

The Clinical Spectrum of Congenital Ichthyosis in Sweden: A Review of 127 Cases

ANDERS VAHLQUIST¹, AGNETA GÅNEMO¹, MARITTA PIGG², MARIE VIRTANEN¹ AND PER WESTERMARK³

Departments of ¹Dermatology, ²Clinical Genetics and ³Pathology, University Hospital, Uppsala, Sweden

Congenital ichthyosis comprises a rare group of usually monogenetic diseases that present at birth as a collodion phenotype or as variable degrees of ichthyosiform erythroderma, with or without superficial blisters. Depending on which gene mutation causes the disease, the skin problems later in life may range from a severe lamellar or bullous ichthyosis to mild or only focally expressed hyperkeratotic lesions. It is obviously important, but sometimes painstakingly difficult, to make a correct diagnosis already in infancy. Fortunately, recent advances in our understanding of the molecular genetics of ichthyosis have led to several new diagnostic tools that are continuously being updated. Based on this development, and on our own 5 years of experience in a national genodermatosis centre, we describe 127 cases of congenital ichthyosis examined in childhood or adulthood. Applying a combination of phenotypic and genotypic criteria, the patients were classified into three main groups: 1) Bullous ichthyosis (epidermolytic hyperkeratosis) and related disorders due to keratin mutations ($n=21$); 2) Non-bullous ichthyosiform erythroderma and lamellar ichthyosis mainly due to transglutaminase 1 mutations ($n=80$); 3) Syndromic ichthyosis, i.e. systemic (multi-organ) diseases due to many different causes ($n=26$). Each group could be further stratified into 4–11 entities using mutation analysis, electron microscopy of epidermis and various other techniques. Our findings are discussed in relation to recent data in the literature emphasizing the clinical usefulness of various diagnostic procedures for ichthyosis. *Key words:* congenital ichthyosis; collodion baby; epidermolytic hyperkeratosis; lamellar ichthyosis; genodermatosis; keratin; transglutaminase; connexin; electron microscopy; DNA test; erythro-keratoderma; neurocutaneous syndromes; pachonychia congenita; Netherton's syndrome.

Acta Derm Venereol 2003; 83 Suppl 213: 34–47

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

Abbreviations: CI: congenital ichthyosis, CHILD: congenital hemilateral ichthyosis with limb defects, CIFS: congenital ichthyosis with fine or focal scaling, Cx: connexin gene, EHK: epidermolytic hyperkeratosis, EKV: erythrokeratoderma variabilis, EM: electron

microscopy, HI: Harlequin ichthyosis, IFAP: ichthyosis follicularis, alopecia and photophobia, LI-TGM: lamellar ichthyosis with transglutaminase 1 gene mutations, LI/CIE: lamellar ichthyosis and/or congenital ichthyosiform erythroderma, KID: keratitis, ichthyosis and deafness, K: keratin, KCLICK: keratosis linearis, ichthyosis congenita and keratoderma, SLS: Sjögren-Larsson syndrome, Tgase 1 – transglutaminase 1 protein, XRI: X-linked recessive ichthyosis.

INTRODUCTION

Congenital ichthyosis (CI) encompasses a large group of mostly monogenetic disorders of keratinization presenting at birth as widespread hyperkeratosis and scaling of the integument, and sometimes associated with erythroderma and skin erosions. Thus defined, the spectrum of CI spans from dominantly inherited skin fragility diseases, such as bullous ichthyosis or epidermolytic hyperkeratosis (EHK), to various forms of mostly autosomal recessively inherited congenital ichthyosiform erythroderma (CIE) and lamellar ichthyosis (LI). Some forms of CI are also associated with major non-cutaneous symptoms, for example Sjögren-Larsson syndrome (SLS), which is a neuroectodermal disease, and Netherton's syndrome, which is associated with atopy. Other, more common monogenetic disorders of keratinization, such as autosomal-dominant ichthyosis vulgaris and Darier's disease, are not included here simply because they do not appear at birth.

When confronted with a case of neonatal ichthyosis it may be difficult even for a specialist to decide which type of CI it is. The rarity of the diseases and the many overlapping features may preclude a diagnosis based on clinical observations. All too often, more sophisticated diagnostic tests are either missing or are too cumbersome for a quick diagnosis. For example, electron microscopy (EM) of epidermis is time-consuming, expensive and not always helpful even when judged by a specialist. Another complication when diagnosing CI is the sometimes conflicting terminology used in different textbooks. Hopefully, with recent progress in the molecular genetics of CI, a new aetiology-based classification and simple DNA tests will soon emerge. Meanwhile, a diagnosis of CI is contingent on a combination of typical findings in the family history, at clinical examination and at laboratory work-up of the patient. Only rarely can a causative gene mutation be demonstrated.

The purpose of this article is to illustrate the phenotypic variability and prevalence of CI in an ethnically fairly homogeneous country like Sweden. Based on our experience from a recent national survey, we also discuss the aetiologies and the diagnostic tools for CI. Some of the results have already appeared in multinational reports focusing on one subtype of CI at a time (1, 2).

MATERIAL AND METHODS

The patients were identified via a national survey on ichthyosis performed in 1997–98 by two of the authors (AV and AG) or were referred to the Department of Dermatology of Uppsala University Hospital, which has official status (since 1999) as a national centre for diagnosing genodermatoses. Some patients were also identified via the Swedish Ichthyosis Society, a patient organization chaired by one of the authors (AG). If not referred to our department, these patients were seen together with dermatologists or paediatricians around the country. All patients were Swedish citizens, but some were previously immigrants mainly from Middle Eastern countries or the former Yugoslavia.

