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ORIGINAL ARTICLE

Quality of life and clinical characteristics of self-improving congenital ichthyosis within the disease spectrum of autosomal-recessive congenital ichthyosis

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Abstract

Background Autosomal-recessive congenital ichthyosis (ARCI) is a heterogeneous group of ichthyoses presenting at birth. Self-improving congenital ichthyosis (SICI) is a subtype of ARCI and is diagnosed when skin condition improves remarkably (within years) after birth. So far, there are sparse data on SICI and quality of life (QoL) in this ARCI subtype. This study aims to further delineate the clinical spectrum of SICI as a rather unique subtype of ARCI.

Objectives This prospective study included 78 patients (median age: 15 years) with ARCI who were subdivided in SICI (n = 18) and non-SICI patients (nSICI, n = 60) by their ARCI phenotype.

Methods Quality of life (QoL) was assessed using the (Children's) Dermatology Life Quality Index. Statistical analysis was performed with chi-squared and *t-Tests*.

Results The genetically confirmed SICI patients presented causative mutations in the following genes: *ALOXE3* (8/16; 50.0%), *ALOX12B* (6/16; 37.5%), *PNPLA1* (1/16; 6.3%) and *CYP4F22* (1/16; 6.3%). Hypo-/anhidrosis and insufficient vitamin D levels (<30 ng/mL) were often seen in SICI patients. Brachydactyly (a shortening of the 4th and 5th fingers) was statistically more frequent in SICI (P = 0.023) than in nSICI patients. A kink of the ear's helix was seen in half of the SICI patients and tends to occur more frequently in patients with *ALOX12B* mutations (P = 0.005). QoL was less impaired in patients under the age of 16, regardless of ARCI type.

Conclusions SICI is an underestimated, milder clinical variant of ARCI including distinct features such as brachydactyly and kinking of the ears. Clinical experts should be aware of these features when seeing neonates with a collodion membrane. SICI patients should be regularly checked for clinical parameters such as hypo-/anhidrosis or vitamin D levels and monitored for changes in quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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Introduction

Autosomal-recessive congenital ichthyosis (ARCI) is a heterogeneous group presenting at birth (OMIM ARCI 1-14).[1] The prevalence of ARCI in the German population is approximately 1.7 : 100.000.[2] The major subtypes of ARCI are lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE). Harlequin ichthyosis (HI; OMIM 242500) is very rare but considered to be the most severe and potentially fatal form of ARCI. Newborns with ARCI often present a collodion membrane at birth. Apart from the characteristic cracking and recurrent peeling of the collodion membrane, these neonates often exhibit eclabium and ectropion. In some cases, the skin spontaneously improves considerably after birth and only discrete residual scaling, xerosis cutis and/or hypo-/anhidrosis persist (Fig. 1).[1] These conditions are described inconsistently in the literature as self-improving collodion or congenital ichthyosis (SICI), self-healing collodion baby (SHCB) or pleomorphic ichthyosis.[3,4] SHCB with complete healing is associated with mutations in *TGM1*, the gene for transglutaminase-1 (OMIM 242300).[5]

More than 12 genes have been identified in ARCI patients encoding among others, transport proteins of the lipoxygenase pathway, cross-linking proteins and proteins involved in formation of the cornified lipid envelope in the stratum corneum (OMIM ARCI 1-14; Appendix S1, Supporting Information).

The phenotype of ARCI can be very diverse ranging from mild or localized to generalized scaling and mild to severe erythema, respectively. Some forms of ARCI show severe, dark brown and coarse scaling as usually seen in patients with *TGM1* mutations. In addition to clinical key characteristics such as scaling, itching or reduced ability to perspire, further characteristics were recently described. Patients with *ABCA12* (OMIM 242500) mutation demonstrated hand deformities such as brachydactyly of the 4th-5th fingers (Fig. 2), and patients with *ALOX12B* (OMIM242100) mutation showed ear helices anomalies – known as overfolded ear or kink of the ear's helix (Fig. 3).[6]

Although Vahlquist *et al*.[4] showed associations between SICI and mutations in *ALOX12B* and *ALOXE3*, data on SICI as a characteristic clinical variant within the ARCI spectrum are still limited.

