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Cross-Sectional Survey on Disease Severity in Japanese Patients with Harlequin Ichthyosis/Ichthyosis: Syndromic Forms and Quality-of-Life Analysis in a Subgroup

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Highlights

- Disease severity correlates with QOL impairment in congenital ichthyosis patients.
- Netherton syndrome is a risk for allergy to food or environmental allergens.
- Keratitis-ichthyosis-deafness syndrome patients are prone to skin infections.

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Cross-Sectional Survey on Disease Severity in Japanese Patients with Harlequin Ichthyosis/Ichthyosis: Syndromic Forms and Quality-of-Life Analysis in a Subgroup

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Conflicts of interest

The authors have no conflicts of interest to declare.

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ABSTRACT

Background

Congenital ichthyoses (CIs) adversely affect quality of life (QOL) in patients. However, the effects of CIs on patient QOL have not been studied sufficiently.

Objective

To investigate the association between disease severity and QOL in patients with harlequin ichthyosis (HI) and ichthyosis: syndromic forms (ISFs)

Methods

Clinical information of patients with HI and ISFs from 2010 to 2015 were obtained from 100 dermatology departments/divisions of principal institutes/hospitals throughout Japan. We examined the relationship between disease severity and QOL in patients with HI and ISFs. Patients who were aged 8 years or older and participated in a multicenter retrospective questionnaire survey in Japan were assessed by dermatology life quality index (DLQI, range of 0 - 30) and clinical ichthyosis score (range of 0 - 100).

Results

Netherton syndrome patients had a significantly higher risk of allergy to food or environmental allergens than patients with other phenotypes. KID syndrome patients

showed a significantly higher risk of skin infections than patients with other phenotypes.

Complete data on DLQI were obtained from 13 patients, whose median age was 21 (8-71) years. Nine patients were male, and 4 were female. Systemic retinoids were administrated to 2 of the 3 HI patients. The Spearman's correlation coefficient between the clinical ichthyosis score and DLQI was 0.611 ($P < 0.05$).

Conclusion

We confirmed that Netherton syndrome and KID syndrome patients have a higher risk of allergy to food or environmental allergens and of skin infections, respectively. QOL impairment correlates with disease severity in HI and ISFs patients.

KEY WORDS

clinical ichthyosis score, harlequin ichthyosis, congenital ichthyosis, ichthyosis: syndromic forms, quality of life

INTRODUCTION

Congenital ichthyoses (CIs) are a group of genetic disorders caused by mutations in genes involved in skin barrier functions. Patients with CI clinically suffer from persistent scaling and hyperkeratosis that are often associated with erythema from birth or the neonatal period.

CIs are divided into two groups: non-syndromic ichthyoses, and ichthyoses: syndromic forms (ISFs) [1]. Non-syndromic ichthyoses have phenotypes that are limited to skin lesions [2]. In contrast, ichthyoses: syndromic forms have phenotypes involving not only the skin, but also other organs [3].

The severity of the skin symptoms varies from mild to severe, depending on the type of ichthyosis and on the particular case/family with the same type of ichthyosis [4]. Harlequin ichthyosis (HI) (OMIM 242500) is the most severe phenotype of non-syndromic ichthyoses [5]. The quality of life (QOL) for CI patients is assumed to be much lower for CI patients than for healthy controls, although the QOL for CI patients varies probably depending on the severity of the overall symptoms. However, few studies have assessed the relationship between disease severity and QOL in patients with CI. Therefore, we investigated the association between disease severity and QOL in patients with HI and ISFs by multicenter retrospective questionnaire-based survey in

Japan.

Furthermore, it is known that Netherton syndrome (OMIM 256500) has characteristics of atopic dermatitis [6, 7] and that keratitis-ichthyosis-deafness (KID) syndrome (OMIM 148210) makes the patient prone to skin infections [8]. Therefore, we evaluated the risks of allergy to food or environmental allergens and the history of skin infections in all the patients involved in the present study.

MATERIALS AND METHODS

Study design

This study was designed as a Japanese cross-sectional observational study. The objective was to assess the correlation between the disease severity and QOL in patients with HI and ISFs. The procedures were in accordance with the Helsinki Declaration of 1975, revised in 1983.