The inclusion criteria for CI are described in the Introduction. Blistering disorders such as epidermolysis bullosa and erythroderma due to infections or nutritional deficiencies were excluded by appropriate tests. A congenital onset of the disease was ascertained either by examining the affected baby soon after birth or by interviewing parents or adult patients about the neonatal skin symptoms, sometimes after first consulting the patient's file. Apart from a full history and a thorough clinical examination, skin biopsies were routinely taken for histology and EM analysis, as previously described (2). Blood (and in some cases epidermis) was collected and stored at -70°C pending DNA extraction. When appropriate, a screening for mutations in the K1, K6a, K10 and TGM1 genes was performed as previously outlined (1, 3–5). All male patients were considered for the possibility of x-linked recessive ichthyosis (XRI) using serum-lipoprotein electrophoresis to detect steroid sulphatase deficiency (6). Patients prone to infections were examined for the presence of lipid droplets in leukocytes indicating Chananin-Dorfman disease (7); those with abnormal hair growth were examined microscopically for the presence of tichorrexis invaginata in the hair shafts, indicating Netherton's syndrome (7). Patients with extracutaneous findings, i.e. CNS, eye and ear problems, were also examined by other specialists to assess the possibility of for example SLS, Vohwinkel's syndrome or Keratitis-Ichthyosis-Deafness (KID) syndrome.

The study was approved by the local ethics committee of Uppsala University. All patients (or parents) gave informed consent to participation.

RESULTS AND DISCUSSION

One-hundred-and-twenty-seven patients, representing the cumulative number of Swedish patients with CI encountered by us in the period 1996–2002, were included in the study. After thorough investigations (see Material and Methods) and based on whether or not the ichthyosis was blistering or associated with a previously described syndrome, the patients were provisionally classified into three

main groups (Table I). The first group ($n=21$) comprised patients with bullous ichthyosis or EHK (which is a pathologic description) due to keratin mutations (clinical pictures in Fig. 1). The second and largest group ($n=80$) comprised patients with non-bullous ichthyosis of the LI/CIE types (Figs 2 and 3), a large proportion of whom (47%) carried TGM1 mutations. The third group ($n=26$) was patients with various syndromes with or without known aetiology (Fig. 4). The three main groups are discussed separately below, with an emphasis on within-group variations in phenotypes and the usefulness of various diagnostic tests.

Bullous ichthyosis (syn. epidermolytic hyperkeratosis)

This group of disorders, which in our study included nevoid EHK and pachonychia congenita, is almost invariably caused by dominant negative keratin mutations (8). The clinical heterogeneity of the so-called keratinopathies is mainly determined by which of the keratin genes (K1, K2e, K6a, K10, K16 or K17) is affected, where in the gene the mutation resides, and on how the mutation has originated (via inheritance or via a *de novo* mutation in gonadal cells or post-conceptionally). As a rule, keratin mutations are inherited via an autosomal-dominant trait, but spontaneous mutations are common (representing 80% of the generalized EHK cases in our study). Of course, a genetic mosaicism causing nevoid EHK is always a spontaneous event, but provided a substantial number of gonadal cells are also affected this trait can be transmitted to the next generation as generalized EHK. Interestingly, most of the patients with EHK in our study were children below the age of 15 (1). While this might indicate that the number of spontaneous keratin mutations in Sweden has increased over the last decennium, an increasing incidence of EHK might also be explained by a higher survival rate of severely affected babies today compared to 30–50 years ago.

It is usually easier to make a clinical diagnosis of generalized EHK in adult patients and children above the age of a few months than it is in neonates, when skin symptoms can readily be mistaken for epidermolysis bullosa, generalized mastocytosis, zinc or biotin deficiency and staphylococci scalded skin syndrome (Fig. 1). Incidentally, skin infections frequently complicate EHK, increasing the tendency to blisters and causing the malodour that is a big problem for many patients also in adulthood. A skin biopsy showing prominent degeneration in the granular layer and suprabasal epidermolysis will confirm the EHK diagnosis (Fig. 5a). Further proof can be obtained if EM analysis shows clumping of tonofilaments around nuclei in suprabasal keratinocytes (Fig. 6a). Of course none of these techniques will yield any information about which of the keratin proteins, K1 or K10, is mutated. However some clinical guidance can be obtained by the fact that palmoplantar keratoderma (Fig. 1g) is almost invariably



Fig. 1. Clinical spectrum of various keratinopathies: (a) a newborn girl with epidermolytic hyperkeratosis (EHK, syn. bullous ichthyosis) due to a K10 mutation, (b) the same patient a few months later, (c) another case of neonatal EHK due to a K10 mutation, (d–f) a 9-year-old boy with EHK due to a K10 mutation showing generalized involvement of the trunk, velvety hyperkeratosis around the neck (close up), and intense erythema and hyperkeratosis around the knees, (g) epidermolytic plantar keratoderma in a patient with generalized EHK due to a K1 mutation, (h) a 30-year old man with severe EHK, especially in the flexures, (i) a boy with suspected nevroid EHK, (j) an adolescent boy with pachyonychia congenita and foot blisters due to a K6a mutation, and (k) a close-up view of the finger nails in another boy with the same disease.



