High rate of self-improving phenotypes in children with non-syndromic congenital ichthyosis: case series from south-western Germany

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Abstract
Background Non-syndromic congenital ichthyosis describes a heterogeneous group of hereditary skin disorders associated with erythroderma and scaling at birth. Although both severe and mild courses are known, the prediction of the natural history in clinical practice may be challenging.

Objectives To determine clinical course and genotype-phenotype correlations in children affected by non-syndromic congenital ichthyosis in a case series from south-western Germany.

Methods We performed a retrospective observational study of 32 children affected by non-syndromic congenital ichthyoses seen in our genodermatosis clinic between 2011 and 2020. Follow-ups included assessment of weight and severity of skin involvement utilizing a modified Ichthyosis Area Severity Index (mIASI). mIASI was calculated as a sum comprising the previously published IASI score and an additional novel score to evaluate palmoplantar involvement. Linear regression was assessed using Pearson correlation, and statistical analysis was performed using the Wilcoxon–Mann–Whitney test.

Results This study included 23 patients with autosomal recessive congenital ichthyosis, seven with keratinopathic ichthyosis and two with harlequin ichthyosis. Cutaneous manifestations improved in more than 70% of the children during the follow-up. Especially in patients with mutations in ALOXE3 and ALOX12B, mIASI scores dropped significantly. The most common phenotype observed in this study was designated ‘mild fine scaling ichthyosis’. Severe palmoplantar involvement occurred in patients with KRT1 and ABCA12 mutations; most patients demonstrated hyperlinearity as a sign of dryness and scaling. Weight was mainly in the normal range and negatively correlated with the severity of skin involvement.

Conclusions Congenital ichthyosis that self-improves and evolves with mild fine scaling ichthyosis was the most common phenotype observed in our patients. This type might be underdiagnosed if the genetic diagnosis is not performed in the first year of life. mIASI is an easy and fast instrument for scoring disease severity and adding additional points for palmoplantar involvement might be valuable.

Keywords: ARCI, genodermatosis, genotype-phenotype correlation, Hereditary skin disease, ichthyosis.

Introduction
Congenital ichthyosis may manifest with erythroderma, collodion- or thick plate-like scales, or with blisters and erosions and represents an emergency situation for newborns.1 Prognosis is important for family counselling and disease management. For collodion babies, in particular, the course of the disease is extremely difficult to predict solely based on clinical features.
Congenital ichthyoses are clinically and genetically heterogeneous. They are classified into syndromic and non-syndromic disorders, the latter including autosomal recessive congenital ichthyosis (ARCI), comprising harlequin ichthyosis, lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE) and keratinopathic ichthyoses (KPI). KPI is an umbrella term for ichthyoses caused by keratin mutations, namely epidermolytic ichthyoses (EI), superficial EI and other minor variants.

To date, mutations in more than 50 genes are known to result in various types of ichthyoses with a multitude of mutated alleles. Large cohort studies reporting pathogenic variants usually do not describe the clinical course of the disease.

To determine the severity of ichthyosis, several score systems exist, among them the validated Congenital Ichthyoses Severity Index evaluating scaling, erythema and alopecia, and the Ichthyosis Area Severity Index (IASI), including scaling and erythema referring to the affected body area. These scores offer reliable methods in satisfying the need for clinical evaluation but have some limitations regarding palmoplantar involvement.

This study outlines the natural history of a series of consecutive paediatric cases with non-syndromic congenital ichthyoses, including ARCI and KPI. We used retrospective observational follow-up data, with a focus on the course of disease severity and genotype-phenotype correlations.

Materials and methods

Patients and clinical follow-up

Thirty-two consecutive cases with non-syndromic congenital ichthyoses born between 2011 and 2020 referred to the Department of Dermatology were included in this retrospective study. Ethical approval was obtained from the University of Freiburg (EK-Dermatology were included in this retrospective study. Ethical approval was obtained from the University of Freiburg (EK-12294/2020). The current mean age is 4.1 years (49.6 months, range 7–120 months), and the gender distribution almost equal (17 female and 15 male). Nineteen cases were of German descent, four originated from Eastern Europe and nine from the Middle East. Consanguinity was reported in nine families.