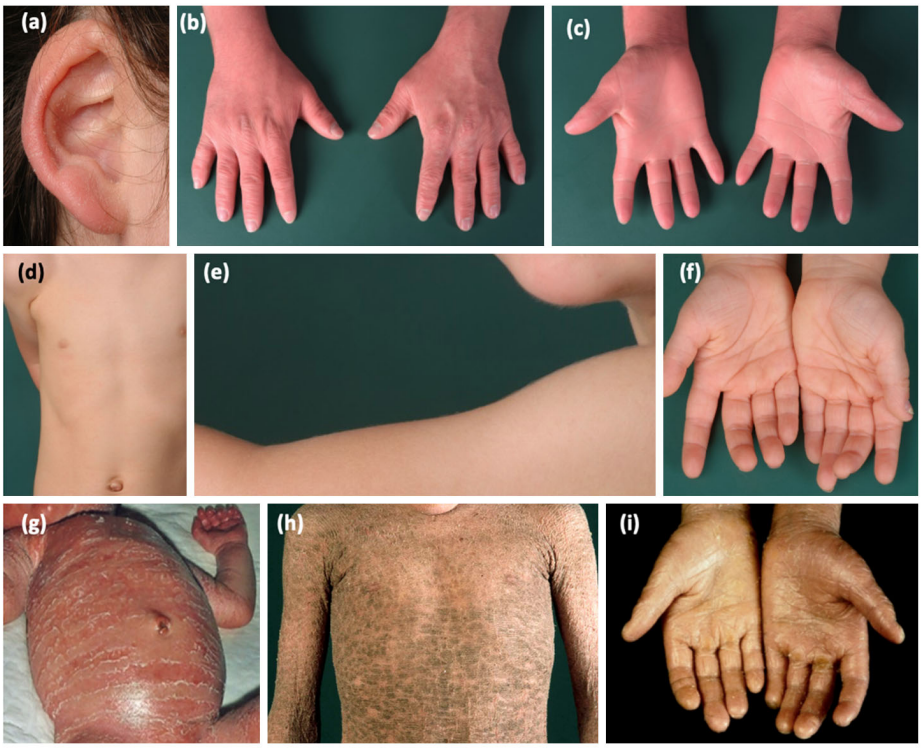

Figure 1 Ear configuration, brachydactyly and palmoplantar phenotype in ARCI patients. ARCI patients with *ALOXE3* mutation (b, c) with typical kinking ear (a), brachydactyly of the 5th finger (b) and palmar hyperlinearity (c); patient with SICI and *ALOXE3* mutation (d–f), patient shows mild scaling (xerosis cutis) and aspects of atopy. Collodion membrane at birth (g) and lamellar ichthyosis (h) with mild palmar hyperlinearity (i). Parts of Fig. 1 were published before.[1]

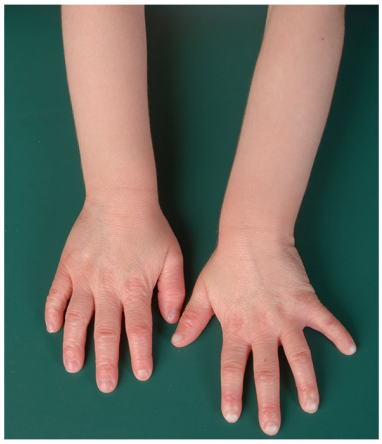

Figure 2 Brachydactyly of the 5th finger.

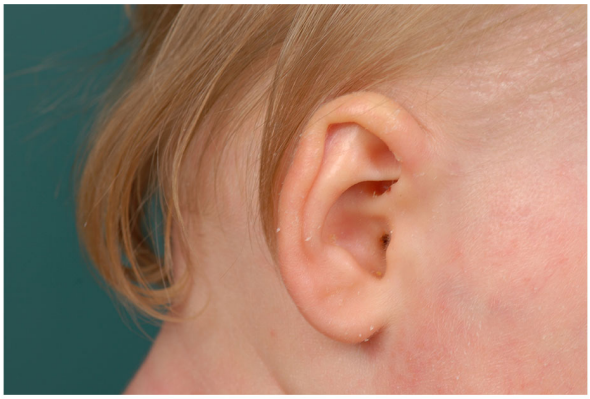

Figure 3 Ear configuration in a patient with SICI and *ALOX12B* mutation.

To identify possible associations, we analysed 78 ARCI patients and conducted a systematic study to determine whether clinical features of the SICI phenotype differ from other ARCI subtypes and whether these are associated with certain subsets of gene mutations.

Considering the spectrum of disease expression, there are no data on psychological strain and personal burden of the SICI subtype. Therefore, we studied the quality of life (QoL) in ARCI and the SICI subgroup using established tools.

Materials and methods

This study was conducted according to the Declaration of Helsinki principles and approved by the institutional review board of the University of Münster (2XTrau1). All patients gave their informed consent and were prospectively enrolled in the registry of the network for ichthyoses and related keratinization disorders (NIRK registry).

This study included 78 patients with ARCI. Clinical diagnosis was consistently assessed >24 h after last topical treatment by two dermatologists of the Reference Center for Ichthyoses and Palmoplantar Keratoses (ReCIP) in Münster. A third physician independently evaluated photographs of these patients. In all cases, the diagnosis of ARCI was made by clinical means, and in 87.2% (68 cases), diagnosis was confirmed by molecular genetic analysis.

Concerning the phenotyping, we defined the following clinical subtypes: CIE, LI, HI, bathing suit ichthyosis (BSI), SICI and SHCB. These subtypes were based on specific clinical criteria as seen in Table 1. Since we had no patients with complete healing, the subgroup of SHCB was not the subject of this study.

For phenotyping of our cohort, all subtypes were additionally checked for specific characteristics (prematurity, consanguinity, brachydactyly (shortening of the 4th and 5th fingers), a kink of the ear's helix, hypo-/anhidrosis (reduced or lack of ability to perspire), joint pain, itch, insufficient vitamin D levels, gene mutations). Clinical data were collected during a clinical visit and by a questionnaire designed by the ReCIP. The questionnaire assessed criteria like hypo-/anhidrosis or frequency of itch with a verbal rating scale (VRS). Then, the SICI subgroup was compared with the non-SICI ARCI subgroups (nSICI).