Fig. 2. The childhood spectrum of non-bullous, non-syndromic ichthyosis (*a*) a collodion baby who later developed a mild congenital ichthyosis with fine or focal scaling (CIFS) phenotype (i.e. 'self-healing collodion baby'), (*b*) a newborn baby with congenital ichthyosiform erythroderma (CIE) (EM type I and no TGM1 mutations'— see Fig. 6 and Table I for explanation), (*c*) a case of harlequin ichthyosis 5 days after birth, (*d*) a 6-month-old baby with lamellar ichthyosis (LI) due to TGM1 mutations (EM type II), (*e*) a prematurely born baby with CIFS (EM type IV), (*f*) a 7-month-old baby with clumped fingers and toes (harlequin-like EM picture), (*g*) a 2-month-old baby with LI due to TGM1 mutations (EM type II), (*h*) a 4-year-old girl with LI due to TGM1 mutation (EM type II), and (*i*) a 10-year-old boy with TGM1 mutation and a focal appearance of LI (EM type II).

associated with K1 mutations (see Table I and refs. 1 and 9), whereas patients with a good response to retinoid therapy usually have K10 mutations (1). For a more exact diagnosis, a screening for hotspot mutations in the K1 and K10 genes is recommended. This can be relatively easily accomplished by restriction enzyme mapping on blood DNA or, in the case of nevoid EHK, on RNA or DNA extracted from lesional skin. Quite frequently, however, both genes have to be sequenced before a mutation can be found (5). In our material, disease-causing K1 or K10 mutations were identified in all patients with generalized EHK and in one case of nevoid EHK (Table I) (1). So far we have

found no Swedish patient with the Siemen's type of superficial EHK known to be due to K2e mutations (10).

Patients with pachyonychia congenita have typical nail changes (Fig. 1k) and often present with focal hyperkeratosis of the palms and soles, with blistering reminiscent of epidermolysis bullosa simplex (Fig. 1j). Furthermore, five out of eight patients in our study showed widespread follicular ichthyosis and hair abnormalities, and one patient had the frequently described association to mucous membrane abnormalities and multiple sebaceous cysts (11). Two of the patients have also been reported in childhood by another Swedish group (12). One of the patients in our study was found to carry a K6a mutation (P. Bowden et al., unpublished observation), whereas the other patients

Table I. Classification of 127 patients with congenital ichthyosis (incl. data from refs. 1, 2, 29 and 32)

Clinicogenetic main type of ichthyosis	Additional diagnostic findings	Total no. of pat. (females)	No. of families	Age (yr) median (range)	Hair & nail defects	Presence of palmoplantar keratoderma
Bullous (n=21)	<i>Mutations in:</i>					
Generalized	Keratin 1	4 (0)	4	16 (12-32)	0	4
	" 10	6 (4)	4	16 (10-74)	0	0
Nevoid EHK	" 10	3 (2)	3	9 (8-20)	0	0
Pachonychia cong.	" 6a	8 (3)	6	26 (10-50)	8	4
Non-bullous (n=80)	<i>EM findings:</i>					
LI/CIE (due to TGM1 mutations)	Type I and II	38 (21)	31	19 (1-71)	14	32
LI/CIE (other causes)	Type I and III Harlequin-like	19 (13) 3 (2)	17 3	30 (2-81) 3 (1-33)	6	14 3
CIFS	Type I and IV	18 (10)	17	22 (1-79)	4	9
KLICK	Abnormal keratohyaline	2 (1)	2	32, 34	0	2
Syndromes (n=26)	<i>Varia:</i>					
XRI	SS-deficiency	3 (0)	2	7 (3-30)	0	0
CHILD	Typical histology	1 (1)	1	16	0	1
Netherton	Trichorrhexis	7 (3)	7	10 (1-50)	7	2
KID	Cx 26 mutation	2 (2)	2	15, 40	0	2
IFAP	XR inheritance	1 (0)	1	1	1	0
Vohwinkel	Cx 26 mutation	1 (0)	1	60	0	1
EKV	Typical histology	2 (1)	2	30, 50	0	1
Sjögren-Larsson	Linkage analysis	4 (3)	4	39 (1-49)	0	1
Refsum	Phytanic acid/s ↑	1 (1)	1	60	-	-
Tay	Excl.diagnosis	3 (0)	2	5 (1-6)	3	1
Porcupine Man	Typical histology	1 (0)	1	72	1	1
Total		127 (67)	111	1-81	44	78

EHK: epidermolytic hyperkeratosis, LI/CIE: lamellar ichthyosis and/or congenital ichthyosiform erythroderma, TGM1: transglutaminase 1, CIFS: congenital ichthyosis with fine or focal scaling, KLICK: keratosis linearis, ichthyosis congenita and keratoderma, XRI: x-linked recessive ichthyosis, CHILD: congenital hemilateral ichthyosis with limb defects, KID: keratitis, ichthyosis and deafness, IFAP: ichthyosis, follicularis, alopecia and photophobia, EKV: erythrokeratoderma variabilis; SS: steroid sulfatase.

have not yet been studied in this respect.

Non-bullous ichthyosis (e.g. lamellar ichthyosis)

This heterogeneous group of non-syndromic ichthyosis consists of many entities, most of which remain to be genetically defined. Although autosomal recessive inheritance is the rule for LI/CIE, a rare dominant form of LI has also been described (13). In a previously reported case, a Swedish family with a mother and her two daughters affected by CIE (14), the father of the children was later found to carry one disease allele, thus explaining a pseudo-dominant inheritance pattern (2, 15).

There is a spectrum of clinical presentations between LI and CIE during childhood (Fig. 2) and in adulthood (Fig. 3). Some authors call these two extremes: EARLI and NEARLI (erythematous and non-erythematous autosomal recessive lamellar ichthyosis). In addition, there are very mild forms of CI best described as: non-LI/non-CIE (16, 17) or, as we prefer to call it, CIFS (congenital ichthyosis with fine or focal scaling) (2). In all forms of non-bullous CI, a history of collodion baby-appearance at birth (2, 18) and more or less permanent problems with ectropion, palmoplantar keratoderma, partial alopecia and hypohidrosis are common (2).

