Congenital ichthyosiform erythroderma with epidermolysis due to a novel frameshift mutation in *KRT10*

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INTRODUCTION

Neonatal erythroderma (NE) is an erythema that covers at least 90% of the body surface and occurs at birth or in the first 4 postnatal weeks.[1] The incidence of NE in patients in the Netherlands has been estimated by dermatologists to be 10 per 100,000 newborns.[1] In congenital ichthyosiform erythroderma (CIE), the presence or absence of a collodion membrane and/or extracutaneous findings is crucial to narrow down possible differential diagnoses. Here, we describe a keratinopathic form of NE or CIE due to a mutation in the *KRT10* gene. Additionally, 2 variants, 1 pathogenic and 1 of unclear significance, of *FLG* were detected.

CASE REPORT

A newborn (2 hours old) female infant presented with NE. She was born at 38 weeks and was delivered vaginally without any complications. She was the first child of healthy, nonconsanguineous parents and was born without a collodion membrane. However, her body was partially covered with large, thin, white and yellowish confluent scales on the sides of the upper portion of the body, ie, CIE. There was no epidermis on the back, upper portion of the arms and legs, and gluteal region (Fig 1, *A* and *B*). Palmoplantar keratoderma was also observed. As an extracutaneous finding, we found microtia. Her hair, eyebrows, and eyelashes were noticeably sparse (Fig 1, *C*). Her eyes showed no abnormalities.

Abbreviations used:

CIE: congenital ichthyosiform erythroderma
NE: neonatal erythroderma

No other family members had similar skin manifestations.

Based on the absence of the collodion membrane, clinical presentation of ichthyosis, and ear deformity, a keratinopathy was suspected. To prevent infection due to the lack of epidermis, systemic antibiotic treatment with ampicillin was started (weight adjusted) and breast feeding was postponed. Her fluid balance was monitored, and she was kept in humidified air within an incubator.

Mild keratolytics containing evening primrose oil and glycerin were applied multiple times daily, which led to rapid and significant improvement of hyperkeratosis within a few days (Fig 1, *D*). During follow-up, the skin did not show any erythroderma and desquamation. Genetic testing revealed a keratinopathy due to a mutation in the *KRT10* gene and additional variants of *FLG*. The patient's parents underwent genetic counseling, including the clinical spectrum of *KRT10* keratinopathy, respective risk of recurrence (low but above average because of the possibility of germline mosaicism), and clinical features and risk of recurrence of *FLG*-associated disorders. Reconstruction of the ears with cartilage

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Fig 1. Clinical picture of the patient. **A,** Severe erythroderma with large, white desquamation on the trunk and yellowish confluent scales on the sides of the upper portion of the body. **B,** Severe shinny erythroderma on the patient's back. **C,** Marked ear deformity. **D,** Clinical picture of the patient after 10 days of topical treatment, without erythema and desquamation.

was planned for early childhood. Consent for the publication of the patient's photographs and medical information was provided by the authors at the time of article submission to the journal stating that the patient's parents gave consent for her photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

DISCUSSION

Congenital ichthyoses, primary immunodeficiencies, metabolic disorders, drug reactions, skin infections, atopic dermatitis, psoriasis, and seborrheic dermatitis can cause NE.[1] Congenital ichthyosis (CIE) is considered to be the main cause of NE. The mortality rate is high in children with NE (16% after a mean of 17 months) because of complications of erythroderma, such as dehydration, electrolyte imbalance, and infection. Therefore, the exact diagnosis should be confirmed as early as possible.

The newborn female infant reported herein presented with CIE with pronounced lack of epidermis, palmoplantar keratoderma, and microtia.

Prenatally, amniotic fluid was genetically tested, and it was found that the unborn child carried a de novo pathogenic variant in exon 7 of the *KRT10* gene while she was compound heterozygous for the *FLG* class 5 variant c.2282_2285delCAGT, p.S761Cfs*36, and the variant of unknown significance c.11959G>A, p.G3987S, at the same time.

Overall, the result of clinical assessment was in accordance with a *KRT10*-associated keratinopathy. The mutation found in *KRT10*, c.1530dupC, p.G511Rfs*70, was not present in the lymphocytes of either of the patient's parents. It has not yet been described as pathogenic and is not listed in control databases (eg, single nucleotide polymorphism database and genome aggregation database). It is a frameshift mutation that leads to premature translational arrest and, thus, to either loss of function of the affected allele via premature degradation of the

mutant messenger RNA or a truncated protein with reduced or aberrant function. Furthermore, loss-of-function mutations in *KRT10* in the respective exons are a known disease mechanism (eg, c.1544dupG, p.G516Rfs*65).[2] Pathogenic variants of *KRT10* have been described as being causative of keratinopathic ichthyoses with epidermolysis or congenital reticular ichthyosiform erythroderma[3] and may exhibit additional extracutaneous features. Interestingly, in ichthyosis with confetti, somatic reversion leads to partial loss of the dominant disease—causing *KRT10* mutation.[4] Because of the location of the mutation and the type of the variant of the *KRT10* gene, it can be assumed that the child might also exhibit ichthyosis with confetti in the future.

Ichthyosis vulgaris may be associated with the mutation c.2282_2285delCAGT, p.S761Cfs*36, in the *FLG* gene, which is one of the most frequent *FLG* mutations in the European population.[5] It is a frameshift mutation that leads to early translational arrest and, thus, to either loss of function of the affected allele via premature degradation of the mutant messenger RNA or a truncated protein with reduced or aberrant function.[5] The *FLG* variant c.11959G>A, p.G3987S, has not yet been described as pathogenic. Based on homozygous detection in 4 control individuals in the gnomAD database, this variant was assessed as a variant of unclear significance with a tendency toward a probable benign variant. Heterozygous loss-of-function *FLG* mutations usually lead to a mild form of ichthyosis vulgaris, often associated with atopic dermatitis,[6] whereas biallelic loss-of-function *FLG* mutations can cause a more severe form.[5] Ichthyoses due to heterozygous *FLG* mutations are not usually present at birth. However, it has been speculated that additional *FLG* mutations might act as modifiers of disease severity in other ichthyoses. The contribution of the detected variant(s) to this case ultimately remains unclear at present.

To sum up, we reported the case of a newborn girl with NE. Her body was partially covered with large, thin, white scales, and the epidermis was missing on the back, upper portion of the arms and legs, and gluteal region. Microtia was present at birth, and there was no collodion membrane. Genetic testing revealed a pathogenic heterozygous de novo variant in the *KRT10* gene. Additionally, 2 compound heterozygous variants of the *FLG* gene, 1 classified as pathogenic and the other classified as a variant of unknown significance, which does not influence the phenotype, were identified. It has been repeatedly suggested that *FLG* and *STS* mutations (*STS* being the gene compromised most frequently in X-linked ichthyosis, see OMIM#308100) are coinherited. However, without functional data, it remains unclear whether the pathogenic variant of *FLG* identified in addition to the variant of *KRT10* in this case might also modify the individual clinical presentation now or in the future.

Conflicts of interest

None disclosed.

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