In the first year of life, follow-up visits took place every 3 months and thereafter every 6 or 12 months, depending on the clinical severity. All patients received topical moisturizing therapy containing ingredients such as glycerol, dexpanthenol, and after the age of 1 year, 3–10% urea creams. Antiseptics were used as cleansing lotions either once per week, or daily, during episodes of cutaneous infections. Topical corticosteroids were only sporadically used during episodes of eczema. Systemic therapy with acitretin was initiated in the most severely affected cases, but discontinued due to fear of the parents of adverse events in all, except of one case (case 32 in Table S1, Supporting Information).

Bodyweight measurements at several time points were retrieved from patients’ records, and percentiles were calculated according to the WHO Child Growth Standards. A representative value was used for evaluation at an age that corresponds to the second score for cutaneous manifestations (see below). The patients in this manuscript have given written informed consent to publication of their case details.

Scoring of cutaneous manifestations

Cutaneous manifestations were described in the patients’ records, photographically documented and quantified using a modified IASI (mIASI) score at an early visit, and at a later time point on follow-up examinations (designated as IASI/mIASI-1 and -2) by at least two examiners. mIASI-1 was calculated during the initial consultation after shedding off the collodion membrane, while mIASI-2 was assessed at an age between 3 and 77 months. Topical moisturizing therapy was performed as usual before the visits. IASI comprised both erythema (IASI-E) and scaling (IASI-S) that were graded into degrees of severity (0 = healthy; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) and multiplied with the percentage of affected area and a default factor (total range 0–48). The mIASI score comprised the sum of IASI-E, IASI-S and a score for palmoplantar involvement. The score for palmoplantar involvement was as follows: 0 = none; 1 = hyperlinearity/focal keratoderma; 2 = 25–75% involvement; 3 = >75% involvement; 4 = presence of rhagades/blistering.

Laboratory investigations

Skin biopsies were not routinely taken from collodion or harlequin babies; in cases 3, 9, 15 and 18, biopsies were obtained in the neonatal period and H&E staining was performed. Biopsies were taken from newborns with KPI and analysed by H&E staining and immunofluorescence antigen mapping to rule out epidermolysis bullosa, and other differentials. Microbiologic swabs were obtained if clinical signs of infection were present. Other laboratory parameters were determined according to the clinical context (e.g. suspected atopy, acitretin treatment).

Molecular genetic analyses

After informed consent, genetic testing was performed at the Institute for Human Genetics or Genetikum® Stuttgart/Neu-Ulm using Sanger or next-generation sequencing (NGS) with custom designed multiple-gene panels as previously described. In brief, genes associated with Mendelian disorders of cornification were analysed by NGS using an Agilent HaloPlex or SureSelect Custom Kit (Agilent, Santa Clara, CA, USA) on an Illumina MiSeq (Illumina, San Diego, CA, USA).

In case 15, quantitative real-time PCR was performed to detect a monoallelic large deletion in PNPLA1. To analyse the consequences of the genetic variants in case 29, total RNA was isolated from skin sections and reverse-transcriptase PCR was performed.
performed for KRT10 and GAPDH (as a loading control). Amplicons were cloned into the TOPO-TA vector and Sanger sequenced as described before.⁹

**Statistical analysis**

Statistical analysis and visualization of the results were done using GraphPad Prism version 9.0.0 (GraphPad Software, La Jolla, CA, USA). Statistical analysis was performed using the Wilcoxon–Mann–Whitney test calculating P-values. The significance level was set at 0.05. For measurements of linear dependence, Pearson correlation was calculated by GraphPad Prism version 9.0.0 (GraphPad Software).

**Results**

**Genetic basis and clinical manifestations at birth**

This study included 32 patients, 25 with ARCI and seven with KPI (Table S1, Supporting Information). The genetic basis was disclosed in all except of case 23, in whom the family did not agree with testing. Pathogenic variants were found in the following genes: ALOX12B (4/31), ALOXE3 (6/31), CERS3 (2/31), CYP4F22 (2/31), PNPLA1 (2/31), NIPAL (1/31), TGM1 (3/31), SDR9C7 (1/31), SLC27A4 (1/31), ABCA12 (2/31), KRT1 (5/31) and KRT10 (2/31).