A major cause of LI/CIE is deficiency of transglutaminase 1 (Tgase 1), a cross-linking enzyme essential for the formation of cornified cell envelopes (3, 19, 20). In fact, homozygous or compound heterozygous mutations in the TGM1 gene – encoding for Tgase 1 – were the most common cause of LI/CIE in our material (see Table I and refs. 1 and 5). This calls for an early screening of all collodion babies for possible TGM1 mutations, especially since on routine skin histology there are no clear-cut differences between patients with and without TGM1 mutations (Fig. 5b–d). However, as already shown by others (21) and confirmed by us in a few patients, immunohistochemical analysis usually reveals a dramatically decreased expression of Tgase 1 in patients with TGM1 mutations, which contrasts with the normal or even up-regulated expression in patients without TGM1 mutations (Fig. 5e–h).

The further subtyping of non-bullous CI is complicated by a lack of suitable candidate genes and by the marked variations in phenotype seen in many patients over time (even when disregarding the impact of climatic factors and dermatotherapy). Ultrastructurally, however, diagnostic abnormalities can often be found in the granular and horny layers of epidermis, findings which seem to be independent of treatment (Dr K.-M. Niemi, personal communication). Based on EM analysis, Anton-Lamprecht (22) and Niemi et al. (23–26) have proposed a classification of CI into four subtypes which only partially harmonize with a clinical distinction into LI, CIE or CIFS. Fig. 6 gives examples of the EM findings in our study; the results in this

and previous studies are summarized in Table I (2, 27, 29). EM type I, which is the most common abnormality, was seen in virtually all clinico-genetic subtypes of non-bullous CI. EM type II, on the other hand, was almost exclusively confined to patients carrying TGM1 mutations. The remaining EM types were only rarely encountered in our study: EM type III was found in three patients with LI of unknown cause (see Fig. 3f for clinical picture), and EM type IV was seen in two male patients with “prematurity ichthyosis” and a marked improvement of skin symptoms later in childhood. The latter type of ichthyosis is characterized by masses of keratotic material, especially on the scalp and eyebrows of infants born 4–6 weeks prematurely and exhibiting neonatal asphyxia (Fig. 2e) (25). The usefulness of EM analysis for separating this condition from other forms of CI is illustrated by one of the premature babies in our study who had skin symptoms compatible with type IV ichthyosis (Fig. 4a) but no characteristic EM findings; she was later diagnosed as having SLS (see below).

Additional EM findings were: (i) abnormalities of the lamellar bodies in a girl with Harlequin ichthyosis (HI) (Fig. 2c) previously described in detail (28), (ii) HI-like ultrastructural abnormalities in 3 patients with severe CIE and claw-like fingers and toes (Figs 2f and 3g) also described previously (29), and (iii) several forms of non-diagnostic EM abnormalities previously reported in patients with CIFS (2). Three adults and two children in the latter group had a severe but transient phenotype at birth (Fig. 2a), a phenomenon entitled ‘self-healing collodion baby’ (30).

Patients with KCLICK (keratosis linearis, ichthyosis congenita and keratoderma), always exhibiting typical striae in the flexures (Fig. 3j), also fit within this group. This presumably recessively inherited disease (31) is of unknown aetiology, but has no obvious extracutaneous involvement. On EM, the patients show abnormally large keratohyaline granules (32), but the exact role of this in the pathogenesis of KCLICK is unknown.

Syndromes with congenital ichthyosis

Twenty percent of the patients in our study had associated extracutaneous symptoms suggesting an underlying multi-organ disease. Eleven different syndromes, representing all four modes of Mendelian inheritance, were diagnosed (Table I). X-linked recessive ichthyosis (XRI) with a very rare congenital onset of skin symptoms was identified in three male patients, two of whom were siblings. XRI (usual prevalence 1:5000 males) is a systemic disease due to deficiency of cholesterol sulphatase (33). It leads to accumulation of cholesterol sulphate, as reflected in decreased tissue levels of cholesterol (34), corneal opacities, retention of otherwise normal corneocytes (Figs 5 and 6), an



Fig. 3. The adult spectrum of non-bullous, non-syndromic ichthyosis. Examples *a–e* are cases due to TGM1 mutations: (*a*) a man with severe, non-treated lamellar ichthyosis (LI), (*b*) a woman with a LI-congenital ichthyosiform erythroderma (CIE) overlap (EM type II), (*c*) a mild LI in an adolescent girl, (*d*) keratoderma in association with LI (EM type II), (*e*) women with severe LI and total alopecia (EM type I), (*f*) female with LI (EM type III), (*g*) a man with severe CIE, note abnormal fingers (harlequin-like EM picture), (*h*) a woman with moderate CIE (EM type I), (*i*) a woman with mild LI, and (*j*) a man with KCLICK syndrome (keratosis linearis, ichthyosis congenita and keratoderma) and striate hyperkeratosis in the flexures

