Acta Derm Venereol 2003; 83: 24–30

Taylor&Francis
healthsciences

CLINICAL REPORT

Autosomal Recessive Congenital Ichthyosis in Sweden and Estonia: Clinical, Genetic and Ultrastructural Findings in Eighty-three Patients

AGNETA GÅNEMO[1]*, MARITTA PIGG[2]*, MARIE VIRTANEN[1], TERJE KUKK[5], HELI RAUDSEPP[5], INGRID ROSSMAN-RINGDAHL[3], PER WESTERMARK[1], KIRSTI-MARIA NIEMI[4], NIKLAS DAHL[2] and ANDERS VAHLQUIST[1]*

Departments of [1]Medical Sciences (Dermatology) and [2]Genetics and Pathology, Uppsala University, Uppsala, and Departments of Dermatology, [3]Sahlgrenska University Hospital, Gothenburg, Sweden, [4]Helsinki University Central Hospital, Helsinki, Finland, and [5]Tartu University Clinics, Tartu, Estonia

Congenital (non-bullous) ichthyosis is a rare group of keratinizing disorders which can be tentatively subclassified based on clinical criteria, analysis of transglutaminase 1 gene mutations and electron microscopy of epidermis. We studied 83 patients who were all on topical therapy and in 16 cases also on oral retinoids. Three main groups of patients were distinguished: (A) those *with* transglutaminase 1 gene mutations ($n=44$), (B) those *without* transglutaminase 1 gene mutations showing a coarse, generalized scaling ($n=19$), and (C) those *without* transglutaminase 1 gene mutations showing only fine or focal scaling ($n=20$). On clinical scoring, patients in group A were more hyperkeratotic and less erythematous than those in group B ($p<0.05$). Anhidrosis was recorded in nearly all patients ($\geq 80\%$), but ectropion and a collodion phenotype at birth were more common in group A versus other groups. Ultrastructurally, a high frequency of type I (Anton-Lamprecht's classification) was found in all three groups (37–63%), 20 cases of type II in group A and a few cases of types III and IV in groups B and C, respectively. In conclusion, transglutaminase 1 gene mutation is a major cause of congenital ichthyosis in Sweden and Estonia, and is often associated with severe scaling and ultrastructural type II in corneocytes. The transglutaminase-unrelated cases are more heterogeneous, probably reflecting a more varied aetiology. *Key words: electron microscopy; lamellar ichthyosis; transglutaminase 1 mutation.*

(Accepted September 13 2002.)

Acta Derm Venereol 2003; 83: 24–30.

Anders Vahlquist, Department of Dermatology, University Hospital, SE-751 85, Uppsala, Sweden. E-mail: anders.vahlquist@medsci.uu.se

Autosomal recessive congenital ichthyosis (ARCI) is characterized by epidermal hyperkeratosis with widespread scaling and a variable degree of erythema. In contrast, the more common types of non-bullous ichthyosis, autosomal-dominant ichthyosis vulgaris and X-linked recessive ichthyosis are clinically less severe and hardly ever present at birth (1). Depending on the prevailing clinical features, non-syndromic ARCI is traditionally separated into lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE), each with a prevalence of $\leq 1/100{,}000$ (1), but the distinction is often ambiguous. Adding to the complexity, a rare autosomal-dominant form of LI has also been described (2).