Within the ARCI group, 20 patients for whom information was available were born with a collodion membrane (for cases 5, 17 and 21 no information available). Patients with premature termination codon mutations in ABCA12 were born as harlequin babies covered with plates of thick scales. At birth, KPI patients presented with blisters and erosions and in some cases even with erythroderma and were suspected to suffer from epidermolysis bullosa. Five patients (cases 3, 7, 9, 22, 32) of this cohort were born preterm.

**Clinical course and natural history**

To assess the clinical severity and the course of ichthyosis in our patients, we determined mIASI scores at two different time points during the observation period (Fig. 1a, Table S2, Supporting Information). mIASI-1 was evaluated in most of the cases shortly after birth or at the first visit (mean age 7.8 months, range 1–56). mIASI-2 was surveyed within the first (13/32) or within the second (6/31) year of life, or at a later time point (mean age 22.6 months, range 3–77 months). One case (number 10 in Table S1, Supporting Information) was lost from follow-up.

In 74.1% of our patients (23 of 31), mIASI decreased in the follow-up (median mIASI-1 18.8 versus mIASI-2 8.6, P = 0.0002; Fig. 1b). Especially in eight of the 10 patients with ALOX12B and ALOXE3 mutations, a significant decrease in the mIASI score with a drop of more than 10 points was noted (for ALOX12B median 14.7 vs. 8.9, P = 0.02, and for ALOXE3 20.9 vs. 7.6, P = 0.02). The cutaneous condition of only one patient, case 9, with a homozygous premature termination codon ALOXE3 mutation worsened after birth and evolved into a LI (score 8.2 vs. 17.4). mIASI scores increased in four of five patients with KPI due to KRT1 mutations (median 17.5 vs. 20.3, P = 0.89). In one of the two harlequin babies, systemic retinoids (acitretin 1–0.7 mg/kg) were administered, leading to a significant improvement of cutaneous condition (mIASI 52 at 1 day, 20.6 at 3 months).

Since hands and feet are particularly important for daily activities, including walking, we additionally evaluated palmoplantar involvement separately (Fig. 1c,d). Eight patients had marked palmoplantar dryness manifesting as hyperlinearity and scaling, without functional impairment, but need for frequent application of moisturizers. Patients with LI and TGM1 mutations demonstrated large adherent scales on hands and feet accompanied by recurrent fissures, leading to pain and functional restraints. The highest scores of four points were reached by patients with KRT1 and ABCA12 mutations. These children had limited mobility, severe pain and started walking later. Scores for palmoplantar involvement increased during the observation period, although the difference did not reach statistical significance.

In general, more severely affected patients, especially those with TGM1, KRT1, ABCA12 mutations, often suffered from recurrent infections (intertrigo, impetigo, folliculitis), but even patients with mild scaling developed cutaneous infections. Hypohidrosis, pruritus and recurrent episodes of eczema were noticed in ARCI patients, including those with a considerable mild skin involvement (Table S1, Supporting Information).

The majority of patients showed constant weight gain and maintained their percentile ranks in accordance with the WHO growth standards for children during the observation period. Five children (16.6% of 30 cases for whom data were available) grew below the 3rd percentile of weight; they had either ABCA12, TGM1 or KRT1 mutations. Case 22 (3rd percentile of weight) had a developmental delay of unknown aetiology. A significant negative correlation (Pearson correlation –0.39) was observed between weight (at a mean age of 27.2 months) and mIASI score (at a mean age 22.6 months; P = 0.03; Fig. 1e).

**Genotype-phenotype correlations**

Five distinct cutaneous phenotypes were seen in our ARCI patients (Fig. 2a). The classical forms, LI (five patients with TGM1, CERS3 or ALOXE3 mutations) and CIE (two patients with ALOXE3 and PNPLA1 mutations, respectively) were observed in only seven cases. Fifteen children (65.2% of 23 ARCI cases) had self-improving, mild ichthyosis with fine scaling, one case (19) had bathing suit ichthyosis, and case 17 had a peculiar phenotype resembling keratoderma variabilis. Hence, the largest group designated here as mild ‘fine scaling congenital ichthyosis’ had a broad heterogeneous genetic background (Fig. 2a). These patients designated as ‘self-healing
collodion babies’ according to the 2010 classification system,2 presented with fine scaling without erythroderma; when moisturizers were regularly applied, the phenotype resembled ‘dry skin’ (cases 1–3, 5–8, 10, 12–14, 16, 21–23 in Table S1, Supporting Information, Fig. 2b). These patients had combinations of missense and non-sense mutations or splicing mutations, some of them being already reported in cases with self-improving ichthyosis (e.g. ALOX12B – p.Tyr521Cys, ALOXE3 – p.Pro630Leu, p.Arg234Ter10). Due to this mild ichthyosis phenotype, four families did not request prenatal diagnosis for subsequent pregnancies.