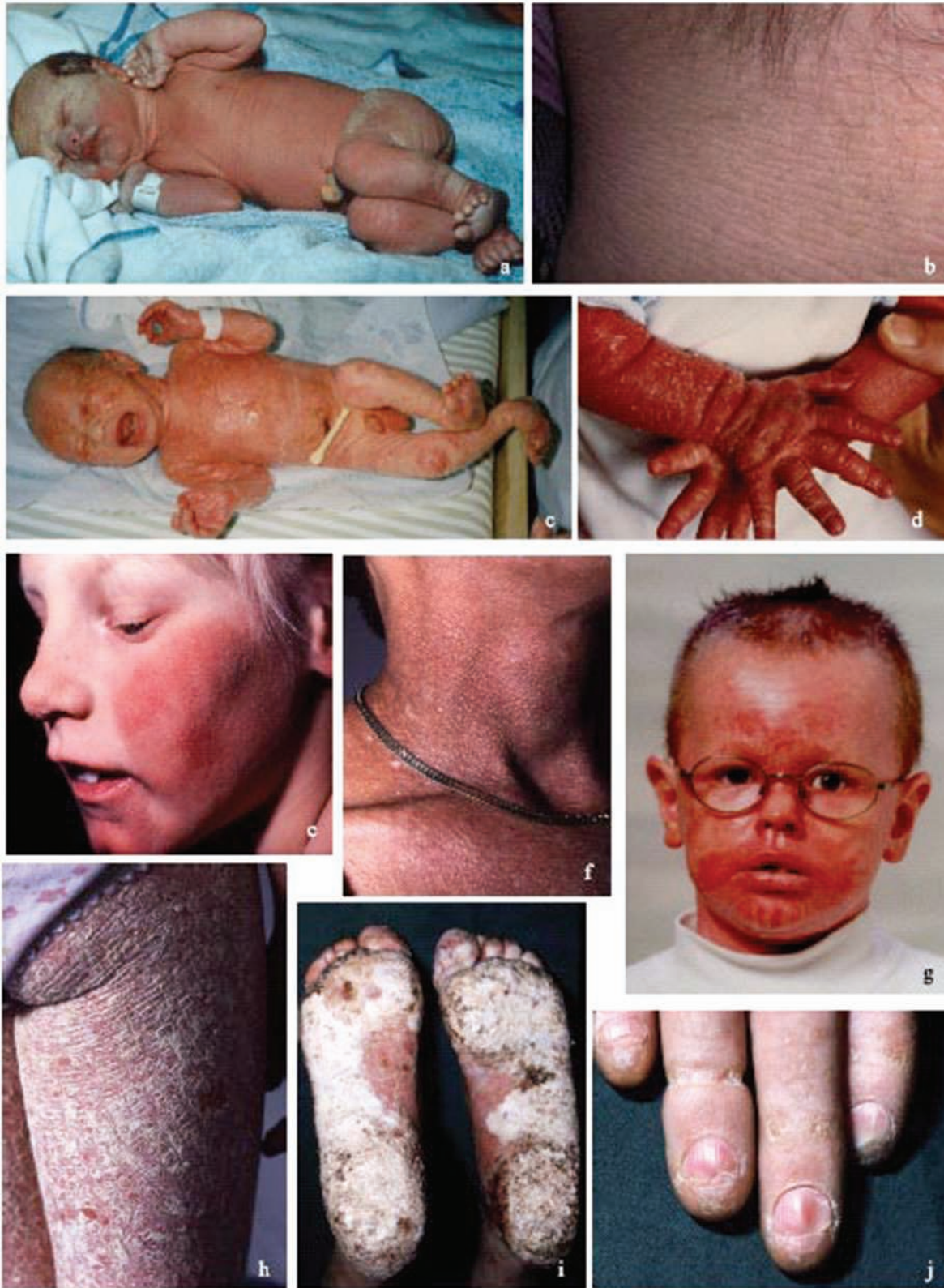


Fig. 4. Clinical spectrum of syndromic ichthyosis: (a) a newborn girl with Sjögren-Larsson syndrome (SLS); note the thick scales on the scalp and face (picture by Dr L. Bergfelt, Borås County Hospital), (b) right flank of an adult male with SLS, (c) a newborn boy with Netherton's syndrome, (d) a 10-day-old baby with the same syndrome; note severe erythroderma of the arms, (e) girl with keratitis-ichthyosis-deafness (KID) syndrome and typical ichthyotic plaques on the cheek, (f) the neck of an adult woman with suspected KID syndrome, (g) the face of the same boy as in (c), although 8 years later, (h) right thigh of a girl with erythrokeratoderma variables, and (i-j) the feet and fingers of a man with Vohwinkel's syndrome showing mutilating keratoderma and constriction bands (pseudoainhum) around the finger.

abnormal pH-gradient over the horny layer (35), and disturbances in the steroid hormone metabolism, leading to testicular maldescent and placental malfunctioning in female carriers (7).

Owing to variable deletions of large parts of Xp22.3, including the XRI gene, so-called contiguous gene syndromes can sometimes arise (36). Two examples are Kallman's syndrome (ichthyosis, stippled bones and unilateral renal agenesis) and Conradi-Hunermann disease (chondrodysplasia punctata, linear ichthyosis and short stature) (37). No such patients were encountered in our study, but a case of CHILD syndrome (congenital hemidysplasia with ichthyosiform nevus and limb defects) due to genetic mosaicism of an x-linked dominant trait (lethal to male fetuses) (38) was diagnosed in a girl from Afghanistan. She also had gastrointestinal involvement and biopsies of her skin and gastric epithelium showed massive hyperkeratosis and typical foam cells (results not shown). She was partially responsive to oral retinoids and improved after repeated excision surgery and skin transplantations of major skin areas. The causative gene mutation (39) remains to be investigated in this patient.

Netherton's syndrome, which is an autosomal recessive genodermatosis characterized by ichthyosis linearis circumflexa, erythroderma and hair shaft abnormalities (7), was identified in 7 patients, one of whom died at the age of 6 months. One of the adult patients has previously been reported in childhood (40). Two of the patients had siblings also affected by the same disease, but who died just several weeks after birth (not examined by us). Netherton's syndrome is due to mutations in SPINK5, a gene that encodes for an anti-protease important for skin barrier homeostasis (41). Although mutations in SPINK5 were not investigated in our patients, the diagnosis could eventually be confirmed by hair microscopy demonstrating trichorrhexis invaginata. It can be very difficult to separate Netherton's syndrome from other types of severe CIE and erythroderma, especially in the neonatal period, when the hair abnormality is often missing and erythroderma, hypernatraemia, life-threatening infections and failure to thrive are the prevailing symptoms (Fig. 4c–d) (42). However, later in life a combination of typical hair and skin signs and atopy makes diagnosis simpler (Fig. 4g).