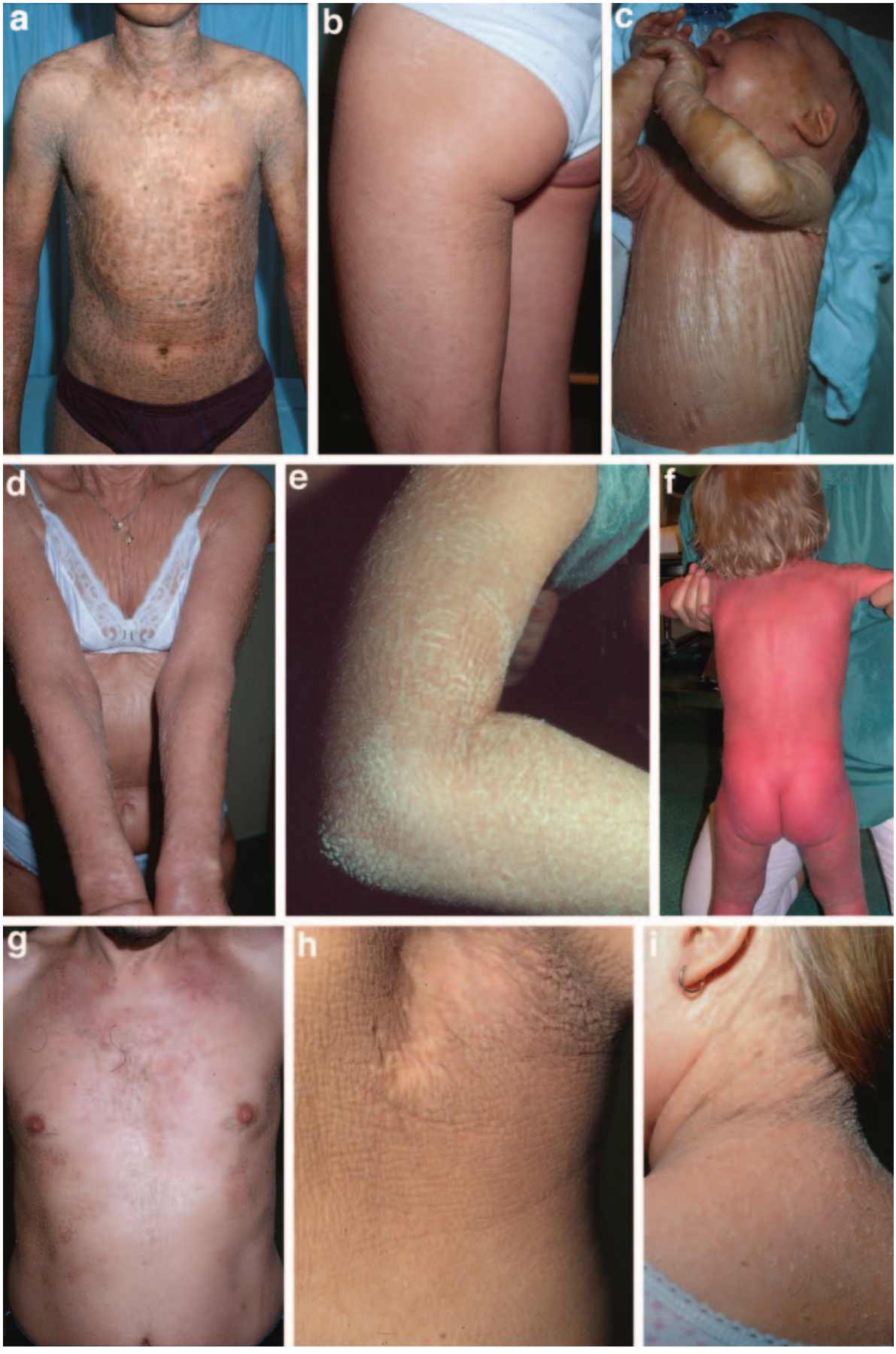
A recently discovered cause of some forms of ARCI is deficiency of transglutaminase 1 (Tgase 1), a cross-linking enzyme that is essential for the formation of cornified cell envelopes in epidermis (3). Homozygous or compound heterozygous mutations in the Tgase 1 gene (TGM1) on chromosome 14q11.2 explain about half the cases of ARCI (4–6). Additional loci have recently been mapped to chromosomes 2q34, 3p21, 17p13, 19p12-q13 and 19p13 (7–9), but the exact relationship between these findings and the pathogenesis of ARCI is still enigmatic.

The complexity of the aetiopathogenesis is also apparent when epidermis from ARCI patients is studied by electron microscopy (EM) (10). At least four different EM patterns have been found: type I, characterized by lipid droplets in corneocytes; type II, showing so called cholesterol clefts; type III, showing perinuclear, elongated membranes; and type IV, characterized by membrane aggregations in upper epidermal cells (11–14). Exactly how these different EM types relate to the aetiology and clinical subgroups of ARCI is presently unclear.

