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1071

1072 **FIGURE LEGENDS**

1073

1074 **Figure 1.** Clinical examples of common ichthyosis: accentuated palmoplantar markings of
1075 ichthyosis vulgaris (IV) in white skin (a); IV with atopic eczema (b); exaggerated scaling after 3
1076 weeks of life as an early presentation of X-linked recessive ichthyosis (RXLI) (c); RXLI with
1077 brownish scales in a 14-year old boy (d); RXLI with white to grey scales in an elderly patient (e).

1078

1079 **Figure 2.** Clinical examples of autosomal recessive congenital ichthyosis (ARCI): Harlequin
1080 ichthyosis (HI) at birth (a); HI evolves into generalized exfoliating erythrodermic ichthyosis (b, c);
1081 collodion membrane with ectropion and eclabion in lamellar ichthyosis (LI) (courtesy of Dr. Hagen
1082 Ott) (d); LI in childhood (e); LI due to 'severe' mutations in *TGM1* in a 79-year old man (f);
1083 congenital ichthyosiform erythroderma (CIE) in early infancy (g); mild CIE in an adult patient with
1084 *ALOXE3* mutations (h); bathing suit ichthyosis represents a LI variant characterized by localized
1085 healing of extremities (i).

1086

1087 **Figure 3.** Clinical examples of keratinopathic ichthyosis (KPI): superficial blister formation and
1088 erythema at birth in epidermolytic ichthyosis (EI) due to *KRT10* mutation (note that palm is spared)
1089 (a); palmoplantar keratoderma in EI due to *KRT1* mutation (b); in infancy EI often shows
1090 hyperkeratoses with predilection of friction areas and over joints (c); superficial epidermolytic
1091 ichthyosis (SEI) confined to particular skin areas of the arm and axillary region (d); annular EI
1092 represents an intermittent or transient presentation of EI (e); 'moulting' phenomenon in SEI (f);
1093 epidermolytic nevi may indicate a gonadal mosaicism (elbow flexure of the parent of the patient
1094 shown in a) (g).

1095

1096 **Figure 4.** Clinical examples of other non-syndromic forms of ichthyosis: erythrokeratodermia
1097 variabilis (EKV) that evolved like progressive symmetric erythrokeratodermia (PSEK) (a);

palmoplantar keratoderma in EKV (b); palmar honeycomb pattern of loricrin keratoderma (c); peeling skin disease (d); congenital reticular ichthyosiform erythroderma (CRIE) (e); Keratosis linearis-ichthyosis congenita-keratoderma (KLICK).

**Figure 5.** Clinical examples of syndromic forms of ichthyosis: trichothiodystrophy (a); Sjögren-Larsson syndrome (b); keratitis ichthyosis deafness (KID) syndrome (c); ichthyosis follicularis-alopecia-photophobia (IFAP) syndrome (d); ichthyosis prematurity syndrome (IPS) (e), Conradi-Hünermann-Happle syndrome (CDPX2) (f); neutral lipid storage disease with ichthyosis (g); Netherton syndrome (NS) (n); ichthyosis hypotrichosis syndrome (IHS) (courtesy of Dr. Dan Ben Amitai).

**Figure 6**. Concept for the diagnostic approach: The diagnosis is based on dermatological evaluation, a careful family and medical history, and can be strongly supported by directed morphological examinations and other special analyses. If available, molecular analyses are suggested to confirm the diagnosis, allow for testing of family members, and prenatal diagnosis.