KID (keratitis, ichthyosis and deafness) syndrome, which was identified in two unrelated women born in Sweden (Fig. 4e–f), is due to mutations in one of the connexin proteins, cx 26, which constitute the gap junctions (43, 44). A causative cx 26 mutation was recently identified in one of our patients (Bondeson and Vahlquist, unpublished observation); EM analysis showed dispersed keratohyaline in the other (Fig. 6h). Although this latter finding is not pathognomonic for KID syndrome (45), ultrastructurally abnormal keratohyaline is one of the hallmarks of a closely related disease, hystrich-like ichthyosis with deafness syn-

drome (see ref. 7 for a review). This disease is also caused by cx 26 mutations (44). Another disease clinically resembling KID syndrome is ichthyosis follicularis with alopecia and photophobia (IFAP) (46). This syndrome was recently identified in a 1-year-old boy from northern Sweden who reportedly has a maternal uncle with similar symptoms. IFAP is probably an x-linked disease of unknown origin. It is characterized by spiny follicular hyperkeratosis, a progressive alopecia during the first year of life, and a gradual onset of keratitis eventually leading to photophobia.

Vohwinkel's syndrome, also caused by abnormal gap junction proteins (43, 47), was identified in a 60-year-old man with no previous family history of the disease. The syndrome is characterized by ichthyosis, neurosensory deafness, constriction bands (pseudo-ainhum) around the fingers (Fig. 4j) and mutilating keratoderma (Fig. 4i), which in our patient led to foot ulcers and squamous cell carcinoma despite continuous treatment with oral retinoids. A causative cx 26 mutation has been identified in this patient (Bondeson and Vahlquist, unpublished observation), a finding which unequivocally distinguishes Vohwinkel's syndrome from Vohwinkel's disease (mutilating keratoderma *without* hearing problems) due to mutations in the loricrin gene (48).

Two patients with erythrokeratoderma variabilis (EKV) were included in the group, notwithstanding the fact that the syndromic (multi-organ) involvement in this disease is uncertain. EKV has been linked to cx 31 and cx 30.3 mutations (43, 49), although this was not examined by us. As reflected in the name of the disease, it has a variable phenotype but is usually characterized by large, sometimes confluent and erythematous, hyperkeratotic plaques (Fig. 4h). The symptoms are successfully suppressed by oral acitretin, as previously reported in one of the patients (50).

Four patients with SLS were identified, all with the characteristic velveted skin (51), especially around the neck and trunk (Fig. 4a–b). On EM, a widening of the intercellular spaces was seen in the stratum corneum of some of the patients (Fig. 6g). The diagnosis was confirmed by genetic coupling analysis (52). But exactly how the skin symptoms in SLS are related to a deficiency of fatty aldehyde dehydrogenase is not known (53). Reportedly, another 20 mentally and neurologically handicapped SLS patients are living in northern Sweden (Dr S. Jagell, personal communication). Of several known cases of Refsum's disease in Sweden we only investigated one, who had a mild, diffuse CI and predominantly neurological symptoms. Refsum's disease is due to deficiency of phytanoyl-CoA hydroxylase (54) leading to an accumulation of toxic levels of phytanic acid in blood and tissues (55).

Another neurocutaneous disease, Tay's syndrome or IBIDS (ichthyosis, brittle hair, intellectual impairment, decreased fertility and short stature) (7, 11), was tentatively

identified in a 5-year-old boy and in a couple of male twins born as collodion babies (one of whom died at the age of 1 month). We are aware of at least one additional case reported from Sweden (56). No diagnostic tests were available for this disease.

Lastly, we identified a patient with the very rare Porcupine Man syndrome (*malformatio ectodermalis generalisata*). This syndrome of unknown aetiology occurs sporadically and in our 70-year-old patient was associated with a mild mental retardation. He responded well to continuous treatment with oral acitretin, but also long before this was introduced in the 1980s he was given short courses of high-dose vitamin A therapy with good results (57).

CONCLUDING COMMENTS

To the best of our knowledge this is the first report describing the overall spectrum and frequency of various types of CI in one and the same country. We have reason to believe that the 127 cases described here represent the vast majority of CI patients living in Sweden around the turn of the millennium. Needless to say, patients with mild CI who fail to seek dermatologic advice, and those who suffer from syndromes with predominantly extracutaneous symptoms, were probably under-represented in our study. We are also aware of some patients with severe ichthyosis who for one reason or the other were not available for examination. Taking this into account and given a population figure of 9 million, the prevalence of CI in Sweden is estimated at 1/50 000. This falls within the range of figures reported for many other countries (for review, see ref.7). However, certain ethno-geographical peculiarities in Sweden, such as consanguinity and local founder effects, may influence the incidence of some types of CI. For example, SLS shows genetic clustering to northern Sweden (51) and 'prematurity ichthyosis' (EM type IV) is scarcely found outside Scandinavia (Dr T. Gedde-Dahl Jr, personal communication).

Although the phenotypic and genotypic variability is considerable even within one subgroup of CI, we believe that a useful classification can be obtained if clinical and ultrastructural findings are combined with an analysis of already established causes of CI. Thus classified, keratin mutations account for about 15%, TGM1 mutations for 30% and various syndromes with known aetiology for 15% of all CI cases observed in Sweden (see Table I). For the remaining 40% of cases, a few interesting candidate genes have recently emerged. Thus mutations in the ALOXE3 and ALOX12B genes linked to chromosome 17 have been found in North-African patients with CIE (58) and CGI-58 mutations have been found to cause Chanarin-Dorfman disease (59), characterized by CI, myopathi and proneness to bacterial infections. However, the latter disease was al-

ready excluded in our patients after examining their blood leukocytes for lipid inclusions (7). Hopefully, with the advance of molecular genetics, several new causes will soon be identified, thus improving the classification of CI. Indeed, coupling analysis has already indicated several more loci for LI/CIE (60–62).