Fig. 1. Examples of clinical presentations in group A (a–c), group B (d–f) and group C (g–i), (see Table I for group definition and abbreviation). a) severe LI in an Estonian male with EMtype I, b) a woman with extensively treated LI, c) infant with LI (after shedding of collodion) with EM-type II, d) well-treated LI/CIE in a woman with EM-type III, e) LI predominantly expressed on the arms (EM-type I), f) CIE in a 2-year-old girl with EM-type I, g) patchy ichthyosis mainly confined to the trunk (EM-type I), h) focal velveted hyperkeratosis in the axillae of a man with EM-type IV, and i) fine scaling with no erythema (CIFS) in an Estonian girl with EM-type I.

*These authors contributed equally to this work.

 ISSN 0001-5555


a
b
c
d
e
f
g
h
i

Our aim was to show the characteristics and prevalence of various subtypes of ARCI in a large group of patients with or without TGM1 mutations. Details of the TGM1 analysis will be presented elsewhere[1]. Patients with syndromic CI were excluded in this study.

MATERIAL AND METHODS

Patients

Eighty-three patients from 64 Swedish and 8 Estonian families fulfilling the criteria for non-syndromic ARCI (for review, see ref. (1)) were included in the study. The patients were recruited in the period 1997–2001 through contacts with the Swedish patient organization for ichthyosis, via letters to all dermatology departments in Sweden and Estonia, and by visits to many of these departments for personal interviews and examination of patients. Exclusion criteria were: (i) signs of syndromic ichthyosis, (ii) lack of information about ichthyosis in infancy, (iii) congenital ichthyosis but no follow-up after the neonatal period, and (iv) a family history incompatible with autosomal recessive inheritance. Male patients without a proper knowledge of their family history were screened for steroid sulphatase deficiency (15) to exclude early onset X-linked recessive ichthyosis. Patients with a history of repeated bacterial infections were screened for lipid vacuoles in blood cells to exclude Chanarin-Dorfman syndrome (1). Other types of syndromic ichthyosis, e.g. the Sjögren-Larsson, Refsum, KID, Tay, Comel-Netherton and Vohwinkel syndromes, were excluded based on their typical clinical features (for review, see ref. 1).

There was no family history of ichthyosis in any of the patients, except when two siblings were affected (10 families) and in one previously reported family (4) in which the mother was also affected by LI and the father carried a TGM1 mutation. Eight of the Swedish patients were of foreign extraction: two from Iraq and one each from Cuba, Finland, Iceland, Norway, Poland and the USA.

The patients (or parents) were given written information about the study and were asked about their willingness to participate. The study was approved by the local ethics committees at Uppsala University and Tartu University.

All patients were examined by at least two of the authors (AG and AV) using a standardized protocol focusing on any abnormalities in body stature, psychomotor function, dental status, eyes, ears, nails and hair. The type of scaling was characterized (generalized or focal, lamellar or fine) and, whenever possible, was classified as LI or CIE. In addition, the severity of ichthyosis and the severity of erythema were scored separately from 0 (none) to 4 (very severe) in 9 different skin regions (trunk, arms, legs, face, scalp and neck, hands, feet, knees/elbows, and flexural areas). The sum of the 9 scores was calculated after multiplying each value by a factor proportional to the size of the corresponding skin area relative to the whole body surface (calculated from the ''rule of nine'', i.e. trunk 0.36, legs and feet 0.36, arms and hands 0.18, etc.). In this way, a weighted total score of maximally 4.0 was achieved for ichthyosis and erythema, respectively.

The patients (or parents) also completed a questionnaire, the answers to which were discussed at the time of examination. Questions highlighting the patient's family history, skin symptoms at birth, sweating ability and ongoing or previous therapies were included.

Laboratory investigations

Mutation screening: DNA was prepared from blood of all patients and analysed for TGM1 mutations as described elsewhere (6).

Electron microscopy: A punch biopsy (3 mm) of involved skin was performed in 72 patients. The skin samples were fixed in 3% glutaraldehyde before being processed for transmission EM according to standard procedures.

Statistics

The chi-square test was employed to compare the three diagnosis groups regarding sex and clinical characteristics. Analysis of variance (ANOVA) and post hoc analysis with the Tukey honestly significant difference test was used to compare the same groups regarding differences in age, ichthyosis and erythema scores.