Data on QoL were collected using the established *Dermatology Life Quality Index* for patients ≥16 years (DLQI) and patients 4–16 years (CDLQI).[7] This questionnaire was answered by the ARCI patients or with the help of their parents (<6 years). It contains 10 questions concerning the daily life (symptoms/feelings, daily activities, leisure, work/school, personal relationships, treatment) of patients with skin diseases to assess the influence of the skin condition on QoL. Each question can be answered with 0–3 depending on the severity. A score between 0 and 30 can be reached – the higher the score, the greater the impairment of QoL.[7] For a better overview in this study, scores were weighted. A score ≤10 indicated a small, and a score >10 indicated a great impairment of QoL.

The data were entered pseudonymously into an Excel table. Statistical analyses were performed using IBM SPSS® Statistics version 26 for Windows (IBM Corporation, Somers, NY, USA). Inter-group comparisons concerning categorical data were made by chi-squared test. *t-Test* was performed to identify differences between the means of QoL in SICI and nSICI patients. All tests of significance were two-tailed, and for each test, a *P*-value ≤0.05 was considered to be statistically significant.

Molecular genetic analysis

In 68 patients with the clinical diagnosis of ARCI, genetic analysis was performed using different sequencing methods including Sanger sequencing or next-generation sequencing (NGS). Most patients of our cohort were genetically analysed at the Institute

Table 1 Patients with ARCI were divided into subgroups: CIE, LI, BSI, SICI, SHCB and HI

Clinical definition	Birth				Clinical course				
	Collodion	Erythroderma	Ectropion	Eclabium	Erythema	Scaling			Scalp abnormalities
						Type	Colour	Distribution	
CIE	±	+++	±	±	Pronounced	Fine	White, grey	Generalized; focally pronounced possible	Scarring alopecia possible
LI	+++	+	+	±	Variable, mild to moderate/–	Coarse, large (plate like)	Brownish, dark	Generalized; focally pronounced possible	Scarring alopecia possible
SICI	±	+	+	±	Mild to moderate	Fine	White	Possibly generalized	-
SHCB	++	±	±	±	–	–	–	–	–
BSI	++	±	±	±	Unusual	Coarse, large (plate like)	Brownish, dark	On warmer skin areas	Scarring alopecia possible
HI	+	+++	+++	++	Very pronounced	Coarse, large (plate like)	White, grey, yellowish	Generalized	Scarring alopecia

Division is based on distinct clinical criteria at birth: collodion, congenital ichthyosiform erythroderma, ectropion, eclabium and in the course of disease: erythema, scaling (type, colour, distribution) and scalp abnormalities.
+++, pronounced; ++, moderate; +, mild; ±, can be present; –, not present

of Human Genetics, Medical Center University of Freiburg, Germany. In all patients, genomic DNA was isolated from peripheral blood lymphocytes, and PCR amplification, Sanger sequencing or NGS methods were performed. All coding exons and flanking intronic sequences of the genes *ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, NIPAL4, PNPLA1, SDR9C7, SULT2B1* and *TGM1* were analysed. In general, Sanger sequencing methods for individual genes were used until 2010-2015, and NGS methods through multi-gene panel testing, either in a targeted way or by whole-exome sequencing, were applied and mutations validated by Sanger sequencing according to methods described in detail previously.[8] In a large part of the cohort, DNA sequences were enriched by a HaloPlex Custom Kit or SureSelect Custom Kit (Agilent Technologies, Inc. Santa Clara, CA, USA). Resulting data were analysed using an in-house bioinformatic pipeline and the commercial software SeqNext (JSI medical systems).

For in silico analysis, we used following bioinformatics tools: Mutation Taster (http://www.mutationtaster.org/),[9] PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/),[10] fathmm v2.3 (http://fathmm.biocompute.org.uk/),[11] SIFT (http://sift.jcvi.org/),[12] Provean v1.1.3 (http://provean.jcvi.org/index.php),[13] NetGene2 v2.4 (http://www.cbs.dtu.dk/services/NetGene2/),[14] NNSplice version 0.9 (http://www.fruitfly.org/)[15] and SSP v2.1 (https://varseak.bio/, developed by JSI medical systems GmbH, Ettenheim, Germany). In addition, the following databases were used: The Genome Aggregation Database version v2.1.1 (gnomAD; http://gnomad.broadinstitute.org/), HGMD® Professional version 2020.3 (http://www.biobase-international.com/product/hgmd), Database of Single-Nucleotide Polymorphisms version build 151 (dbSNP; http://www.ncbi.nlm.nih.gov/projects/SNP/), PubMed (http://www.ncbi.nlm.nih.gov /pubmed/) and ClinVar version December 2020 (https://www.ncbi.nlm.nih.gov/clinvar/).

Results

In this study, 78 subjects with ARCI were enrolled. The median age in this group was 15 years (3–93 years). 62.8% (49/78) were female, and in 16.7% (13/78) consanguinity of the parents was found. We defined five subgroups. The most common phenotype of this group was the LI phenotype (43/78; 55.1%) followed by SICI (18/78; 23.1%), CIE (10/78; 12.8%), BSI (4/78; 5.1%) and HI (3/78; 3.8%). Patients were born prematurely in 26.9% (Table 2).

