Results of a nationwide epidemiologic survey of autosomal recessive congenital ichthyosis and ichthyosis syndromes in Japan

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Background: Autosomal recessive congenital ichthyosis (ARCI) and ichthyosis syndrome (IS) are rare genetic skin disorders.

Objective: To estimate the number of patients with ARCI and IS in Japan and clarify the clinicoepidemiologic features of these diseases.

Methods: We performed a nationwide survey of patients treated for ARCI or IS during January 2005-December 2009. We developed diagnostic criteria and conducted a primary survey in a stratified random sample of Japanese hospitals to quantify the number of outpatients and inpatients with ARCI or IS. We performed a secondary survey of clinicoepidemiologic features in positive cases.

Results: The estimated number of patients receiving treatment for ARCI and IS during 2005-2009 was 220 (95% confidence interval [CI] 180-260). The estimated disease distribution was as follows: 95 (95% CI 80-110) patients with nonbullous congenital ichthyosiform erythroderma, 30 (95% CI 20-40) with lamellar ichthyosis, 15 (95% CI 10-20) with harlequin ichthyosis, and 85 (95% CI 50-120) with IS.

Limitations: Patients with a mild case of the disease might not have visited a dermatology department, potentially causing underestimation of affected patients.

Conclusion: We report the estimated number of patients with ARCI and IS in Japan and sex differences in the age distribution. (J Am Acad Dermatol 2019;81:1086-92.)

Key words: autosomal recessive congenital ichthyosis; congenital ichthyosiform erythroderma; epidemiology; harlequin ichthyosis; ichthyosis syndrome; lamellar ichthyosis; nationwide survey; nonbullous congenital ichthyosiform erythroderma.

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Autosomal recessive congenital ichthyosis (ARCI) induces scaling, dyskeratosis, erythroderma, and related symptoms of the skin of the entire body. The forms of ARCI include nonbullous congenital ichthyosiform erythroderma (NBCIE), which does not demonstrate bullae; lamellar ichthyosis (LI), with widespread scaling but no erythema; and harlequin ichthyosis (HI), with very hard armor plate-like skin. Ichthyosis syndrome (IS) involves extra-skin manifestations.

Because the number of affected patients is estimated to be low, there are few reports detailing the clinicoepidemiologic features of these diseases. Further, the causes are incompletely described. Thus, appropriate treatments for the different forms of ARCI are lacking.

The Ministry of Health, Labour, and Welfare of Japan defined intractable diseases as rare diseases of unknown etiology without established therapies and has instituted measures to promote intractable disease research. The congenital ichthyosiform and IS disease group was designated as intractable by the Japanese Ministry of Health, Labour, and Welfare in 2008, and the Rare and Intractable Skin Diseases Research Committee established several research projects to investigate the diseases in this category.

In 2013, we reported the results of our nationwide survey of bullous congenital ichthyosiform erythroderma (keratinolytic ichthyosis) in Japan.[1] The objectives of the current study were to estimate the number of patients with ARCI and IS with a primary survey in multiple facilities throughout Japan, to record information from affected patients with a secondary survey, and to clarify the clinicoepidemiologic features of these diseases.

CAPSULE SUMMARY

- Autosomal recessive congenital ichthyosis and ichthyosis syndrome are rare genetic skin disorders.
- About 220 (95% confidence interval, 180-260) patients received treatment in Japan in 2005-2009 for these disorders. The proportion of female patients was higher among patients >10 years of age.
- The results provide important epidemiologic and clinical information on these diseases.

METHODS

Our team and the Research Committee on Epidemiology of Intractable Diseases jointly conducted this descriptive, cross-sectional study. The study protocol was performed in accordance with the Nationwide Epidemiologic Survey manual[2] issued by the committee and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Clinical criteria

Before conducting our survey, we developed diagnostic criteria for congenital ichthyosiform erythroderma (both NBCIE and BCIE), LI, HI, and IS and a secondary survey questionnaire.