RESULTS

Delimiting three groups of patients

Of the 83 patients (72 families) fulfilling the inclusion criteria for ARCI, 44 (35 families) were found to carry disease-causing TGM1 mutations on both alleles. On DNA sequencing of the protein coding region, the remaining 39 patients (37 families) were all negative for TGM1 variations (except for a single nucleotide polymorphism – pm520 – on one allele). Based on these results and on the clinical examination, three groups of patients were distinguished (Table I). The largest group (A) comprised patients *with* TGM1 mutations who presented with LI or CIE, except in two cases that had only mild or focal ichthyosis mainly confined to the trunk (Fig. 1a–c). Group B also included patients with LI or CIE, but *without* TGM1 mutations (Fig. 1d–f). In contrast, patients in group C (who also lacked TGM1 mutations) had fairly mild symptoms with little or no erythema (Fig. 1g–i). This phenotype was distinguished as *c*ongenital *i*chthyosis with *f*ine or focal *s*caling (CIFS).

Distribution of nationality gender and age

The Swedish and Estonian patients were similarly distributed between the groups (see Table I), but not surprisingly the Estonians were always in the minority (population sizes: Estonia 1.4 million, Sweden 8.9 million). Both sexes were equally represented in group A, but a preponderance of women (60–76%) was seen in groups B and C. The mean age was similar in the three groups, but a look at the age distribution (Fig. 2) shows that as many as 57% of the patients in group A were below the age of 20, as compared to 32–45% in groups B and C.

[1]Pigg M, Vahlquist A, Gånemo A, Matson H, Virtanen M, Gedde-Dahl Jr T, Westermark P, Dahl N. The transglutaminase 1 gene in autosomal recessive congenital ichthyosis from Sweden and Estonia: Identification of nine novel mutations. Hum Genet (submitted).

Table I. *Clinical and electron microscopic (EM) findings in the three groups of patients*

Group	A		B		C
Main clinical subtype TGM1 mutation	LI or CIE yes		LI or CIE no		CIFS no
No.					
Families, Swedish/Estonian	30/5		17/1		17/2
Patients, Swedish/Estonian	37/7		18/1		18/2
Females *n* (%)	22 (50)		13 (67)		12 (60)
Age					
Mean ± SD	24 ± 18		30 ± 25		26 ± 24
Median (range)	19 (0.5 – 71)		30 (1 – 81)		23 (0.5 – 79)
Clinical scores			$p < 0.001$[a]		
Ichthyosis, mean ± SD	2.6 ± 1.0	$p < 0.05$	2.0 ± 0.8	$p < 0.05$	1.2 ± 0.3
Erythema, mean ± SD	0.7 ± 0.6	$p < 0.05$	1.1 ± 1.0	$p < 0.001$	0.3 ± 0.4
Born with collodion *n* (%)					
Typical	35 (80)***		7 (37)		7 (35)
Atypical or uncertain	7 (16)		11 (53)		8 (40)
Ectropion *n* (%)	31 (71)***		8 (42)		1 (5)
Alopecia *n* (%)	15 (34)		5 (26)		2 (10)
Anhidrosis *n* (%)	39 (87)		19 (100)		16 (80)
Palmoplantar keratoderma *n* (%)	38 (86)		15 (79)		10 (50)**
Assoc. abnormalities *n* (%)					
Neurological[b]	3 (7)		2 (11)		2 (10)
Malformation[c]	5 (11)		6 (32)		–
EM type *n* (%)					
I	13 (37)		11 (58)		12 (63)
II	20 (57)		1 (6)		–
III	–		3 (17)		–
IV	–		–		2 (11)
Harlequin-like	–		3[d](17)		–
Non-definita	3 (6)		–		5 (26)

**$p < 0.01$, ***$p < 0.001$ = Significant difference vs. the other two groups (chi-square).
[a]Anova analysis (Tukey HSD).
[b]Neurological findings were: mentally retarded, speech disturbance, deafness and neuropathy in an arm.
[c]Malformation of ears, fingers and toes.
[d]Two of the patients are reported in a previous publication (ref. 16). LI = lamellar ichthyosis, CIE = congenital ichthyosisform erythroderma. CIFS = congenital ichthyosis with fine or focal scaling, TGM1 = transglutaminase 1gene.