For the cross-sectional observational study in the present study, we distributed preliminary questionnaires to 100 departments/divisions of dermatology or pediatrics at major institutes/hospitals, mainly university hospitals, throughout Japan in September 2015 (Figure 1). The first questionnaire consisted of simple questions to investigate the number of cases with HI and ISFs from 2010 to 2015, and their diagnoses and

treatments. To the departments/divisions from which we received positive answers for the presence of cases with HI or ISFs, we sent a second questionnaire. It consisted of more detailed questions, including a series of questions to evaluate ichthyosis disease severity and DLQI. The physicians were asked to provide detailed clinical information to evaluate the patients' ichthyosis severity; in parallel, patients were asked to complete the QOL questionnaires.

Assessments of ichthyosis disease severity and QOL in the patients

Ichthyosis disease severity was evaluated using a specific clinical ichthyosis score comprised of objective signs of disease (disease extent and intensity) and subjective short-term symptoms (pruritus and pain). The clinical ichthyosis scores ranged from 0 to 100 points, with a high score indicating high disease severity [9]. We interpreted the terms "retraction: hand" and "retraction: foot" in the item "e" of the clinical ichthyosis score [9], as "difficulty in extending the fingers due to severe hyperkeratosis" and "difficulty in extending the toes due to severe hyperkeratosis", respectively. We applied the clinical ichthyosis scoring system to the Netherton syndrome patients, although the patients with Netherton syndrome were excluded from the study in the original paper by Bodemer et al. [9]. We expected that we could evaluate the ichthyosis severity itself

adequately using the severity score even in Netherton syndrome patients, although it might be debatable whether this score assesses the problems of Netherton syndrome appropriately and we cannot completely rule out the effects of coexisting atopic eczema on patients' severity scores. QOL was assessed using translated Japanese editions of the Dermatology Life Quality Index (DLQI), comprising 10 questions evaluating disease impact on key aspects of patient lives [10, 11]. The DLQI scores ranged from 0 to 30 points, with a high score indicating increased QOL impairment [11].

Inclusion and exclusion criteria

All patients who were diagnosed with HI and ISFs (Netherton syndrome, Sjögren-Larsson syndrome (OMIM 270200), Dorfman-Chanarin syndrome (OMIM 275630), KID syndrome, and trichothiodystrophy (OMIM 601675)) were included in the study. The patients with congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome (OMIM 308050) were excluded from the data analysis, because the skin symptoms vary year by year and the disorder shows fluctuations in severity. Infants (< 4 years of age) are difficult to assess by DLQI and were therefore excluded from the analysis. Young children answered the questionnaires with parental/guardian assistance.

Statistical analyses

Variables are expressed as medians (range) or n (%), and they were compared between two groups using the Wilcoxon's rank sum test and Fisher's exact test. The severity scores were compared among the different types of CI using the Kruskal–Wallis test. Correlation analysis was conducted using Spearman's rank correlation coefficient. All P-values were

two-tailed. P-values of < 0.05 were considered statistically significant. All statistical analyses were performed using the SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

General information of the patients with HI and ISFs

Among the 100 departments/divisions of dermatology or pediatrics at major institutes/hospitals throughout Japan to which we sent our preliminary questionnaires, we received responses from 77 institutes/hospitals (77.0 %). Clinical data of 46 patients from 2010 to 2015 were obtained from 27 institutes/hospitals (27.0 %). 3 cases from 3 institutes/hospitals were excluded because the reported phenotypes were lamellar

ichthyosis (LI) (OMIM 146750), erythrokeratoderma variabilis (EKV) (OMIM 133200), and epidermolytic ichthyosis (EI) (OMIM 113800). We distributed the second questionnaires to the remaining 24 institutes/hospitals and received responses from 21 of these institutes/hospitals (87.5 %). 6 patients were excluded because the final diagnosis was neither HI nor ISFs (Figure 1). 3 patients were infants (younger than 4 years of age). Therefore, they were excluded from the analysis. DLQI was not obtained for 14 patients, and they were excluded from the correlation analysis between ichthyosis severity and QOL (Figure 1).

We obtained clinical information of ichthyosis and complications on 30 HI or ISF patients. The clinical data are shown in Table 1. We compared the disease severities among different types of CI, but no significant differences were obtained among them (Table 2).