Mutations were identified in 68 of 78 cases (87.2%). Missing data in 10 samples are due to lack of informed consent for genetic testing. The majority of the causative mutations in the whole cohort were found in *TGM1* 27.9% (19/68) followed by *ALOX12B* 16.2% (11/68), *ALOXE3* 14.7% (10/68), *NIPAL4* 13.2% (9/68), *ABCA12* 13.2% (9/68), *PNPLA1* 7.4% (5/68), *CYP4F22* 5.9% (4/68) and *SDR9C7* mutations 1.5% (1/68; Appendix S2, Supporting Information).

Considering the clinical overlap of CIE and SICI, we divided the overall group into two major cohorts: SICI and nSICI. 18 patients in our cohort were clinically diagnosed with SICI.

Two SICI patients did not undergo gene analysis. The other 16 patients showed *ALOXE3* mutations in eight cases (50%),

Table 2 Demographic data of the study cohort

	n of cases (%)
N	78
Sex (female)	49 (62.8)
Age in years [Median (Q25–Q75)]	15 (9.00–29.5)
≤16	40 (51.3)
>16	38 (48.7)
Prematurity	21 (26.9)
Consanguinity	13 (16.7)
Phenotype	
LI	43 (55.1)
SICI	18 (23.1)
CIE	10 (12.8)
BSI	4 (5.1)
HI	3 (3.8)

ALOX12B in six cases (37.5%) and both *PNPLA1* (6.25%) and *CYP4F22* (6.25%) in one case each. Compared to the nSICI group, no mutations in *ABCA12*, *TGM1*, *NIPAL4* or *SDR9C7* were found (Table 3).

Mutations in *ALOXE3* and *ALOX12B* were statistically more frequent in the SICI subgroup: SICI patients had *ALOXE3* mutations in 8/16 (50.0%) and *ALOX12B* mutations in 6/16 (37.5%) compared with nSICI patients (*ALOXE3* mutations: 2/52; 3.8%, $P < 0.001$ and *ALOX12B* mutations: 5/52; 9.6%, $P = 0.016$). Mutations in *TGM1* were absent in SICI patients (0/16; 0%) but frequent in nSICI patients (19/52; 36.5%; $P = 0.003$). Differences in *CYP4F22, PNPLA1* (both $P = 1.000$) and *ABCA12, SDR9C7* and *NIPAL4* ($P = 0.103$, $P = 1.000$, $P = 0.103$) were not statistically remarkable (Appendix S3, Supporting Information). Exact mutations that were detected in our cohort are shown in Appendix S4, Supporting Information. Both, SICI babies (80.0%) and nSICI babies (82.5%, $P = 1.0$) showed a collodion membrane at birth. In 25.0% SICI patients suffered from ectropion compared to 42.3% of the nSICI group ($P = 0.253$).

The clinical feature brachydactyly (of the 4th and 5th fingers) was significantly different ($P = 0.023$) between SICI patients (10/18; 55.6%) and nSICI patients (13/52; 25.0%). A kinking ear was found in almost half of the SICI patients (8/17; 47.1) compared with 22.2% (12/54) nSICI patients ($P = 0.065$). 82.4% of SICI patients and 91.4% of nSICI patients had hypo-/anhidrosis ($P = 0.374$; Table 4).

Both SICI patients (9/10; 90.0%) and nSICI patients (49/51; 96.1%) showed insufficient vitamin D values without a significant difference between both groups ($P = 0.421$). Subjectively moderate-to-severe itching sensation was observed in 90.9% of SICIs and 71.7% of nSICI ($P = 0.261$; Table 4).

Since itch and hypo-/anhidrosis are common but QoL limiting symptoms in patients with ichthyosis, QoL was measured by evaluating the scores for 47 patients who completed the (C) DLQI questionnaire (SICI $n = 12$, nSICI $n = 35$).

Younger patients who answered the CDLQI questionnaire were between 3 and 15 years old [median age: 9 (Q25–Q75: 6–12.00) years]. The DLQI questionnaire was answered by the older patients [18–93 years, median age: 30 (Q25–Q75: 22.00–47.50) years]. In our cohort, QoL in SICI and nSICI patients was moderately impaired. SICI patients seem to be slightly less affected although the difference was not statistically remarkable (8.17 vs. 10.51; $P = 0.273$).

Both younger SICI and nSICI patients showed a distinctly less impaired QoL (5.44 ± 4.876 vs. 8.45 ± 5.733; $P = 0.228$), whereas older patients in the SICI and the nSICI group scored considerably higher indicating a stronger impairment of QoL (16.33 ± 5.132 vs. 11.46 ± 6.227; $P = 0.207$; Table 5).