Clinical scores and some special features

The clinical scores further illustrated the phenotypic differences between the groups (see Table I). The ichthyosis score was significantly higher in group A than in group B ($p < 0.05$), and in turn higher than in group C ($p < 0.05$). The erythema score, on the other hand, was highest in group B ($p < 0.05$ vs. group A and $p < 0.001$ vs. group C). Despite the differences in clinical severity, a high proportion of patients in all three groups were born as typical collodion babies (35 – 80%), had palmoplantar keratoderma (50 – 86%) and suffered from anhidrosis (80 – 100%). Ectropion, however, was much more common in group A (71%) than in group C (5%), and group B had the highest prevalence of extracutaneous abnormalities (42%).

Electron microscopy findings

At the ultrastructural level, many different abnormalities were seen in the upper epidermis, some of which appeared to be group-specific (see Table I). Thirty-six patients in group A were available for EM analysis, the majority of which showed type I (37%) or type II (57%) according to the Anton-Lamprecht classification (10). In contrast, the EM findings in groups B and C were mainly of type I (58 – 63%). However, one case of type II and several cases of type III and a harlequin ichthyosis (HI)-like EM picture (16) were found in group B, and 2 cases of type IV (a boy and an unrelated man from northern Sweden – see Fig. 1h) and several examples of still unclassified EM abnormalities were found in group C.

Preferred treatments

All patients were on some type of topical therapy for ichthyosis (but were asked not to apply anything for $\geq$12 h prior to examination) (Table II). About 1/3 of the patients in groups A and B had past or ongoing treatment with oral acitretin (0.5 – 1.0 mg/kg/day). In contrast, only 10% of the patients in group C had this experience. A plethora of different topical therapies, usually applied 1 – 2 times per day, was reported by the patients. There were no consistent differences between

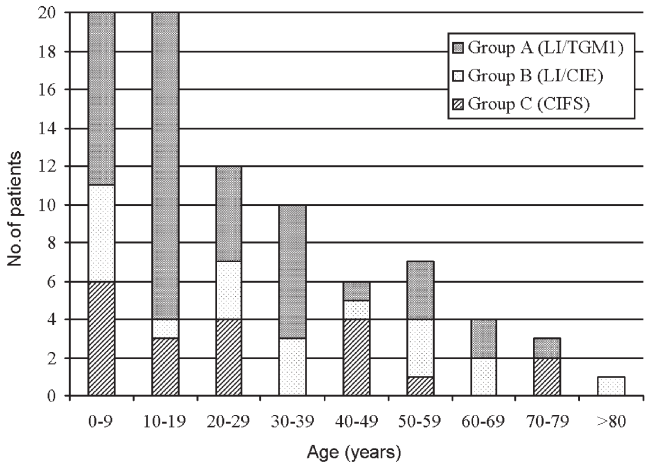


Fig. 2. Age distribution of patients belonging to different groups of ichthyosis. Groups as in Table I.

the groups in this respect, but ointments containing salicylic acid and calcipotriol were only rarely used by severely affected adult patients. The three most popular cream additives were (in decreasing order of frequency): (i) urea, 4–10%, (ii) alpha-hydroxy-acids (e.g. lactic acid, 5%), and (iii) a combination of lactic acid and propylene glycol (5%/20%) in a semi-occlusive cream base.

DISCUSSION

Our study, which comprises one of the largest series of patients with ARCI hitherto reported, clearly illustrates the clinical and aetiologic heterogeneity of this group of rare diseases. We estimate that the 73 Swedish patients represent a majority of patients with ARCI living in this country, corresponding to a prevalence of about 1/100,000 also reported by others (1, 5, 6, 17). However, we cannot exclude the possibility that patients with mild forms of ARCI (e.g. CIFS in group C) may have escaped our detection and are underrepresented in the study. Similarly, failure among older and disillusioned patients to seek dermatological advice despite having a major skin problem is a reality that might contribute to the skewed age distribution, especially in group A (see Fig. 2). It is also possible that a high neonatal mortality of collodion babies in the past may have contributed to a reduced number of older individuals in our study, whereas today life expectancy is almost normal for a patient with ARCI. Finally, one should not totally disregard the possibility that the unexpectedly high number of children in our study (ARCI prevalence 1–20 years, approx. 1/50,000) represents a real increase in incidence of the disease over the past 15–20 years.