As a disease modulating factor, we identified an additional heterozygous FLG mutation in case 13, who suffered from recurrent eczema, while his sister, case 14, with the identical homozygous mutations in CYP4F22, demonstrated a mild scaling phenotype (Fig. 2c).

Case 17 with a phenotype that resembled keratodermia variabilis had light brown keratotic plaques and discrete scaling that changed and ‘moved’ over time (Fig. 2d). Skin involvement in this patient was considerably mild, with large areas for ‘normal appearing’ skin, and gradual improvement with age (Fig. 2d). His heterozygous NIPAL4 variant c.520+3A>G has only been

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**Figure 1** Clinical course of non-syndromic congenital ichthyosis in children. (a) miASI scores for two different time points depending on the genotype. (b) In most cases, miASI scores decreased during the observation period between time point 1 and 2. (c) Assessment of palmoplantar involvement at time point 1 and 2. (d) Representative pictures of palmoplantar involvement. The patient’s number, affected gene and palmoplantar score are indicated in each panel. (e) Negative correlation between weight percentile and miASI-2. The red line indicates the 3rd percentile; the blue line represents the linear regression (Pearson r = −0.39).
reported in a heterozygous state with a minor allele frequency of 4.014e-6 (Genome aggregation database). On the other allele, c.527C>A, p.Ala176Asp was found, which is recurrent in ARCI patients.\textsuperscript{11}

While patients with KRT1 mutations demonstrated severe phenotypes that rather aggravated over time (median mIASI-1 17.5 vs. mIASI-2 20.3), patients with KRT10 mutations demonstrated a decrease in severity (median mIASI-1 22.6 vs. mIASI-2

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**Figure 2**  Genotype-phenotype correlations. (a) Phenotypes in autosomal recessive congenital ichthyosis patients; BSI, bathing suit ichthyosis; CIE congenital ichthyosiform erythroderma; FS, fine scaling; KV-like, keratodermia variabilis-like; LI, lamellar ichthyosis. (b) Clinical pictures of mild fine scaling ichthyosis which was observed in 15 cases. The patient number and the affected gene are indicated. The inset shows a magnification. (c) Siblings, cases 13 and 14 with CYP4F22 mutations and divergent phenotypes due to an additional heterozygous FLG mutation. (d) Case 17 with mutations in NIPAL4 resembling the phenotype of keratodermia variabilis. Note the sharply demarcated keratotic plaques and the ‘normal’ surrounding skin. (e) Left, self-improving autosomal recessive keratinopathic ichthyoses was caused by compound heterozygous KRT10 mutations c.867G>A, p.Glu289= and c.1203T>A, p.Cys401Ter. right, RT-PCR with cDNA generated from the skin of the patient (P) and normal skin (Co), and primers spanning KRT10 exon 3. Note the bands marked by arrow representing the larger amplicons in the patient. TOPO cloning revealed the retention of intron 3 (corresponding to the upper band), the weak lower band could not be resolved. Amplification of GAPDH was used as loading control. The lower graph shows the schematic representation of KRT10 exons. The variant c.867G>A led to aberrant splicing (with arrow in the right panel), inclusion of 87 nucleotides if intron 3 (light grey i3) in the reading frame, and premature termination codon formation (red arrow).
7.0). However, they still had hyperkeratotic and recurrent erosive lesions. Noteworthy, case 29 had biallelic KRT10 mutations, c.867G>A, p.Glu289= and c.1203>T>A, p.Cys401Ter and demonstrated a self-improving course with pruritus and mild scaling on the neck as the only symptoms at the age of 1 year. The variant of uncertain significance, c.867G>A, p.Glu289=, is located in the last nucleotide of exon 3 and is predicted to disturb the canonical donor splice site (confidence from 0.3 to 0, http://www.cbs.dtu.dk/services/NetGene2/). We experimentally proved this prediction by analysing the total RNA from the skin of the patient. Reverse-transcriptase PCR and sequencing showed an aberrant transcript resulting from retention of the 87 nucleotides of intron 3 into the reading frame. Although the reading frame is preserved, intron 3 contains a premature termination codon, p.Glu290Valfs22Ter (Fig. 2e).