Study design and subjects

Our investigation began with the delivery of our primary survey to hospitals throughout Japan. Fig 1 shows the flowchart for the nationwide survey. The dermatology departments in hospitals with ≥20 beds were obtained from a database kept by the Ministry of Health, Labour, and Welfare of Japan. All university hospital dermatology departments and qualified specialist dermatology facilities were included in the study, and general hospitals were selected for participation by random sampling in groups stratified by the number of hospital beds (Supplemental Table I; available at http://www.jaad.org). Sampling rates were approximately 5%, 10%, 20%, 40%, 80%, and 100% in general hospitals with <100, 100-199, 200-299, 300-399, 400-499, and ≥500 beds, respectively. The subjects were patients with NBCIE, BCIE, LI, HI, or IS who received treatment during the 5-year period January 1, 2005-December 31, 2009. We began the primary survey in January 2010 using the diagnostic criteria. The second survey questionnaire was mailed to departments that reported patients who satisfied the primary survey diagnostic criteria. We calculated the estimated number of patients receiving treatment for their disease within the 5-year period using results from our primary and secondary surveys according to the method described in the manual.[1] This method of estimating the number of patients with an intractable disease was used previously in many surveys and found to be valid.[2-15]

The secondary survey data were anonymized so that researchers could not identify individual participants. Informed consent was not obtained from each patient because anonymity was maintained throughout the survey. The Ethical

Abbreviations used:

ARCI: autosomal recessive congenital ichthyosis
BCIE: bullous congenital ichthyosiform erythroderma
CI: confidence interval
HI: harlequin ichthyosis
IS: ichthyosis syndrome
LI: lamellar ichthyosis
NBCIE: nonbullous congenital ichthyosiform erythroderma

Review Board of Juntendo University approved the study protocol (no. 21078, Feb 1, 2010).

RESULTS

Supplemental Table I shows the number of dermatology departments surveyed, the sampling and response rates, and the number of identified cases. From 2878 dermatology departments in Japan, we selected 921 (32.0%) for this study, 157 of which were qualified specialist dermatology clinics. The primary survey showed a response rate of 71.4% (658/921 departments) and identified 148 affected patients (71 with NBCIE, 20 with LI, 11 with HI, and 46 with IS [Supplemental Table I]). The secondary survey response rate was 94.6% (140/148 affected patients). Twenty-one cases were excluded, as they overlapped or did not satisfy the diagnostic criteria (Fig 1). We estimated the number of patients receiving treatment for ARCI or IS in Japan during 2005-2009 to be 220 (95% confidence interval [CI] 180-260); 110 were male patients. The estimated disease distribution was 95 (95% CI 80-110) patients with NBCIE, 30 (95% CI 20-40) patients with LI, 15 (95% CI 10-20) patients with HI, and 85 (95% CI 50-120) patients with IS (Table I). The estimated male:female ratios of patients with NBCIE and LI were both almost 1:1; however, two thirds of the patients with HI were male. There were 35 (95% CI 20-50) male and 50 (95% CI 30-70) female patients with IS. In the primary survey, Netherton syndrome (37%), Sjogren-Larsson syndrome (15%), keratitis-ichthyosis-deafness syndrome (17%), Chanarin-Dorfman syndrome (2%), and others (28%) were reported as IS.