In our series of patients, we could confirm that deficiency of epidermal Tgase1 due to homozygous or compound heterozygous TGM1 mutations is a major cause of ARCI, accounting for more than half of the cases in Sweden and Estonia. Details of the newly discovered TGM1 mutations and about the genotype/phenotype correlations in individual patients are presented elsewhere (see previous footnote). Interestingly, although most of the patients in group A suffered from generalized LI/CIE, two had mild or only focal ichthyosis. This corresponds with previous reports on TGM1 missense mutations associated with a mild phenotype (9, 18), and supports the concept of a generally poor genotype/phenotype correlation in patients with TGM1 mutations (4, 5, 8, 9, 17, 19, 20).

An even greater variation in the clinical presentation was found among TGM1-unrelated forms of ARCI (groups B and C). Patients were assigned to group B when they had LI or CIE of a similar severity as in group A. In contrast, patients in group C had a milder phenotype (CIFS) with fine or focal scaling and little or no erythema. Similar cases have probably been called

Table II. *Treatments used by patients in the three groups (see Table I)*

Treatment	Group A $n=44$	Group B $n=19$	Group C $n=20$	All Patients Swedish $n=73$	Estonian $n=10$
Oral retinoids *n* (%)					
On-going	11 (25)	4 (21)	1 (5)	14 (19)	2 (20)
Previously	6 (14)	3 (16)	1 (5)	10 (12)	–
Creams containing[a] *n* (%)					
Urea 2–10%	21 (48)	11 (58)	8 (40)	32 (44)	8 (80)
LPL[b]	14 (32)	2 (11)	2 (10)	18 (22)	–
AHA[c] 1–5%	3 (7)	1 (5)	3 (15)	7 (8)	–
Salicylic acid 2–5%	4 (9)	2 (11)	–	3 (4)	3 (30)
Calcipotriol	2 (5)	–	–	2 (2)	–
Propylene glycol 10–20%	1 (2)	1 (5)	3 (15)	5 (6)	–
Blend emollient	6 (14)	3 (16)	4 (20)	10 (14)	3 (30)

[a]Some of the patients used more than one cream.
[b]LPL = Lactic acid 5% + Propylene glycol 20% in Locobase (Lipobase) cream.
[c]AHA = Alpha-hydroxy-acid.

non-LI/non-CIE in the past (21). This group of patients is probably at least as heterogeneous as group B in terms of clinical diversity and genetic background. Adding to the complexity of this matter, there are situations when a clear distinction between CIFS and mild forms of CIE or LI simply cannot be made, especially when patients are followed over time or the treatment is changed. For example, seven of the patients in group C showed a severe phenotype at birth, but had only mild skin symptoms after shedding the collodion membrane, a phenomenon also known as "self-healing collodion baby" (22).

One way to circumvent a crude classification of ARCI based on archetypes is to try to quantitate the patient's various skin signs. To our knowledge, no such analysis has been undertaken in ARCI in the past, although this is a common approach in psoriasis and atopic eczema. For this purpose, we designed a PASI-like scoring system (23) that involves only two variables: ichthyosis (=scaling/xerosis) and erythema, recorded in predetermined skin areas. In order to minimize the influence of therapy on the scores, patients were told not to apply any topical agents for $\geq$12 h prior to investigation. The statistical analysis of the area-related mean scores showed predictably that group C differed significantly from the other groups ($p<0.05-0.001$) with respect to both ichthyosis and erythema. Perhaps more intriguingly, ichthyosis was most intense in group A, whereas erythema was most intense in group B ($p<0.05$ vs. the other group), thus confirming our general impression of subtle differences between the phenotypes in the two groups of patients. Incidentally, the sensitivity of the scoring system will probably be useful also when testing new treatments for ichthyosis.

The high prevalence of anhidrosis in all groups of ARCI is worthy of comment. When hot, the patients turn red and become exhausted, but never experience sweating, except possibly in a small area on the upper lip or forehead. The pathophysiology of anhidrosis in the presence of sweat glands is poorly understood, but obstruction of the sweat duct due to hyperkeratosis is the preferred hypothesis. However, this explanation is difficult to reconcile with the lack of correlation between the prevalence of anhidrosis and the severity grade of ichthyosis in the three study groups. Furthermore, the sweating problem is difficult to mitigate even when using potent anti-keratinizing agents like acitretin (AV, unpublished observation).