Discussion
In this retrospective observational study, about 70% of the children with non-syndromic congenital ichthyosis, and specifically 65% of those with ARCI, demonstrated a spontaneous improvement of cutaneous manifestations. More than 10 years ago, Vahlquist et al. noted that in a minority of ARCI cases, the skin condition will improve spontaneously after birth, although slight scaling, xerosis, hypohidrosis and keratoderma usually persist, and proposed the term 'pleomorphic ichthyosis'. The revised nomenclature and classification of inherited ichthyoses recommended the term 'self-healing collodion baby', as a minor form of ARCI. Both terms are rather confusing: 'pleomorphic' (syn. able to assume different forms, or polymorphic) is unspecific, and 'self-healing' is not correct because the disease does not heal.

In our interdisciplinary genodermatosis centre, patients are clinically enrolled soon after birth, and genetic testing is always proposed. This confirms the molecular genetic diagnosis of cases that might otherwise be lost from follow-up, due to the favourable course and mild symptoms. The genetic spectrum of ‘fine scaling congenital ichthyosis’ is broad, suggesting that not only the genetic alteration, but rather the functional consequence of the pathogenic variant dictates this phenotype. Indeed, genetic variants allowing residual protein expression and function, such as amino acid substitutions and splicing mutations, were found in our study. We believe that this ‘self-improving’ phenotype remains underdiagnosed and deserves a proper name and suggest ‘fine scaling congenital ichthyosis’. From a pragmatic point of view, as compared to ‘self-improving’, ‘self-healing’ or ‘pleomorphic ichthyosis’, this term is better suited to designate the disease in patients’ medical records.

In accordance with the mild cutaneous involvement, most of our affected children were within normal weight range. This is in contrast with a recent study describing malnutrition in ichthyosis patients, but those patients were also severely affected by their skin condition suggesting a greater risk of malnutrition in severe cases.13 The relatively high rate of cases with ‘fine scaling congenital ichthyosis’ in this study, in contrast to other case series,14–16 might be a bias of the small number of cases. Other limitations of our study are the retrospective character and the real-life setting with evaluations at various time points.

Another ‘self-improving’ phenotype was observed in case 29 with autosomal recessive KPI who displayed mild skin fragility and xerosis as the main features caused by biallelic KRT10 mutations. Skin fragility manifested as erosions after skin scratching. Discrete grey-brownish scales on the neck were the only ichthyosis feature. In contrast, reported cases of autosomal recessive KPI had a severe, even lethal course.17–22 The mild clinical course suggests that a residual amount of keratin 10 polypeptide is expressed in the skin of our patient despite two predicted null mutations. We hypothesize that the variant c.867G>A induces a leaky splice site which becomes partially functional, allowing synthesis of residual full-length keratin 10 polypeptide and subsequent self-improving ichthyosis. Such leaky mutations have been previously reported in other genes and were associated with milder-than-expected phenotypes.23–25 Also, cases that improved from severe to mild disease due to splicing modulation have been reported before.26 Altogether, the scoring system mIASI proved to be a useful tool for objective assessment of the disease severity in the clinical routine, being easy and fast to calculate. Scoring the palmoplantar involvement might be important, in particular in patients with severe forms of non-syndromic congenital ichthyosis due to pathogenic variants in TGM1, ABCA12 and KRT1. Palmoplantar lesions impact walking and all daily activities and require specific therapy. Nevertheless, validation of this scoring system is required.

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Author contributions
LF collected and analysed the data and drafted the manuscript together with CH; CH planned the study, analysed the data and drafted the manuscript; JF provided expert validation of the data; JF, JK, BZ and AH performed genetic testing and reviewed the genetic data and the manuscript; AK, SH, FC and ART collected data and reviewed them and the manuscript.

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Self-improving ichthyosis phenotypes in children

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Genetic and clinical features.
Table S2. Overview of IASI-scores.