In the 119 secondary survey cases we analyzed, the disease distribution was 59 NBCIE, 16 LI, 8 HI, and 36 IS cases. Table II shows patient age (at the most recent medical consultation) and sex distribution by disease type in the secondary survey. The male:female ratio was 0.83. However, in the subgroup of patients with HI, the male: female ratio was 3.0. Most patients, including all 8 with HI, were <10 years old, but patient age ranged to >60 years. The age distribution of patients with NBCIE and LI showed sex differences, and the proportion of female patients was high among patients ≥10 years of age. Table III shows the clinical manifestations of ARCI and IS by diagnosis. In 29 cases, there was a family history of ARCI or IS. In 100 cases (84.0%), the distribution of skin lesions was generalized. However, the proportion of generalized cases was slightly lower among patients ≥10 years, and the proportion of localized cases was slightly higher. Erythroderma occurred in the majority of NBCIE (76.3% [45]) and HI (75% [6]) cases. The skin scale properties varied by disease type. In NBCIE and IS, most patients had fine scales, accounting for 35 (59.3%) and 21 (58.3%) cases, respectively. In contrast, most patients with LI had large scales (10 cases [62.5%]), and those with HI typically had armor plate-like scales (6 cases [75%]). In all conditions but LI, white scales were most common; white scales were seen in 64.7% (77) of all cases. Among LI cases, the majority of patients demonstrated brown scales (10 cases [62.5%]). Eyelid ectropion was observed in all 8 HI cases, and lip protrusion was present in 6 (75%) HI cases but uncommon in other diseases. Palmoplantar keratosis was observed in more than half of the patients without IS. This sign was seen in 55% (11/20 cases) of patients with IS ≥ 10 years of age. A large percentage of patients with HI had finger constriction (62.5%, 5 cases); however, finger constriction was absent in 79.8% (95) of all cases. Although 104 (87.4%) patients did not have abnormal posture, this sign was identified in at least 10% of patients with HI and IS. Whereas most patients (95 cases, 79.8%) did not have gait disturbance, this sign was observed in at least 10% of patients with a diagnosis other than NBCIE. It should be noted that the proportion of unclassified patients was 10% because patients aged <1 year were included. Collodion baby was found in 39 cases (32.8%). HI accounted for the largest number of cases presenting as collodion baby (6 cases [75%]). Among the 59 patients ≥10 years of age, 9 presented as collodion baby (15.3%). However, the proportion of unknown was >40%. Over the 5-year study period, the mortality rates were 1.7% (1/59) for NBCIE, 25% (2/8) for HI, and 5.6% (2/36) for IS. Of the 5 deaths, all 3 cases of death in babies <1 year of age were in male patients in our survey. Manifestations such as

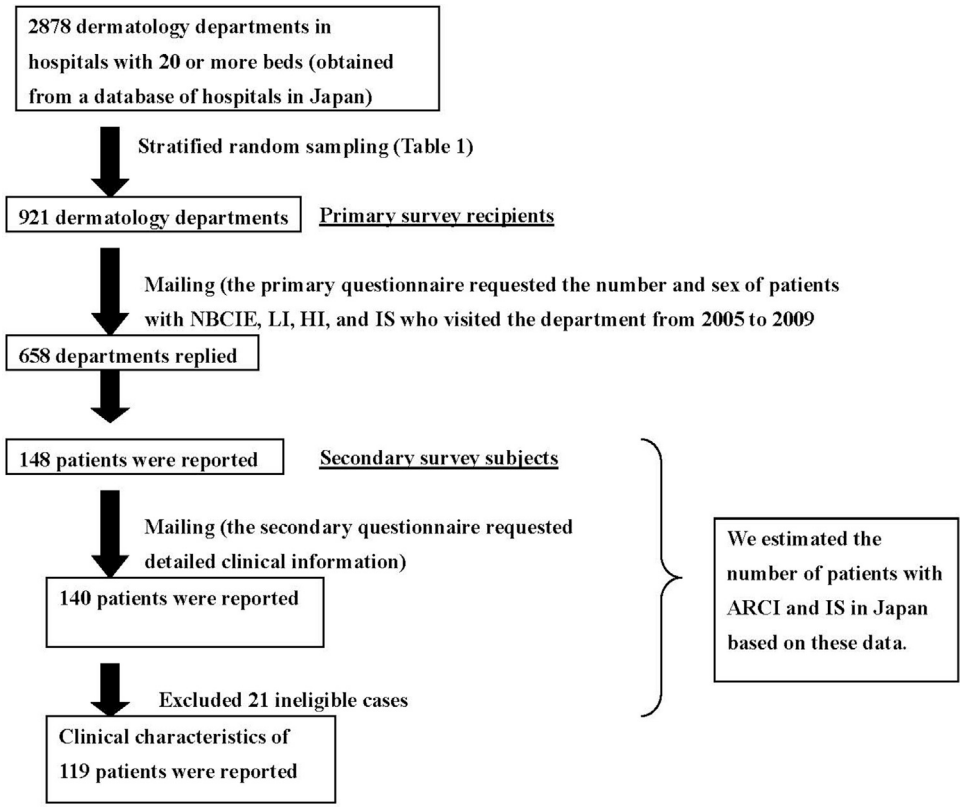

Fig 1. Nationwide survey flow chart for study of ARCI and IS in Japan. *ARCI*, Autosomal recessive congenital ichthyosis; *HI*, harlequin ichthyosis; *IS*, ichthyosis syndrome; *LI*, lamellar ichthyosis; *NBCIE*, nonbullous congenital ichthyosiform erythroderma.