The development of new microarray techniques will soon make genotyping of CI far more effective than it is today. Consequently, the screening of blood DNA for various disease-causing gene mutations can be given a higher priority than for example EM analysis when trying to work out the diagnosis in neonates. A higher diagnostic accuracy and more exact knowledge of the aetiology of CI will also enable: (i) improved genetic counselling, (ii) better patient information, and (iii) development of more specific therapies for CI. The prospects for gene therapy are promising for some of these diseases (63).

ACKNOWLEDGEMENTS

We thank all Swedish colleagues who made this study possible by referring patients to us. The valuable genetic discussions with Drs M.-L. Bondeson and N. Dahl, Clinical Genetics Unit, Uppsala University, and Dr T. Gedde-Dahl, Jr, Oslo University, are gratefully acknowledged. We thank Dr K.-M. Niemi, Helsinki, for expert opinions about EM and Dr Paul Bowden, Cardiff, for helping us to identify some of the keratin mutations. Ms Benita Andersson, Madeleine Jarild and Inger Pihl-Lundin assisted in the histologic and ultrastructural analyses. Financial support came from the Swedish Medical Research Council and Uppsala County Council. The publication of this report was made possible by grants from the E. Welanders and Finsens Foundations.

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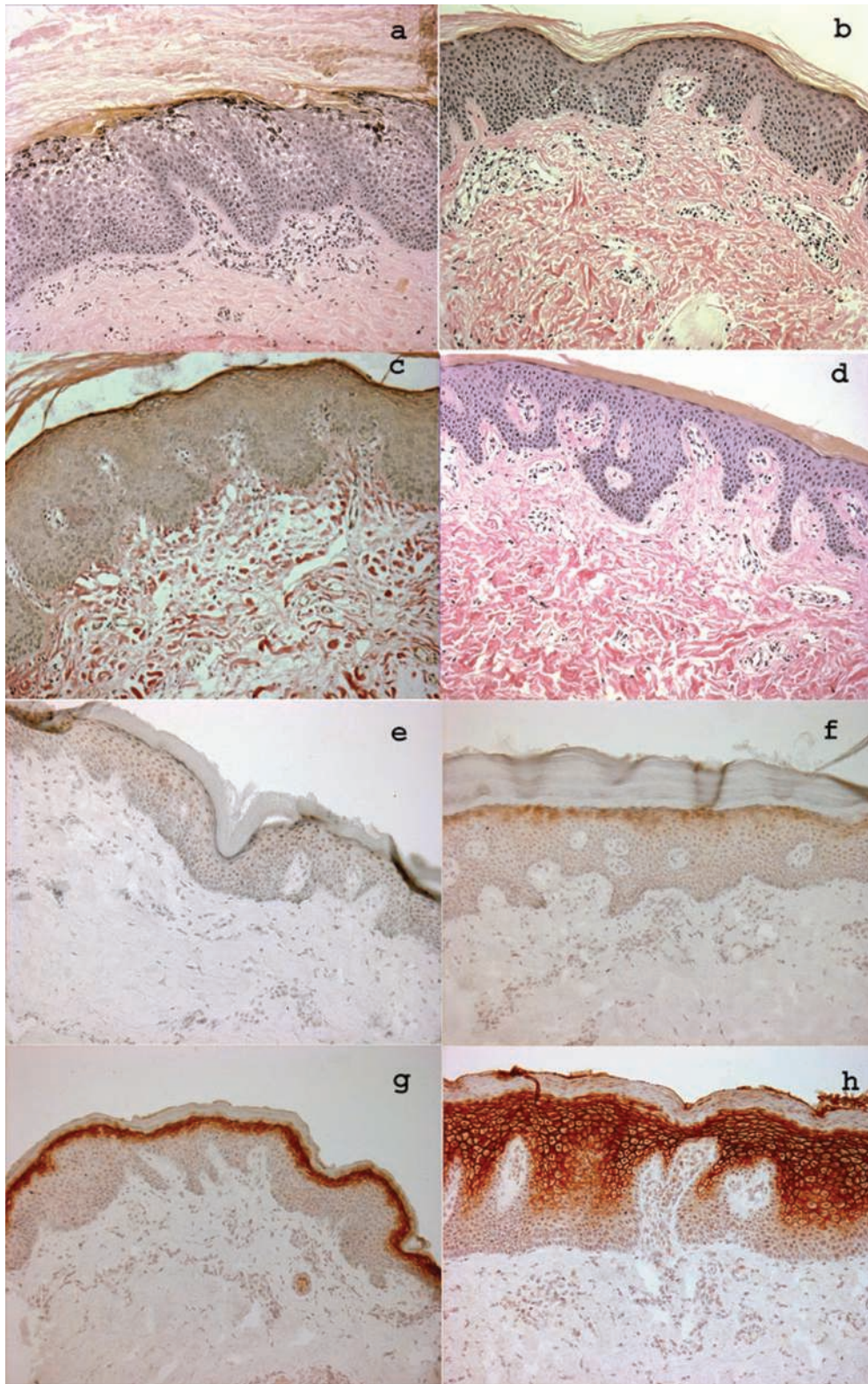


Fig. 5. Histopathologic abnormalities in various types of congenital ichthyosis (*a-d*: van Gieson staining; *e-h*: immunoperoxidase staining using antibodies against transglutaminase 1 (Tgase1)). (*a*) Epidermolytic hyperkeratosis (bullous ichthyosis) showing acanthosis, suprabasal cytolysis and massive hyperkeratosis, (*b*) lamellar ichthyosis (LI) showing mild hyperkeratosis and acanthosis, (*c*) congenital ichthyosiform erythroderma (CIE) with hyperkeratosis, acanthosis and dermal inflammation, (*d*) x-linked recessive ichthyosis with mild orthohyperkeratosis, (*e*) no Tgase1 expression in severe LI due to homozygous TGM1 mutations, (*f*) weak expression in a milder type of LI also due to TGM1 mutations, (*g*) normal expression in LI without TGM1 mutations, and (*h*) overexpression of Tgase1 in CIE without TGM1 mutations.

