remain severe throughout life while CIE findings may improve at puberty.²

Six genes have been associated with ARCI, with mutations in transglutaminase 1 (*TGM1*) accounting for approximately 40% of LI and CIE cases combined.⁴ This mutation is much more closely linked to LI than CIE, accounting for up to 90% of all LI cases.² The remaining individuals with LI and CIE have mutations in the genes arachidonate 12-lipoxygenase (*ALOXE3*), arachidonate lipoxygenase 3 (*ALOX12B*), and ATP-binding cassette transporter 12 (*ABCA12*).⁴ Regardless of the specific mutation, LI and CIE are inherited in an autosomal recessive fashion.⁵ Attempts at establishing definitive genotype-phenotype relationships have been largely unsuccessful; however, *TGM1* mutations are more closely linked with collodion membrane and ectropion at birth.⁵

The diagnosis of LI, CIE, and other ichthyoses is clinical with support from genetic testing.¹ While skin biopsy is not diagnostic in ARCI, it usually demonstrates a thickened stratum corneum with underlying acanthosis.¹ Prenatal diagnosis of LI is possible by fetal skin biopsy performed at 20 weeks showing early thickening of this outer skin layer.⁶ A prenatal biopsy can also be used to test transglutaminase activity, which serves as a reliable marker for LI.⁶ If genotypic information is available in a given family, this is the best method for prenatal diagnosis.

Management of LI and CIE in the neonatal phase involves transfer to the NICU for monitoring of fluids, electrolytes, and sepsis.³ Infection prevention, hydration, and maintenance of body temperature is key, and loss of fluids can be minimized by the use of thick emollients and a high-humidity chamber.³ Mechanical removal of the scale or collodion membrane should be avoided, as it may lead to a tearing of the epidermis and subsequent infection.⁵ In the child or adult patient with ARCI, keratolytics or retinoids may be used to treat the hyperkeratosis.³ This includes propylene glycol under occlusion at night to shed the scales, and the use of oral retinoids under the supervision of a dermatologist.¹ The psychological and emotional status of a child with ichthyosis should be addressed, and a complete medical assessment, including social work and ophthalmology should be

employed. Early referral to support groups through the Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T.) is encouraged.³

Workup of Neonatal Ichthyosis

When working up a neonatal patient with ichthyosis, it is important to consider the major forms of inherited ichthyoses, as well as the hereditary syndromes that may present with an ichthyotic scale. At birth, the presence of a collodion membrane suggests a variety of underlying disorders, the most common cause being ARCI (Figure 3).⁷ It should be noted that approximately 10% of collodion babies will shed the membrane and have no further skin pathology, a condition known as a self-healing collodion baby caused by a unique mutation in *TGMI*.^{5,2} Depending on the onset, appearance, and distribution of the scale, several forms of inherited ichthyosis must be considered (Table 1).¹ Ichthyotic skin can also be present in other hereditary syndromes such as Conradi-Hunermann disease, CHILD syndrome, Sjogren-Larsson syndrome, Netherton syndrome, and Refsum disease, each of which comes with a variety of other non-dermatologic clinical features (Figure 3).^{1,3} Encountering an older child or adult with new onset ichthyosis should suggest an acquired form of the disease due to an underlying condition such as a medication reaction, malignancy, nutritional disorder, or metabolic disease.¹

Conclusion

There are several valuable clinical insights to be learned from this case. First, it is important to recognize the presentation of the congenital ichthyosis so that prompt, adequate treatment can be initiated in the NICU. Second, health care providers should understand the possible causes of collodion baby, given that the prognosis for these underlying conditions can be incredibly diverse. Finally, the mutational heterogeneity of lamellar ichthyosis is often overlooked, and if *TGMI* testing is negative in an ichthyotic patient, doctors should pursue further testing.

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Figure 1.

- a. First child at 4 days of life presents with collodion membrane, ectropion, and eclabium.
b. First child at 17 months presents with minimal scale on face and feet after regular use of topical hydrating creams.

Figure 2.

- a. Second child immediately post-partum presents with more severe collodion membrane, ectropion, and eclabium.
- b. Second child at 5 weeks presents with significant improvement of dermatologic findings after regular use of topical hydrating creams.

Figure 3.
Most Common Causes of Collodion Baby

Table 1

The Major Inherited Ichthyoses

Disorder	Inheritance Pattern	Most Common Gene	Onset	Type of Scale	Site of Scale	Other Findings
Lamellar Ichthyosis	Autosomal Recessive	Transglutaminase	Birth	Dark, platelike, + erythroderma	Generalized with ↑ scale on flexors, palms, soles	• Collodion Membrane • Ectropion • Eclabium • Nail dystrophy • Growth delay • Alopecia
Congenital Ichthyosiform Erythroderma	Autosomal Recessive	Transglutaminase	Birth	White, fine, + erythroderma	Generalized with ↑ scale on flexors, palms, soles	• Collodion Membrane • Ectropion • Eclabium • Nail dystrophy • Growth delay • Alopecia
Epidermolytic Hyperkeratosis	Autosomal Dominant	Keratin 1, 10	Birth	Coarse with erosions, bullae	Generalized with ↑ scale on flexors	• Pyogenic infections • Foul odor
Harlequin Fetus	Autosomal Recessive	ACBA12	Birth	Large thick plates	Generalized	• Ectropion • Eclabium • Dysmorphology of ears and limbs
X-linked Ichthyosis	X-linked	Steroid sulfatase	Birth or Infancy	Brown, coarse	Neck, face, trunk	• Corneal opacities • Anosmia • Cryptorchidism
Ichthyosis Vulgaris	Autosomal Dominant	Filaggrin	Childhood	Fine	Palms, soles, extensors	• Atopy • Keratosis pilaris