Discussion

ARCI is a term for a heterogeneous group of non-syndromic, congenital ichthyoses. SICI is one phenotypic variant of ARCI implying a good prognosis that becomes evident in the first year of life. About 10%–25% newborns with collodion suffer from SICI.[2,4,16,17]

In these cases, the newborns' collodion membrane vanishes significantly within months after birth (Fig. 4).[18] The skin may appear nearly normal. Older SICI infants and adults then present themselves with xerosis cutis or slight scaling.[18] Thus, older patients may be misdiagnosed as common xerosis cutis when the collodion membrane at birth was not recognized properly. It may be useful to screen these patients for additional aggravating mutations such as *filaggrin (FLG)* mutations, which could as well led to xerosis cutis and scaling.[19] Clinically, SICI should be distinguished from ichthyosis vulgaris by the disease onset and course. However, from a genetic point of view, ARCI diagnostic may be combined with a complete *FLG* mutation analysis.[20]

Collodion membranes are found in several genetic types of ichthyosis, and hence, it is important to explain to the parents the different courses of the diseases that may underlie this feature. Therefore, we tried to define a more specific phenotype of SICI, which could support physicians and patients to better describe the course of the disease or decide whether further genetic analysis is needed.

So far, best clinical descriptions of SICI derive from studies from Vahlquist *et al.* (15 Scandinavian SICI patients), from Simpson *et al.* (11 British SICI patients) and recently from Seidl-Philipp *et al.* (13 Austrian SICI patients).[4,6,21] Our study adds the description of 18 SICI patients to this subject.

The most common mutations in our SICI cohort were *ALOXE3* mutations (50.0%) followed by *ALOX12B* mutations (37.5%). Both genes have been described for SICI before and are relatively common in mild types of ARCI.[22,23] Yet, since *ALOXE3* was first described by Vahlquist *et al.* in 2010 in three patients with SICI, this gene seems to be relatively new in association with this form of ARCI.[4] Both genes encode for

Table 3 Overview of the study cohort and analysed clinical and genetical criteria

ID	Age	Sex	Clinical diagnosis	Kink of the ear's helix	Brachy-dactyly	Palmoplan-tar Keratosis	Hyper-linearity	Joint pain	Hypo-/ Anhidrosis	Itch	QoL	insufficient Vitamin D levels	Prema-turity	Related parents	Genotype	Phenotype OMIM number	OMIM phenotype	Addition-al findings
1	32	F	SICI	+	+	+	+	–	+	+	22	+	–	–	ALOXE3	606545	ARCI3	Overlap CIE
2	13	M	SICI	–	–	–	+	–	+	+	2	–	–	–	ALOXE3	606545	ARCI3	
3	7	F	SICI	+	+	–	–	–	+	+		+	–	–	ALOX12B	242100	ARCI2	
4	12	F	SICI	–	+	–	+	–	–			+	–		ALOX12B	242100	ARCI2	
5	22	F	SICI	–	–	–	–	–	+	+	12	+	–	–	ALOXE3	606545	ARCI3	
6	12	F	SICI	–	–	–	+	–	+	+	15	+	+	–	ALOXE3	606545	ARCI3	
7	9	F	SICI		+								–		CYP4F22	604777	ARCI5	
8	9	F	SICI	+	+	+	–	–	+		3		–	–				
9	6	M	SICI	+	+	–	+	–	–		0		+		ALOX12B	242100	ARCI2	
10	11	M	SICI	–	+	–	+	+	+	+	7		+	–	ALOX12B	242100	ARCI2	
11	4	M	SICI	+	+	–	+	–	+	+		+	+	+	PNPLA1	615024	ARCI10	
12	6	F	SICI	+	+	+	+	–	+	+	3	+	–	+	ALOX12B	242100	ARCI2	
13	4	M	SICI	+	–	–	+	–	+		6		–	+				
14	54	M	SICI	–	–	–	+	–	+	+	15	+	–	–	ALOXE3	606545	ARCI3	Overlap CIE
15	12	F	SICI	–	–	+	+	–	+	+	11		–	–	ALOXE3	606545	ARCI3	
16	9	F	SICI	+	+	+	+	–	+	+	2	+	–	+	ALOX12B	242100	ARCI2	
17	24	F	SICI	–	–	–	+	–	+						ALOXE3	606545	ARCI3	
18	10	F	SICI	–	–	+	–	–	–				–		ALOXE3	606545	ARCI3	
19	19	F	LI	–	–	+	+	–	+	+	6	+	–	–	PNPLA1	615024	ARCI10	
20	46	M	LI			+	–	–		+		+	–		ABCA12	601277	ARCI4A	
21	6	M	LI	–	–	+	–	–	+	+		+	–		TGM1	242300	ARCI1	
22	52	F	LI	–	–	+	–	+	–	+	15	+	–	–	NIPAL4	612281	ARCI6	
23	53	F	LI			–	–	+	+	+	11	–	–	–	PNPLA1	615024	ARCI10	
24	15	F	LI	–	–	+	–	–	+	+		+	–		NIPAL4	612281	ARCI6	
25	15	F	LI	–	–	+	–	–	+	+		+	+		NIPAL4	612281	ARCI6	
26	19	M	LI		+	+	–	–	+	+		+	–	–	TGM1	242300	ARCI1	
27	28	F	LI	–	–	+	–	–	+	+	16	+	+	–	NIPAL4	612281	ARCI6	
28	14	F	LI	–	+	+	+	–	+	+	15	+	–	–	NIPAL4	612281	ARCI6	
29	25	F	LI	–	–	+	–	–	+	+	16	+	–	+	NIPAL4	612281	ARCI6	
30	34	M	LI	–	–	–	–	–	+			+	+	–	PNPLA1	615024	ARCI10	
31	28	F	LI	–	–	–	–	–	+			+	+	–	PNPLA1	615024	ARCI10	
32	18	F	LI	–	–	+	–	–	+				–	+				
33	4	M	LI	–	+	+	–	–	+	+		+	+	+	ABCA12	601277	ARCI4A	
34	73	F	LI	–	–	+	–	–	+	+	10	+	+	–				
35	46	F	LI			+	–	+	+	+	14	–	–	–	NIPAL4	612281	ARCI6	
36	22	F	LI	+	–	+	–	–	+	+	16	+	+	–	ALOX12B	242100	ARCI2	
37	32	M	LI	+	+			–	+	+	26		+	–	ABCA12	601277	ARCI4A	
38	3	M	LI	–	–	+	–	–	+	+	4	+	–	–	TGM1	242300	ARCI1	
39	7	F	LI	–		–	+	–	–				–		ALOX12B	242100	ARCI2	
40	93	M	LI	–	–	+	–	–	+	+	6	+	–	–	TGM1	242300	ARCI1	
41	53	F	LI			+	–	–	+		7	+			TGM1	242300	ARCI1	
42	34	F	LI	–	–	+	+	–	+	+	9	+	–	–	NIPAL4	612281	ARCI6	
43	15	M	LI	+	–	+	+	–	+	+	10	+	–	–	SDR9C7	617574	ARCI13	
44	31	F	LI	–		+	–	–	+	+		+	–	–	TGM1	242300	ARCI1	
45	8	M	LI	–	–	+	–	–	+			+	–					
46	5	F	LI	+	–	–	–	–	+	+	12	+	–	–	TGM1	242300	ARCI1	
47	14	F	LI	–	+	+	–	–	+		7	+	+		TGM1	242300	ARCI1	
48	4	M	LI	+	–	–	–	–	–	+		+	–	–	ABCA12	601277	ARCI4A	
49	42	F	LI	–	–	+	–	+	+	+	5	+	–	–	ABCA12	601277	ARCI4A	
50	20	F	LI	–	–	+	–	–	+	+	6	+	+	+	TGM1	242300	ARCI1	
51	19	M	LI	–		+	–	–	+		16	+	–		TGM1	242300	ARCI1	
52	21	F	LI	–	–	–	+	–	+	+	6	+	–					
53	7	F	LI	–	–	+	–	–	+	+		+	+	–	TGM1	242300	ARCI1	
54	4	M	LI	–	–	+	–	–	+	+		+	+	+	TGM1	242300	ARCI1	