Allergies and skin infections in the HI or ISFs patients

Among the 30 patients, allergies to food or environmental allergens were observed only in 6 patients (Table 1). All 6 patients were affected with Netherton syndrome and all the Netherton syndrome patients had allergy to food or environmental allergens. Interestingly, none with HI or other types of ISFs were reported to have allergies to food

or environmental allergens. Statistical analysis revealed that the Netherton syndrome patients had a significantly higher risk of allergy to food or environmental allergens than patients with HI and other types of ISFs had (Fisher's exact test, $P < 0.001$) (Table 3). The serum IgE levels were very high in the Netherton syndrome patients, although serum IgE concentration data were obtained from only a limited number of the patients with HI or ISFs other than Netherton syndrome (Table 1).

Concerning skin infections, 6 patients had episodes of cutaneous infection, such as skin abscesses, cellulitis and impetigo contagiosa (Table 1). Of these 6 patients, 4 patients were affected with KID syndrome. Indeed, all 4 of the KID syndrome patients in the present series of HI or ISFs patients had histories of skin infections. In contrast, of the 26 non-KID syndrome patients, only 1 HI patient and 1 Netherton syndrome patient had episodes of cutaneous infections. Statistical analysis confirmed that the KID syndrome patients showed a significantly higher risk of skin infections than patients with HI and other types of ISFs (Fisher's exact test, $P < 0.001$) (Table 4).

Correlation between ichthyosis severity and QOL in HI or ISFs patients

Complete data on the clinical ichthyosis scores and DLQI were obtained from 13

patients, whose median age was 21 (8-71) years. Nine (69.2 %) of the patients were male, and 4 (30.8 %) were female. Patients with each disease numbered 5 for Netherton syndrome, 3 for HI, 2 for Sjögren-Larsson syndrome, 1 for Dorfman-Chanarin syndrome, 1 for KID syndrome, and 1 for trichothiodystrophy. Causative genes were detected in all cases (100 %), 5 of them being *SPINK5* for patients with Netherton syndrome, 3 being *ABCA12* for patients with HI, 2 being *ALDH3A2* for patients with Sjögren-Larsson syndrome, 1 being *GJB2* for a patient with KID syndrome, 1 being *ABHD5* for a patient with Dorfman-Chanarin syndrome, and 1 being *GTF2H5* for a patient with trichothiodystrophy (Table 1) [12-23]. All 13 (100 %) were survivors. Systemic retinoids were administrated to 2 of the patients (15.4 %), both of whom were HI patients and 1 of whom (7.7 %) had received intensive care in a neonatal intensive care unit (NICU). The Spearman's correlation coefficient between the clinical ichthyosis score and DLQI was 0.611 ($P < 0.05$) (Figure 2).

No differences by age ($P = 0.774$ for DLQI, $P = 0.668$ for severity) or sex ($P = 0.535$ for DLQI, $P = 0.757$ for severity) were found between the 13 identified patients with complete data (Table 5). The correlation coefficient and P-value for each question of DLQI and the clinical ichthyosis score were analyzed according to patient age. There were no significant differences between these items for all patients ($N = 13$), nor for

only patients with ISFs except for patients with HI (N = 10) (Supplementary Table 1). We also compared the QOL data of Netherton syndrome patients and HI patients, but there was no significant difference between these two disease patient groups (Table 6).

DISCUSSION

Recently, sensitization to exogenous allergens—not only to environmental ones, but also to food ones—is thought to occur mainly at the skin [24]. In this context, defects in the skin barrier, especially in the stratum corneum barrier, are an important risk factor for allergen sensitization and the occurrence of allergic disorders. Generally, ichthyosis patients have defects in the stratum corneum barrier function [25-27]. If the barrier function deficiency in ichthyotic skin were always to lead to accelerated allergen sensitization, then allergic conditions to exogenous allergens would be seen frequently in the present series of patients with HI and ISFs. However, the history of clinically apparent allergy was obtained only for the Netherton syndrome patients. Concerning the pathogenic mechanisms, patients with Netherton syndrome have a deficiency of serine protease inhibitor LEKTI in the stratum corneum, resulting in increased activity of serine proteases, accelerated desquamation of corneocytes, thinning of the stratum corneum and breakdown of the stratum corneum barrier [6]. In contrast, patients with