Table I. Estimated number of patients with autosomal recessive congenital ichthyosis and ichthyosis syndrome treated in 5 years

Disease	Estimated no. treated	95% CI
Total	220	180-260
NBCIE	95	80-110
Lamellar ichthyosis	30	20-40
Harlequin ichthyosis	15	10-20
Ichthyosis syndrome	85	50-120

CI, Confidence interval; *NBCIE*, nonbullous congenital ichthyosiform erythroderma.

impaired hearing, small stature, ocular disease, reduced intelligence, hair follicle disease, and shortened limbs were reported in IS cases. Pathologic diagnosis was accomplished in >60% of patients overall, while diagnosis required genetic studies in 51 cases (42.9%). However, in some cases, a definitive diagnosis could not be made, or there was no diagnostic information provided. Arachidonate 12-lipoxygenase R type (*ALOX12B*), ATP-binding cassette subfamily A member 12 (*ABCA12*), and transglutaminase-1 were identified in disease types other than IS. Serine protease inhibitor Kazal type 5 (*SPINK5*), connexin 26, and aldehyde dehydrogenase 3 family member A2 (*ALDH3A2*) were identified in IS.

DISCUSSION

In 2013, we reported the results of our nationwide survey of bullous congenital ichthyosiform erythroderma (epidermolytic ichthyosis) in Japan.[1] The results of our 2 surveys (the previous survey and the current one) revealed the clinical and epidemiologic characteristics of the disease in Japan.

The response rate for the primary survey was relatively high (71.4%) compared with response rates for other nationwide surveys of intractable diseases in Japan, which have ranged 41.0%-66.6%.[3-16] We estimated the number of patients with ARCI and IS over a 5-year period.

Previous studies in Spain[17] and France[18] reported the prevalence of ARCI as 7.2 and 7.0 per million people, respectively. Our survey covered a 5-year

Table II. Patient age and sex distribution by disease type in the secondary autosomal recessive congenital ichthyosis and ichthyosis syndrome survey

	NBCIE		Lamellar ichthyosis		Harlequin ichthyosis		Ichthyosis syndrome		Total	
Age, y*	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
≤9	14	7	6	1	6	2	5	10	31	20
10-19	6	4	1	0	0	0	3	4	10	8
20-29	0	3	0	2	0	0	1	3	1	8
30-39	3	1	1	1	0	0	2	3	6	5
40-49	1	4	0	1	0	0	0	0	1	5
50-59	2	3	0	2	0	0	0	1	2	6
≤60	0	3	0	1	0	0	1	2	1	6
Unknown	1	7	0	0	0	0	1	0	2	7
Total	27	32	8	8	6	2	13	23	54	65

NBCIE, Nonbullous congenital ichthyosiform erythroderma.
*Age at the secondary survey.

period; thus, we cannot estimate the yearly prevalence. However, it appears to be lower than the prevalence found by the 2 studies in Europe.[17,18]

The results of the secondary survey revealed the clinical features by disease type. The sex distribution by disease type in the secondary survey was nearly identical to that in the primary survey. In the secondary survey, the male:female ratio was 0.83. However, in the subgroup of patients with HI, the male:female ratio was 3.0. In other studies in Japan, 57% of affected patients were male,[19] whereas in a survey in the United Kingdom, 46.5% of patients were male.[20] However, as there were few cases of HI, the male predominance we found might not accurately represent the true sex distribution of HI in Japan. In this survey, >40% of patients were <10 years old. This result is similar to that of the Spanish and French surveys.[17,18] All 8 patients with HI were <10 years of age in our survey, which might be because of the high rate of early mortality in this disease. The HI mortality rate in this study was 25% (2 cases). In another Japanese study, the HI mortality rate was 18.7%,[19] while in the UK study it was 44%.[21] Further, some reports indicate that the HI mortality rate is about 50%.[22,23] Of the 5 deaths, all 3 cases of death <1 year of age occurred in male patients in our survey. The age distribution of patients with NBCIE and LI showed sex differences, and the proportion of female patients was high among patients ≥10 years of age. These results could mean that the mortality among male patients is higher than that among female patients.