Table 3 *Continued*

ID	Age	Sex	Clinical diagnosis	Kink of the ear's helix	Brachy-dactyly	Palmoplan-tar Keratosis	Hyper-linearity	Joint pain	Hypo-/ Anhidrosis	Itch	QoL	insufficient Vitamin D levels	Prema-turity	Related parents	Genotype	Phenotype OMIM number	OMIM phenotype	Addition-al findings
55	60	M	LI	–	–	–	–	+	+	+	9	+	+	–				
56	13	F	LI	+	+	+	+		+				–					
57	20	F	LI	–	–	+	–	–	+	+			–		TGM1	242300	ARCI1	
58	25	F	LI	–	–	+	–	–	+		6	+	+	–	TGM1	242300	ARCI1	
59	27	F	LI	–	–	+	–	–	+		13	+	+	–	TGM1	242300	ARCI1	
60	11	F	LI	+	+	+	+	–							ALOX12B	242100	ARCI2	Overlap SICI
61	6	M	LI	+	+	+	+	–							ALOX12B	242100	ARCI2	
62	25	M	HI	+	+	+	–	+	+	+	14	+	–	–	ABCA12	242500	ARCI4B	
63	6	F	HI	–	–	+	–	+	+	+			+	–	ABCA12	242500	ARCI4B	
64	12	M	HI	+		+	–	–	+	+		+	–	–	ABCA12	242500	ARCI4B	
65	15	F	CIE	–	–	+	–	–	+	+	9	+	+	–	ABCA12	601277	ARCI4A	
66	26	F	CIE	–	–	–	+	–	+	+		+	–	–	CYP4F22	604777	ARCI5	
67	35	F	CIE	–	+	+	–	+	+	+	24	+	–	–	ALOX12B	242100	ARCI2	
68	11	M	CIE	+	+	–	+	–	+	+	11	+		+	ALOXE3	606545	ARCI3	
69	65	F	CIE	–	–	–	+	+	+	+	18	+	–	–	CYP4F22	604777	ARCI5	
70	56	M	CIE	–	–	–	+	–	–	+	2	+	–	–	ALOXE3	606545	ARCI3	
71	12	F	CIE	–	+	–	+	–	+	+	19	+	–	–				
72	12	F	CIE	+	+	+	–	–	+	+	3	+	–	–				
73	6	M	CIE	–	–	–	–	–	+	+			–	–	NIPAL4	612281	ARCI6	
74	32	F	CIE	–	–	–	+		+			+		+	CYP4F22	604777	ARCI5	
75	6	M	BSI	–	–	+	–	–	+	+	3	+	–	–	TGM1	242300	ARCI1	
76	12	F	BSI		–	+	–	–	–	+	0	+	–	+	TGM1	242300	ARCI1	
77	29	M	BSI	–	–	–	–	–	+	+		+	–	+	TGM1	242300	ARCI1	
78	18	M	BSI	–	–			–	+	+	4	+	–	–	TGM1	242300	ARCI1	

f, female; m, male; +, present; –, not present; blank cells indicate no data available. Due to the number of patients and different ages, some criteria may be missing.