other types of HI and ISFs have abnormalities of epidermal lipid synthesis, metabolism and transport as pathogenic genetic causes, except for KID syndrome. KID syndrome patients have aberrantly functioning gap junctions, leading to the abnormal differentiation and proliferation of epidermal keratinocytes, which are the pathomechanisms [8]. Thus, from the results of the present study, we assume that the skin barrier defects due to increased activity of serine proteases are associated with accelerated percutaneous allergen sensitization, but barrier defects in other types of ichthyosis, HI or ISFs other than Netherton syndrome, by the abnormal epidermal lipid synthesis/metabolism/transport or gap junction malfunction, do not increase the risk of clinically apparent allergies. However, the major limitation of this study is that serum IgE concentration, an important marker for allergen sensitization, was measured only in a limited number of the patients with HI or ISFs other than Netherton syndrome, although the serum IgE levels were obviously high in the Netherton syndrome patients (Table 1). Thus, we cannot rule out the possibility of allergen sensitization in other types of CI, even if concomitant allergic diseases were not clinically observed.

As for skin infections, all of the KID syndrome patients had episodes of skin infection, but the patients with HI or other types of ISFs infrequently showed skin infections in the present study. As we mentioned above, patients with KID syndrome have aberrantly

functioning gap junctions and the abnormal differentiation of epidermal keratinocytes [8]. From the results of the present study, we speculate that KID syndrome patients might have skin immunodeficiencies from the decreased production of anti-microbial peptides and cytokines due to keratinocyte differentiation defects.

The clinical findings of the present series of HI and ISFs suggest that, when we take care of Netherton syndrome and KID syndrome patients, we should pay special attention to preventing percutaneous sensitization and skin infections, respectively.

We observed that patients with severe ichthyosis phenotypes also had a lower QOL than patients with milder ichthyosis phenotypes with a statistically significant positive correlation between DLQI and the clinical ichthyosis score ($r = 0.611$). The clinical ichthyosis score was proposed originally by Bodemer et al. to evaluate disease severity in ichthyosis patients [9]. Given these data, it is reassuring to find that decreases in QOL correlate with increases in disease severity in HI and ISFs patients. In addition, paraclinical traits such as age and sex seem not to affect QOL significantly in patients with HI and ISFs. From these findings, the clinical ichthyosis score is appropriate for evaluating the ichthyosis phenotype severity in HI and ISFs patients universally.

Clinical features of patients with HI at birth include severe ectropion, eclabium, flattening of the ears, and large, thick plate-like scales over the entire body [5, 28]. It is reported that loss-of-function mutations in the adenosine triphosphate (ATP)-binding cassette subfamily A member 12 (ABCA12) gene underlie HI [29]. Lack of ABCA12 function leads to the disruption of lamellar granule lipid transport in keratinizing keratinocytes of the upper epidermis [29, 30]. Because of its severe clinical presentations at birth, HI is generally not difficult to diagnose, although detecting the pathogenic mutations in *ABCA12* is the most important diagnostic confirmation [2]. We have to consider the functional consequences of the epidermal barrier defect, such as increased risk of systemic absorption and toxicity, especially in infants [1, 31, 32]. It is sometimes fatal and neonatal death is not rare. Neonates with severe phenotypes require intensive care using humidified incubators to avoid temperature fluctuations and hypernatremic dehydration, and they require observation for signs of cutaneous infection and septicemia [1]. In addition to the appropriate therapy in the NICU, early systemic retinoid treatment has been shown to increase the survival rates of patients with HI [33]. We reported that systemic retinoids and intensive care in the NICU are considered to contribute to relatively good outcomes and high survival rates for HI

patients in the Japanese population [34]. As our former study showed, our data also reveal high survival rates for HI patients (100 %) in Japan who are administered appropriate treatments. Treatment of ichthyoses is usually not type-specific, but rather the goal is to relieve symptoms. Emollients, keratolytics and sometimes oral retinoids are used in most patients [35]. However, pathogenesis-based topical therapis are now available, such as combined lovastatin and cholesterol therapy for CHILD syndrome [36]. Indeed, 7 patients with CHILD syndrome were treated with a topical cream containing 2 % cholesterol and 1 % atorvastatin. The combined atorvastatin and cholesterol therapy improved the patients' skin condition significantly. 25 cases from 6 phenotypes of ICFs were included in the present study. These diseases are rare and the total number of subjects was small. Further studies with larger numbers of CI patients are needed to update and expand our knowledge about CI in order to elucidate the disease nature of CI and to develop effective and innovative treatments. Further studies will clarify how CI adversely affects QOL correlatively with the severity of the ichthyosis phenotype.