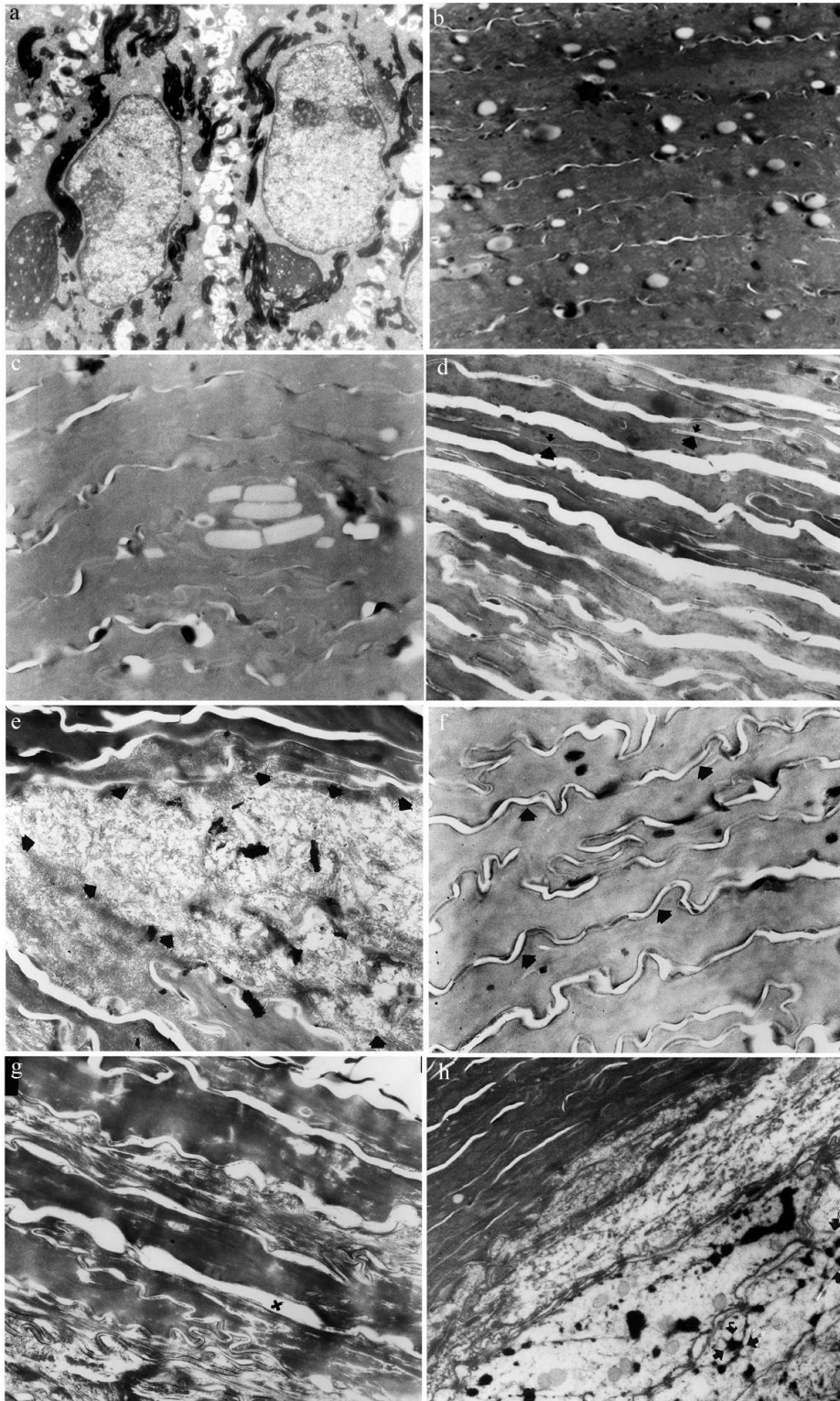


Fig. 6. Electron microscopy (EM) analysis of superficial epidermis in various types of congenital ichthyosis showing: (a) clumping of tonofilaments around the nuclei in bullous ichthyosis (epidermolytic hyperkeratosis), (b) numerous intra-corneocyte droplets in congenital ichthyosisform erythroderma (CIE) of unknown cause (EM type I), (c) aggregates of "cholesterol clefts" in lamellar ichthyosis (LI) due to TGM1 mutations (EM type II), (d) elongated intra-corneocyte membranes (arrowheads) in LI of unknown cause (EM type III), (e) lentiiform areas in stratum corneum filled with membrane inclusions (arrowheads) in "prematurity ichthyosis" (EM type IV), (f) densely packed corneocytes with well-developed cell envelopes (arrows) in x-linked ichthyosis, (g) abnormally wide intercorneocyte spaces (x) in Sjögren-Larsson syndrome (picture by Dr H. Nordlinder), and (h) dispersed keratohyaline in KID syndrome, previously reported also in hystrix-like ichthyosis with deafness (7).

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