Table 4 Specific clinical characteristics in SICI and nSICI patients were checked on for delineation of SICI

Clinical criteria	SICI *n* of cases (%)	nSICI *n* of cases (%)	*P*-values
Brachydactyly of the 4th and 5th fingers	10/18 (55.6)	13/52 (25.0)	0.023
Kinking ear	8/17 (47.1)	12/54 (22.2)	0.065
Hypo-/Anhidrosis	14/17 (82.4)	52/57 (91.4)	0.374
Joint pain	1/17 (5.9)	9/58 (15.5)	0.439
Ectropion	4/16 (25.0)	22/52 (42.3)	0.253
Prematurity	4/17 (23.5)	17/55 (30.9)	0.762
Insufficient vitamin D values	9/10 (90.0)	49/51 (96.1)	0.421
Collodion	12/15 (80.0)	33/40 (82.5)	1.0
Consanguinity	4/13 (30.8)	9/46 (19.6)	0.455
Itch	10/11 (90.9)	33/46 (71.7)	0.261
Large effect on QoL (>10)	5/12 (41.7)	16/35 (45.7)	1.0
Less effect on QoL (≤10)	7/12 (58.3)	19/35 (54.3)	1.0

$P \leq 0.05$, level of significance.

lipoxygenases in the same metabolic pathway, and the phenotype of *ALOX12B* mutations is considered to be slightly more severe.[6,23,24]

In one case, we detected a *PNPLA1* mutation. According to Zimmer *et al.*, the prevalence of *PNPLA1* mutations in ARCI is about 3% but has not been reported as a cause of SICI so far.[25] Many of these patients born with collodion membrane improve during lifetime and develop a relatively mild skin condition compared with other ARCI phenotypes varying from (i) generalized lamellar ichthyosis with whitish or brownish scaling, (ii) absent to moderate erythema, (iii) variable occurrence of palmoplantar keratoderma or (iv) hyperlinearity, ectropion and eclabium or folded ear.[6,25–27] Since *PNPLA1* mutations are usually associated with LI or CIE, it is not surprising that a mild phenotype caused by *PNPLA1* mutation is diagnosed as SICI.[16,28]

As previously described in two Spanish SICI patients, one patient in our cohort had a *CYP4F22* mutation.[29] In contrast to other published data, we did not detect *TGM1* mutations in our SICI patients.[4,6]

In retrospect, one patient was positive for *ABHD5* and needed to be reclassified as syndromic ichthyosis and excluded later. Therefore, NLSDI should be considered an important differential diagnosis of ARCI, especially in the context of a SICI disease course.

One of the key objectives of phenotyping of SICI is to predict the later outcome of a baby that is born with a collodion

Table 5 Quality of life in younger (<16 years) and elderly (≥16 years) SICI and nSICI patients

	n of cases (%)	SICI *n* of cases (%)	nSICI *n* of cases (%)
N	47 (60.2)	12 (25.5)	35 (74.5)
Mean score (±SD)	9.91 (±6.338)	8.17 (±6.807)	10.51 (±6.157)
Median (Q25–Q75)	9.00 (5.00–15.00)	6.50 (2.25–14.25)	10.00 (6.00–15.00)
QoL score ≤ 10	26 (55.3)	7 (58.3)	19 (54.3)
QoL score > 10	21 (44.7)	5 (41.7)	16 (45.7)
N < 16 years	20 (42.6)	9 (45.0)	11 (55.0)
Mean score (±SD)	7.10 (±5.447)	5.44 (±4.876)	8.45 (±5.733)
Median (Q25–Q75)	6.50 (3.00–11.00)	3.00 (2.00–9.00)	9.00 (3.00–12.00)
QoL score ≤ 10	14 (70.0)	7 (77.8)	7 (63.6)
QoL score > 10	6 (30.0)	2 (22.2)	4 (36.4)
N ≥ 16 years	27 (57.4)	3 (11.1)	24 (88.9)
Median (Q25–Q75)	12.00 (6.00–16.00)	15.00 (12.00–22.00)	10.50 (6.00–16.00)
Mean score (±SD)	12.00 (±6.226)	16.33 (±5.132)	11.46 (±6.227)
QoL score ≤ 10	12 (44.4)	0 (0.0)	12 (50.0)
QoL score > 10	15 (55.6)	3 (100.0)	12 (50.0)

A score ≤10 indicated a smaller and a score >10 indicated a greater impairment of QoL.