The clinical manifestations shown in the secondary survey, were consistent with the features described in the Diagnosis Guide issued in 2009 by the Rare and Intractable Skin Diseases Research Committee and a 2010 consensus paper published in the Journal of the American Academy of Dermatology.[24] From the results of this survey, it seems that there are differences in the manifestation of patients <10 and ≥10 years of age. Patients ≥10 years of age had decreased generalized skin lesions and increased localized skin lesions, and the proportion of palmoplantar keratosis was slightly higher. The proportion of collodion babies was lower among those ≥10 years of age, but the proportion of unknown cases was also high. Therefore, it was difficult to elucidate the relationship between collodion baby and mortality.

The limitations of this study should be considered. Clinical features might differ between patients <10 and ≥10 years of age. However, the number of cases in the survey was small and no clear trend was found. In this survey, it was unclear whether there were patients whose disease was becoming mild as they grew older. Patients with mild cases might not have visited a dermatology department. Thus, the survey might have led to an underestimation of the number of affected patients.

In conclusion, we report the estimated number of patients with ARCI and IS in Japan and important epidemiologic and clinical information about these diseases. The age distribution of patients with NBCIE and LI showed a clear sex difference. To clarify the natural history of ARCI and IS, a follow-up study from birth incorporating genetic information is warranted.

We wish to express our deep gratitude to the physicians who participated in the nationwide survey and provided valuable clinical data.

Table III. Clinical manifestations of autosomal recessive congenital ichthyosis and ichthyosis syndrome