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FIGURE LEGENDS

Figure 1. Flow chart of HI and ISFs patients included in, or excluded from, the present analysis.

Initially, clinical information of 36 patients was obtained from throughout Japan, and 13 patients were included in the ichthyosis severity and QOL analysis.

Figure 2. Associations of DLQI with the clinical ichthyosis score in all the HI and ISFs patients with available DLQI.

Plot of the correlation between DLQI (range of 0-30) and the clinical ichthyosis score (range of 0-100). The blue plots represent males and red plots represent females. Impairment of the patients' QOL is positively correlated with CI disease severity. The Spearman's correlation coefficient between the clinical ichthyosis score and DLQI is 0.611 ($P < 0.05$).

Table 1. Clinical and genetic information of all the patients involved in the present study

Patient	Diagnosis	Causative gene	Age	Sex	Clinical ichthyosis score	Serum IgE (IU/mL)	Treatment	Prognosis	Allergy to food or environmental antigens	History of cutaneous infections	Included in the single linear regression
1	HI	*ABCA12*	8	F	72	N/A	ABC	Alive	None	None	Yes
2	HI	*ABCA12*	13	F	38	309	AB	Alive	None	None	Yes
3	HI	N/A	1	F	44	N/A	A	Alive	None	None	No
4	HI	*ABCA12*	1	M	37	N/A	ABC	Alive	None	Skin abcess	No
5	HI	*ABCA12*	27	M	81	N/A	A	Alive	None	None	Yes
6	Netherton syndrome	*SPINK5*	39	M	43	1880	A	Alive	Dogs, cats, crustacea, artemisia, rice bran	None	Yes
7	Netherton syndrome	*SPINK5*	11	M	42	1214.7	A	Alive	Nuts, buckwheat, alchohol	None	Yes
8	Netherton syndrome	*SPINK5*	15	M	16	1283.3	A	Alive	Nuts, buckwheat	None	Yes
9	Netherton syndrome	*SPINK5*	21	F	30.6	78100	A	Alive	Eggs	None	Yes
10	Netherton syndrome	*SPINK5*	23	M	43	54997	A	Alive	Eggs, shrimp	None	Yes
11	Netherton syndrome	N/A	36	F	11.35	N/A	A	Alive	Latex	Impetigo contagiosa	No
12	KID syndrome	*GJB2*	22	M	38.5	N/A	A	Alive	None	Chronicmucocutaneous candidasis	Yes
13	KID syndrome	*GJB2*	33	M	52	N/A	AB	Dead	None	Cellulitis	No
14	KID syndrome	*GJB2*	28	F	40	28	A	Alive	None	Tineas, cellulitis, skin abcess	No
15	KID syndrome	*GJB2*	17	F	31.1	N/A	AB	Alive	None	Impetigo contagiosa	No
16	Sjögren-Larsson syndrome	*ALDH3A2*	65	F	57	N/A	A	Dead	None	None	No
17	Sjögren-Larsson syndrome	*ALDH3A2*	71	F	26	N/A	A	Alive	None	None	Yes
18	Sjögren-Larsson syndrome	*ALDH3A2*	7	M	Insufficient data	N/A	A	Alive	None	None	No
19	Sjögren-Larsson syndrome	*ALDH3A2*	5	F	Insufficient data	N/A	A	Alive	None	None	No
20	Sjögren-Larsson syndrome	*ALDH3A2*	11	M	34	810	A	Alive	None	None	Yes
21	Dorfman-Chanarin syndrome	*ABHD5*	71	M	26.2	N/A	A	Alive	None	None	Yes
22	Trichothiodystrophy	*GTF2H5*	19	M	28.1	N/A	A	Alive	None	None	Yes
23	Trichothiodystrophy	*XPD*	9	M	7.9	N/A	A	Alive	None	None	No
24	CHILD syndrome	*NSDHL*	3	F	21	N/A	A	Alive	None	None	No
25	CHILD syndrome	*NSDHL*	15	F	40	N/A	A	Alive	None	None	No
26	CHILD syndrome	*NSDHL*	44	F	42.4	N/A	A	Alive	None	None	No
27	CHILD syndrome	*NSDHL*	35	F	19.8	N/A	A	Alive	None	None	No
28	CHILD syndrome	*NSDHL*	24	F	23.9	N/A	A	Alive	None	None	No
29	CHILD syndrome	*NSDHL*	15	F	15.6	N/A	A	Alive	None	None	No
30	CHILD syndrome	*NSDHL*	35	F	12.4	N/A	A	Alive	None	None	No