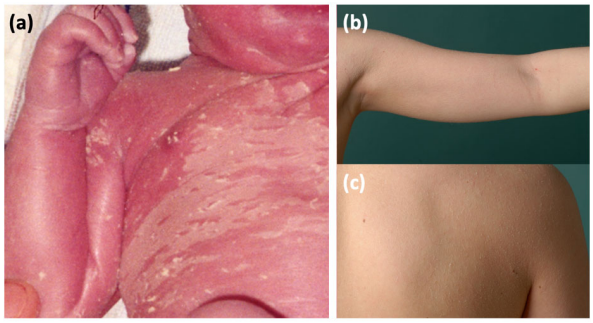

Figure 4 A female patient with SICI. The newborn's collodion membrane vanished significantly within months after birth. At birth (a), the patient presented with erythroderma and collodion membrane. At the age of 21 (b, c), the skin appears nearly normal with mild xerosis cutis and slight scaling.

membrane. Our study identified key features helping to clinically distinguish between SICI and other ARCI phenotypes:

There was a tendency that a kink of the ear´s helix was more frequent in SICI patients than in patients with other ARCI subtypes (47.1% vs. 22.2%, $P = 0.065$). Although the difference was not statistically significant, we assume that in a larger study cohort a stronger association could have been found. Interestingly, a kinking ear was found to be more often in patients with *ALOX12B* mutations (43.8%) compared with other mutations (8.9%; $P = 0.005$). This observation goes along with data from Simpson et al., who described a folded ear in 43% of patients with *ALOX12B* mutations.[6] Hence, a kink of the ear's helix at birth may indicate development of a milder ARCI phenotype in later life.

The clinical feature mild brachydactyly, a short 4th and 5th finger, was significantly associated with SICI patients (55.6% vs. 25.0%, $P = 0.023$). In our study, patients with brachydactyly had an *ALOX12B* mutations in 39.1% of cases. The symptom of mild brachydactyly may be distinguished from more severe hand deformities associated with *ABCA12* mutations as described by Simpson *et al.*[6] Further descriptions of non-syndromic congenital ichthyosis with brachydactyly in the literature are missing. One patient was previously described with a syndromic type of congenital ichthyosis, neurosensory deafness, dental aplasia and also brachy- and clinodactyly.[30] An autosomal-recessive inheritance was assumed but genetic analysis was not performed.

The relatively mild skin findings in SICI patients contrasted with the surprisingly large number of SICI patients suffering from insufficient vitamin D levels (90.0%) and hypo-/anhidrosis (82.4%). In these cases, the mild scaling does not explain the low vitamin D levels. A connection between the existing hypo-/anhidrosis and the resulting avoidance of UV light and heat could be assumed, which can consequently lead to insufficient vitamin D levels. It is remarkable that the difference in severity of skin conditions in SICI and nSICI patients has not led to a significant difference in these two key features.

Among others, hypo-/anhidrosis and itch have been recognized as limiting factors on QoL in ichthyosis.[31] De Palma et al. recently investigated the burden of itch in ichthyosis in a multicentre study.[32] We also found itch very frequently in SICI and ARCI as 90.9% of our SICI patients reported regular itch.

QoL in patients with ichthyosis has been examined with different approaches.[31,33–36] Taken together QoL scores of children and adults, the SICI patients in our cohort seem slightly less affected in QoL compared with nSICI patients. A moderate effect on QoL (score ≤ 10) was evaluated for the majority of

SICI patients (7/12; 58.3%) and likewise for nSICI patients (19/35; 54.3%; $P = 1.0$).

In both the SICI (mean 5.44; small effect on QoL) and nSICI groups (mean 8.45; moderate effect on QoL), the CDLQI score was surprisingly low. These findings are in line with data from a Swedish study which measured a total score of 9.0 for children with congenital ichthyosis, as well as a French study which measured a total CDLQI score of 6.7 for patients with congenital and non-congenital ichthyoses.[34,37] In the whole ARCI cohort, QoL in older patients (≥16 years) was significantly not more impaired than in younger patients (<16 years; 30.0% vs. 55.6%; $P = 0.137$). The mean score in the grown up SICI group was surprisingly high [16.33 (±5.132)]. The higher value may be explained by the very small group of adult patients with SICI and by a strong outlier of one patient.

Our study has the following limitations: Due to the small patient number, which results from the rarity of the disease, *P*-values must be interpreted with caution, although this does not compromise the aim of this study to describe a more distinct phenotype of SICI as a clinical subtype of ARCI.

We conclude that SICI is a considerable phenotype within the heterogeneous group of ARCI with a remarkable percentage within this subgroup. So far, the literature has not paid much attention to SICI. The term SICI is useful to emphasize the spontaneous transition from a severely affected baby with a collodion membrane into a very mild form of ARCI. Considering the situation of clinicians and parents confronted with a collodion baby, the importance of adequate clinical counselling and/or early diagnosis should be emphasized. The impact on QoL in patients with SICI seems to develop less severely than in the rest of ARCI; nonetheless, patients should be monitored for insufficient vitamin D levels and possible hypo-/anhidrosis with tendency to hyperthermia. Still, it does not seem to be possible to predict a specific genotype from the clinical presentation of SICI, but criteria for phenotyping may support further studies to use these distinctive clinical key features and differentiate SICI from other ARCI subtypes.

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Data availability statement

Data available within the main text and Supplementary Materials.

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Supporting information

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

Appendix S1. ARCI phenotypes 1-14 and corresponding OMIM numbers
Appendix S2. Detected gene mutations according to the clinical subgroup of ARCI
Appendix S3. Division of mutations in SICI and nSICI in %
Appendix S4. Overview of mutations of the cohort