Item	NBCIE, N = 59	Lamellar ichthyosis, N = 16	Harlequin ichthyosis, N = 8	Ichthyosis syndrome, N = 36	Total, N = 119
Family history of disease	13 (22.0)	3 (18.8)	2 (25.0)	11 (30.6)	29 (24.4)
Rash distribution					
Generalized	51 (86.4)	13 (81.3)	8 (100.0)	28 (77.8)	100 (84.0)
Localized	7 (11.9)	2 (12.5)	0 (0)	5 (13.9)	14 (11.8)
Unknown	1 (1.7)	1 (6.3)	0 (0)	3 (8.3)	5 (4.2)
Erythroderma					
Present	45 (76.3)	1 (6.3)	6 (75.0)	15 (41.7)	67 (56.3)
None	12 (20.3)	14 (87.5)	2 (25.0)	20 (55.7)	48 (40.3)
Unknown	2 (3.4)	1 (6.3)	0 (0)	1 (2.8)	4 (3.4)
Scales					
Armor plate-like	5 (8.5)	4 (25.0)	6 (75.0)	0 (0)	15 (12.6)
Spiny	0 (0)	0 (0)	0 (0)	1 (2.8)	1 (0.8)
Large	16 (27.1)	10 (62.5)	0 (0)	9 (25.0)	35 (29.4)
Fine	35 (59.3)	2 (12.5)	2 (25.0)	21 (58.3)	60 (50.4)
Unknown	3 (5.0)	0 (0)	0 (0)	5 (13.9)	8 (6.7)
Scale color					
Brown	11 (18.6)	10 (62.5)	1 (12.5)	10 (27.8)	32 (26.9)
White	46 (78.0)	4 (25.0)	5 (62.5)	22 (61.1)	77 (64.7)
Unknown	2 (3.4)	2 (12.5)	2 (25.0)	4 (11.1)	10 (8.4)
Scale shedding					
Yes	43 (72.9)	6 (37.5)	5 (62.5)	16 (44.4)	70 (58.8)
No	11 (18.6)	8 (50.0)	1 (12.5)	18 (50.0)	38 (31.9)
Unknown	5 (8.5)	2 (12.5)	2 (25.0)	2 (5.6)	11 (9.2)
Eyelid ectropion					
Yes	19 (32.2)	4 (25.0)	8 (100)	2 (5.6)	33 (27.7)
No	36 (61.0)	11 (68.8)	0 (0)	31 (86.1)	78 (65.5)
Unknown	4 (6.8)	1 (6.3)	0 (0)	3 (8.3)	8 (6.7)
Lip protrusion					
Yes	7 (11.9)	1 (6.3)	6 (75.0)	0 (0)	14 (11.8)
No	46 (78.0)	14 (87.5)	1 (12.5)	33 (91.7)	94 (79.0)
Unknown	6 (10.2)	1 (6.3)	1 (12.5)	3 (8.3)	11 (9.2)
Palmoplantar keratosis					
Yes	31 (52.5)	8 (50.0)	6 (75.0)	14 (38.9)	59 (49.6)
No	21 (35.6)	7 (43.8)	2 (25.0)	21 (58.3)	51 (42.9)
Unknown	7 (11.9)	1 (6.3)	0 (0)	1 (2.8)	9 (7.6)
Constriction of fingers					
Yes	7 (11.9)	1 (6.3)	5 (62.5)	5 (13.9)	18 (15.1)
No	49 (83.1)	14 (87.5)	3 (37.5)	29 (80.6)	95 (79.8)
Unknown	3 (5.1)	1 (6.3)	0 (0)	2 (5.6)	6 (5.0)
Abnormal posture					
Yes	3 (5.1)	0 (0)	1 (12.5)	4 (11.1)	8 (6.7)
No	53 (89.8)	15 (93.8)	7 (87.5)	29 (80.6)	104 (87.4)
Unknown	3 (5.1)	1 (6.3)	0 (0)	3 (8.3)	7 (5.9)
Gait disturbance					
Yes	4 (6.8)	2 (12.5)	1 (12.5)	5 (13.9)	12 (10.1)
No	51 (86.4)	13 (81.3)	5 (62.5)	26 (72.2)	95 (79.8)
Unknown	4 (6.8)	1 (6.3)	2 (25.0)	5 (13.9)	12 (10.1)
Collodion baby					
Yes	22 (37.3)	4 (25.0)	6 (75.0)	7 (19.4)	39 (32.8)
No	17 (28.8)	3 (18.8)	2 (25.0)	18 (50.0)	40 (33.6)
Unknown	20 (33.9)	9 (56.3)	0 (0)	11 (30.6)	40 (33.6)
Death	1 (1.7)	0 (0)	2 (25.0)	2 (5.6)	5 (4.2)

Values are n (%).

NBCIE, Nonbullous congenital ichthyosiform erythroderma.

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Supplemental Table I. Results of the primary nationwide epidemiologic survey of autosomal recessive congenital ichthyosis and ichthyosis syndrome in Japan

Dermatology department characteristic	No. departments in Japan	No. surveyed departments	Sampling rate, %	No. responding departments	Response rate, %	No. patients reported				
						NBCIE	LI	HI	IS	Total
No. beds										
20-99	999	48	4.8	26	54.2	0	0	0	0	0
100-199	587	56	9.5	26	46.4	0	0	0	0	0
200-299	302	59	19.5	35	59.3	0	0	0	0	0
300-399	323	127	39.3	85	66.9	2	2	0	10	14
400-499	175	139	79.4	99	71.2	6	3	1	6	16
≥500	223	223	100.0	167	74.9	19	2	4	6	31
University hospital	112	112	100.0	102	91.1	42	13	6	20	81
Special facilities	157	157	100.0	118	75.2	2	0	0	4	6
Total	2878	921		658	71.4	71	20	11	46	148

HI, Harlequin ichthyosis; *IS*, ichthyosis syndrome; *LI*, lamellar ichthyosis; *NBCIE*, nonbullous congenital ichthyosiform erythroderma.