CHILD syndrome, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; HI, harlequin ichthyoses; KID syndrome, keratitis-ichthyosis-deafness syndrome; TARC, thymus and activation-regulated chemokine; F, female; M, male; N/A, not available

Treatments: A, topical treatment; B, oral retinoid; C, intensive treatment in a neonatal intensive care unit

Table 2. A comparison of disease severity scores among the different types of CI

Diagnosis	Number of cases	Median (Range)	*P-value
HI	5	44 (37-81)	
Netherton syndrome	6	36.3 (11.35-43)	
KID syndrome	4	39.3 (31.1-52)	0.129
Sjögren-Larsson Syndrome	3	34 (26-57)	
CHILD syndrome	7	21 (12.4-42.4)	

*P-value: Kruskal-Wallis test. CI, congenital ichthyoses;

CHILD syndrome, congenital hemidysplasia with ichthyosiform erythroderma and limb defects;

KID syndrome, keratitis-ichthyosis-deafness syndrome; HI, harlequin ichthyosis

Table 3. Statistical analysis of the risk of allergy to food or environmental antigens in all the patients involved in the present study

Ichthyosis phenotype	Allergy to food or environmental antigens		
	None	Yes	**Total**
Other	24	0	24
Netherton syndrome	0	6	6
Total	24	6	30

Fisher's exact test: P<0.001.

Table 4. Statistical analysis of the risk of cutaneous infections in all the patients involved in the present study

Ichthyosis phenotype	History of cutaneous infections		
	None	Yes	**Total**
Other	24	2	26
KID syndrome	0	4	4
Total	24	6	30

Fisher's exact test: P<0.001. KID syndrome; keratitis-ichthyosis-deafness syndrome

Table 5. Population characteristics of the patients involved in the correlation analysis between ichthyosis severity and QOL

Variable	DLQI		Severity	
	Median (Range)	*P-value	Median (Range)	*P-value
Age				
< 20 years (N=6)	7.5 (1-20)	0.774	36 (16-72)	0.668
> 20 years (N=7)	7 (1-24)		38.5 (26-81)	
Sex				
Male (N=9)	7 (1-24)	0.535	38.5 (16-81)	0.757
Female (N=4)	8.5 (4-20)		34.3 (26-72)	
Ichthyosis subtype				
ISFs (N=10)	6.5 (1-24)	0.497	32.3 (16-43)	0.063
HI (N=3)	7 (6-20)		72 (38-81)	

*P-value: Wilcoxon rank sum test. DLQI, Dermatology Life Quality Index; HI, harlequin ichthyoses; ISFs, ichthyoses: syndromic forms

Table 6. Comparison of DLQI scores between HI and Netherton syndrome patients

Diagnosis	Number of cases subjected to QOL analysis	Median (Range)	*P-value
HI	3	13 (7-27)	0.1797
Netherton syndrome	5	26 (20-40)	

*P-value: Wilcoxon rank sum test

DLQI, Dermatology Life Quality Index; HI, harlequin ichthyosis; QOL, quality of life

Table 2 for Reviewer. Comparison of disease severity scores among the different types of CI

Diagnosis	Number of cases	Mean±SD	Median (Range)	*P-value
HI	5	54.4±20.6	44 (37-81)	
Netherton syndrome	6	31±14.3	36.3 (11.35-43)	
KID syndrome	4	40.4±8.7	39.3 (31.1-52)	0.129
Sjögren-Larsson Syndrome	3	39±16.1	34 (26-57)	
CHILD syndrome	7	25±11.7	21 (12.4-42.4)	

*P-value: Kruskal-Wallis test. CI, congenital ichthyoses;

CHILD syndrome, congenital hemidysplasia with ichthyosiform erythroderma and limb defects;

KID syndrome, keratitis-ichthyosis-deafness syndrome; HI, harlequin ichthyosis;

SD, standard deviation

Table 6 for Reviewer. Comparison of DLQI scores between HI and Netherton syndrome patients