1 **Table I.** Main definitions, and recommended new terms and disease names

| Recommended terms | Definition |
|---|---|
| **General terminology** | |
| Disorder of cornification (DOC) | Disease with abnormal terminal keratinocytic differentiation |
| MEDOC | Mendelian disorders of cornification |
| Inherited Ichthyosis | MEDOC affecting all or most of the integument characterized by hyperkeratosis and/or scaling |
| Common ichthyoses | Ichthyoses with high prevalence: Ichthyosis vulgaris (1:250-1,000) and recessive X-linked ichthyosis (1:2,000-6,000) |
| Acquired ichthyosis | Non-inherited ichthyosis associated with malignancy, autoimmune, inflammatory, nutritional, metabolic, infectious and neurologic diseases or medications |
| Autosomal recessive congenital ichthyosis (ARCI)[1] | Modified *umbrella term* for *non-syndromic* congenital ichthyoses referring to harlequin ichthyosis and the spectrum of lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE) (see Table I.1 and IV) |
| Keratinopathic ichthyosis(KPI)[2] | New *umbrella term* for ichthyoses caused by keratin mutations, namely EI, SEI and other minor variants (see Table I.1 and V) |
| Epidermolytic ichthyosis (EI) | New disease name for *bullous ichthyosis, bullous congenital ichthyosiform erythroderma, epidermolytic hyperkeratosis, ichthyosis exfoliativa* |
| Superficial epidermolytic ichthyosis (SEI) | New disease name for *ichthyosis bullosa Siemens* |
| **Diagnostic main criteria for the classification** | |
| Non-syndromic ichthyosis | The phenotypic expression of the underlying genetic defect is only seen in the skin. |
| Syndromic ichthyosis | The phenotypic expression of the underlying genetic defect is seen in the skin as well as in other organs. |
| **Clinical and dermatological terms** | |
| Collodion membrane | Tight shiny cast encasing the newborn which cracks after some time, resulting in irregularly branched fissures |
| Congenital | The disorder is evident at birth or soon after birth (< week 1). |
| Delayed onset | The disorder becomes evident after weeks, months or years. |
| Hyperkeratosis | Histological: increased thickness of the stratum corneum<br>Clinical descriptive: thick and horny skin. It is not necessarily accompanied by visible scaling. |
| Hystrix | Massive hyperkeratosis, cobblestone-like or spiky |
| Keratoderma | Localized form of hyperkeratosis |
| Lamellar scaling | A phenotype in which scales tend to be coarse and large (plate-like scales) |
| Scaling | Visible flakes of stratum corneum of variable size, color and thickness |

[1] Previously termed lamellar ichthyosis / non-bullous ichthyosiform erythroderma (LI/NBIE)

[2] Previously used umbrella term: bullous ichthyosis, epidermolytic hyperkeratosis (EHK) or exfoliative ichthyosis

2

**Table II.1.** Clinico-genetic classification of inherited ichthyoses - Part A: non-syndromic forms

| INHERITED ICHTHYOSES<br>Part A: Non-syndromic forms | | |
|---|---|---|
| **Disease** | **Mode of inheritance** | **Gene(s)** |
| **Common ichthyoses*** | | |
| Ichthyosis vulgaris (IV) | Autosomal semi-dominant | *FLG* |
| Recessive X-linked ichthyosis (RXLI)<br>- Non-syndromic presentation | X-linked recessive | *STS* |
| **Autosomal recessive congenital ichthyosis (ARCI)** | | |
| **Major types:** | | |
| Harlequin ichthyosis (HI) | Autosomal recessive | *ABCA12* |
| Lamellar ichthyosis (LI)[1] | " | *TGM1 / NIPAL4*[2] */ ALOX12B / ABCA12 /* loci on 12p11.2-q13 |
| Congenital ichthyosiform erythroderma (CIE) | " | *ALOXE3 / ALOX12B / ABCA12 / CYP4F22 / NIPAL4*[2] */ TGM1 /* loci on 12p11.2-q13 |
| **Minor variants:** | | |
| Self-healing collodion baby (SHCB) | Autosomal recessive | *TGM1, ALOX12B* |
| Acral self-healing collodion baby | " | *TGM1* |
| Bathing suit ichthyosis (BSI) | " | *TGM1* |
| **Keratinopathic ichthyosis (KPI)** | | |
| **Major types:** | | |
| Epidermolytic ichthyosis (EI)[3] | Autosomal dominant | *KRT1 / KRT10* |
| Superficial epidermolytic ichthyosis (SEI) | " | *KRT2* |
| **Minor variants:** | | |
| Annular epidermolytic ichthyosis (AEI)[3] | Autosomal dominant | *KRT1 / KRT10* |
| Ichthyosis Curth-Macklin (ICM) | " | *KRT1* |
| Autosomal recessive epidermolytic ichthyosis (AREI) | Autosomal recessive | *KRT10* |
| (Epidermolytic nevi[4] | Somatic mutations | *KRT1 / KRT10*) |
| **Other forms** | | |
| Loricrin keratoderma (LK) | Autosomal dominant | *LOR* |
| Erythrokeratodermia variabilis (EKV)[5] | " | *GJB3 / GJB4* |
| Peeling skin disease (PSD) | Autosomal recessive | locus unknown |
| Congenital reticular ichthyosiform erythroderma (CRIE) | Autosomal dominant (?) (isolated cases) | locus unknown |
| Keratosis linearis-ichthyosis congenita-keratoderma (KLICK) | Autosomal recessive | 13q |

*Often delayed onset (in RXLI mild scaling and erythroderma may be present already at birth.)
[1] Few cases of autosomal dominant lamellar ichthyosis described in the literature (locus unknown)
[2] Also known as *ICHTHYIN* gene
[3] *KRT1* mutations are often associated with palmoplantar involvement.
[4] May indicate a gonadal mosaicism, which can cause generalized EI in the offspring generation
[5] Whether *progressive symmetric erythrokeratodermia* (PSEK) harbors a distinct MEDOC form is debated.