About 1/3 of the Swedish and 1/5 of the Estonian patients (mainly in groups A and B) used oral retinoid therapy on and off. In addition, all patients had tried a variety of topical remedies, including mechanical removal of scales by pumice, etc. The preferred topical therapy differed between the groups and between the countries. Whereas creams containing 5–10% urea were the most popular, a new cream formulation containing lactic acid and propylene glycol (24) was frequently used by Swedish patients, especially in group A. Generally, the Estonian patients appeared to be less vigorously treated than their Swedish counterparts, and mainly used creams containing 2–5% salicylic acid or 5–10% urea.

On EM analysis of epidermis, patients in group A appeared more homogeneous than the other groups of patients. Specifically, 20 cases of EM type II (cholesterol clefts) were found in this group (57% of the investigated samples) but in only one patient in group B. Since previous data also suggested that EM type II is closely linked to TGM1 mutations (17), the exceptional patient in group B will be further studied with respect to his Tgase 1 expression in epidermis. Group B was otherwise characterized by a high (58%) frequency of EM type I (lipid droplets) and a few cases each of type III (perinuclear membranes) and a previously reported harlequin-like EM picture that is coupled to severe CIE with finger/toe malformations (16). Contrary to a Finnish report of type III associated with CIE (13), our 3 patients (2 adult sisters and an unrelated girl) had LI of variable severity (for example see Fig. 1d). Group C, finally, showed a high (63%) frequency of EM type I and a few cases of type IV (membrane aggregations). The latter patients also fulfilled the clinical criteria of "prematurity ichthyosis", i.e. they were males born 8–10 weeks prematurely with signs of asphyxia and massive hyperkeratosis on the scalp, gradually transforming into a mild, non-scaly ichthyosis after the first few weeks of life (14). This type of ARCI has recently been found to be linked to a locus on chromsome 9[2].

In conclusion, although ARCI is a heterogeneous group of diseases with many overlapping features, it is possible to distinguish certain subtypes using a combination of genetic testing, careful clinical examination and EM analysis of skin biopsies. Since several additional causes of ARCI have recently been identified (25, 26), there is reason to be optimistic about a future development where DNA-based screening can be offered for all types of ichthyosis, which would facilitate diagnosis, prognosis making, and genetic counselling.

ACKNOWLEDGEMENTS

We thank all the patients for their willingness to participate in the study and our colleagues in Sweden and Estonia for kindly referring patients to us. Drs F. Pontén, Uppsala, and I. Anton-Lamprecht, Heidelberg, helped interpret some of the EM pictures, and Ms Benita Andersson and Madeleine Jarild, Uppsala, skilfully performed the EM technique. Mr H. Matson performed DNA screening in some of the patients. The statistical analysis was done by Eva Johansson, PhD.

[2]Klar J, Pigg M, Vahlquist A, Gedde-Dahl T, Dahl N. Identification of a novel locus for Ichthyosis-Prematurity Syndrome on Chromosome 9. (abstract) European Human Genetics Conference 2002.

Financial support was received from the Swedish Medical Research Council, the Welander-Finsen Foundations and Uppsala University.