Diagnosis	Number of cases subjected to QOL analysis	Mean±SD	Median (Range)	*P-value
Harlequin ichthyosis	3	15.7±10.3	13 (7-27)	0.1797
Netherton syndrome	5	29.2±9.2	26 (20-40)	

*P-value: Wilcoxon rank sum test

DLQI, Dermatology Life Quality Index; HI, harlequin ichthyosis; QOL, quality of life; SD, standard deviation

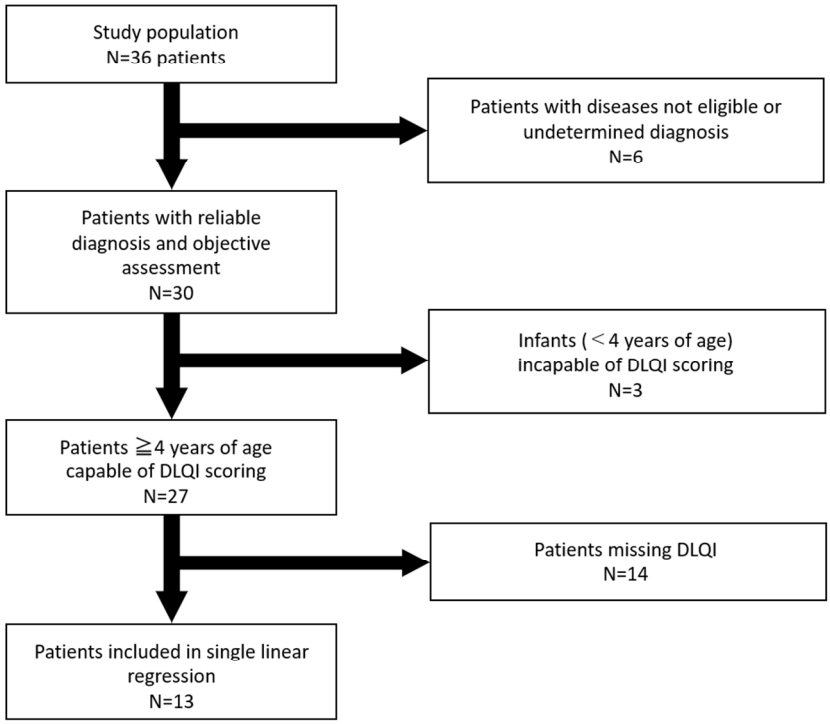

Figure 1. Flow chart of HI and ISFs patients included in, or excluded from, the present analysis. Initially, clinical information of 36 patients was obtained from throughout Japan, and 13 patients were included in the ichthyosis severity and QOL analysis.

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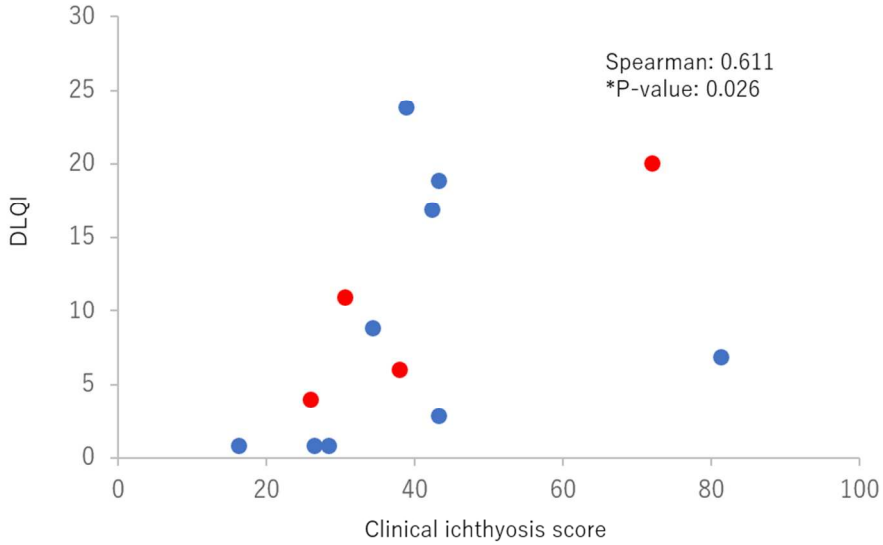

Figure 2. Associations of DLQI with the clinical ichthyosis score in all the HI and ISFs patients with available DLQI.
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