REFERENCES

1. Traupe H The ichthyoses: a guide to clinical diagnosis, genetic counselling and therapy. Berlin: Springer Verlag, 1989.
2. Traupe H, Kolde G, Happle R. Autosomal dominant lamellar ichthyosis: a new skin disorder. Clin Genet 1984; 26: 457–461.
3. Huber M, Rettler I, Bernasconi K, Frenk E, Lavrijsen SPM, Ponec M, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. Science 1995; 267: 525–528.
4. Huber M, Yee VC, Burri N, Vikerfors E, Lavrijsen APM, Paller AS, et al. Consequences of seven novel mutations on the expression and structure of keratinocyte transglutaminase. J Biol Chem 1997; 272: 21018–21026.
5. Laiho E, Ignatius J, Mikkola, Yee VC, Teller DC, Niemi K-M, et al. Transglutaminase 1 mutations in autosomal recessive congenital ichthyosis: private and recurrent mutations in an isolated population. Am J Hum Genet 1997; 61: 529–538.
6. Pigg M, Gedde-Dahl Jr T, Cox D, Hauber I, Anton-Lamprecht I, Dahl N. Strong founder effect for a transglutaminase 1 gene mutation in lamellar ichthyosis and congenital ichthyosiform erythroderma from Norway. Eur J Hum Genet 1998; 6: 589–596.
7. Parmentier L, Lakhdar H, Blanchet-Bardon C, Marchand Dubertret L, Wiessenbach J. Mapping of a second locus for lamellar ichthyosis to chromosome 2q33–35. Hum Mol Genet 1996; 5: 555–559.
8. Virolainen E, Wessman M, Hovatta I, Niemi K-M, Ignatius J, Kere J, et al. Assignment of a novel locus for autosomal recessive congenital ichthyosis to chromosome 19p13.1–p13.2. Am J Hum Genet 2000; 66: 1132–1137.
9. Fischer J, Faure A, Bouadjar B, Blanchet-Bardon C, Karaduman A, Thomas I, et al. Two new loci for autosomal recessive ichthyosis on chromosomes 3p21 and 19p12-q12 and evidence for further genetic heterogeneity. Am J Hum Genet 2000; 66: 904–913.
10. Anton-Lamprecht I. Ultrastructural identification of basic abnormalities as clues to genetic disorders of the epidermis. J Invest Dermatol 1994; 103: 6S–12S.
11. Niemi KM, Kanerva L, Kuokkanen K, Ignatius J. Clinical, light and electron microscopic features of recessive congenital ichthyosis type I. Br J Dermatol 1994; 130: 626–633.
12. Niemi KM, Kanerva L, Kuokkanen K. Recessive ichthyosis congenita type II. Arch Dermatol Res 1991; 283: 211–218.
13. Niemi K-M, Kanerva L, Wahlgren C-F, Ignatius J. Clinical, light and electron microscopic features of recessive ichthyosis congenita type III. Arch Dermatol Res 1992; 284: 259–265.
14. Niemi K-M, Kuokkanen K, Kanerva L, Ignatius J. Recessive ichthyosis congenita type IV. Am J Dermatopathol 1993; 15: 224–228.
15. Ibsen HH, Brandrup F, Blaabjerg O, Lykkesfeldt G. Lipoprotein electrophoresis in recessive x-linked ichthyosis. Acta Derm Venereol 1986; 66: 59–62.
16. Virolainen E, Niemi K-M, Gånemo A, Kere J, Vahlquist A, Saarialho-Kere U. Ultrastructural features resembling those of harlequin ichthyosis in patients with severe congenital ichthyosiform erythroderma. Br J Dermatol 2001; 145: 480–483.
17. Laiho E, Niemi K-M, Ignatius J, Kere J, Palotie A, Saarialho-Kere U. Clinical and morphological correlations for transglutaminase 1 gene mutations in autosomal recessive congenital ichthyosis. Eur J Hum Genet 1999; 7: 625–632.
18. Akiyama M, Takizawa Y, Suzuki Y, Ishiko A, Matsuo I, Shimizu H. Compound heterozygous TGM1 mutations including a novel missense mutation L204Q in a mild form of lamellar ichthyosis. J Invest Dermatol 2001; 116: 992–995.
19. Hennies HC, Küster W, Wiebe V, Krebsová A, Reis A. Genotype/phenotype correlation in autosomal recessive lamellar ichthyosis. Am J Hum Genet 1998; 62: 1052–1061.
20. Bale S, Russel LJ, Minjoo LL, Compton JG, DiGiovanna JJ. Congenital recessive ichthyosis unlinked to loci for epidermal transglutaminases. J Invest Dermatol 1996; 107: 808–811.
21. Bernhardt M, Baden HP. Report of a family with an unusual expression of recessive ichthyosis. Review of 42 cases. Arch Dermatol 1986; 122: 428–433.
22. Frenk E, de Techtermann F. Self-healing collodion baby: evidence for autosomal recessive inheritance. Ped Dermatol 1992; 9: 95–97.
23. Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 1978; 157: 238–244.
24. Gånemo A, Virtanen M, Vahlquist A. Improved topical treatment of lamellar ichthyosis: a double-blind study of four different cream formulations. Br J Dermatol 1999; 141: 1027–1032.
25. Jobard F, Lefèvre C, Karaduman A, Blanchet-Bardon C, Emre S, Weissenbach J, et al. Lipoxygenase-3 (ALOXE3) and 12®-lipoxygnease (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13.1. Hum Mol Genet 2002; 11: 107–113.
26. Lefèvre C, Jobard F, Caux F, Boujdar B, Karaduman A, Heilig R, et al. Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. Am J Hum Genet 2001; 69: 1002–1012.