4 **Table II.2.** Clinico-genetic classification of inherited ichthyoses - Part B: syndromic forms

| INHERITED ICHTHYOSES<br>**Part B: Syndromic forms** | | |
|---|---|---|
| **Disease** | **Mode of inheritance** | **Gene(s)** |
| **X-linked ichthyosis syndromes** | | |
| *Recessive X-linked ichthyosis (RXLI)<br>- Syndromic presentation | X-linked recessive | *STS* (and others[5]) |
| Ichthyosis follicularis alopecia photophobia (IFAP) syndrome | " | *MBTPS2* |
| Conradi-Hünermann-Happle syndrome (CDPX2) | X-linked dominant | *EBP* |
| **Autosomal ichthyosis syndromes (with)** | | |
| **... prominent hair abnormalities** | | |
| Netherton syndrome (NS) | Autosomal recessive | *SPINK5* |
| Ichthyosis hypotrichosis syndrome (IHS)[6] | " | *ST14* |
| Ichthyosis-hypotrichosis-sclerosing cholangitis (IHSC) syndrome[7] | " | *CLDN1* |
| Trichothiodystrophy (TTD) | " | *ERCC2 / XPD*<br>*ERCC3 / XPB*<br>*GTF2H5 / TTDA* |
| *Trichothiodystrophy (not associated with congenital ichthyosis) | " | *C7Orf11 / TTDN1* |
| **... prominent neurologic signs** | | |
| Sjögren-Larsson syndrome (SLS) | " | *ALDH3A2* |
| *Refsum syndrome (HMSN4) | " | *PHYH / PEX7* |
| Mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratodermia (MEDNIK) syndrome | " | *AP1S1* |
| **... fatal diseases course** | | |
| Gaucher syndrome type 2 | " | *GBA* |
| Multiple sulfatase deficiency (MSD) | " | *SUMF1* |
| Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma (CEDNIK) syndrome | " | *SNAP29* |
| Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome | " | *VPS33B* |
| **... other associated signs** | | |
| Keratitis ichthyosis deafness (KID) syndrome | Autosomal dominant | *GJB2 (GJB6)* |
| Neutral lipid storage disease with ichthyosis | Autosomal recessive | *ABHD5* |
| Ichthyosis prematurity syndrome (IPS) | " | *SLC27A4* |

*CDPX2*, Chondrodysplasia punctata type 2; *HMSN4*, Hereditary motor and sensory neuropathy type 4

[5] In the context of a contiguous gene syndrome

[6] Clinical variant: Congenital ichthyosis, follicular atrophoderma, hypotrichosis, and hypohidrosis syndrome

[7] Also known as neonatal ichthyosis sclerosing cholangitis (NISCH) syndrome

5

Table 3

**Table III.** Common forms of ichthyosis: Summary of clinical and morphological findings

| | **Ichthyosis vulgaris (IV)** (Prevalence: 1:250-1,000) | **Recessive X-linked ichthyosis (RXLI)** (Prevalence: 1:2,000-6,000) |
|---|---|---|
| **Mode of inheritance** | Autosomal semi-dominant | XR |
| **Onset** | After ~2-6 month | Exaggerated scaling and/or erythroderma in the newborn period or late onset after ~2-6 months, mild collodion-like skin at birth may be possible |
| **Initial clinical presentation** | Xerosis, scaling, pruritus, eczema | Scaling |
| **Disease course** | Stable, often better in summer | Stable, often better in summer |
| **Cutaneous findings:** | | |
| **Distribution of scaling** | Generalized, antecubital or popliteal fossae often spared | Generalized, sparing of body folds, neck is often more severely involved |
| **Scaling type** | Fine or light | Large rhomboid scales or fine scaling |
| **Scaling color** | White-grey | Dark-brown or light-grey |
| **Erythema** | Absent | Absent |
| **Palmoplantar involvement** | Accentuated palmoplantar markings | No accentuated markings |
| **Hypohidrosis** | Possible | Possible |
| **Scalp abnormalities** | Absent | Absent |
| **Others** | Eczema | - |
| **Extracutaneous involvement** | Strong association with atopic manifestations | Incidence of cryptochidism/ testicular maldescent seems to be increased (estimated numbers rang from 5% up to 20%), subclinical corneal opacities in ~50%; insufficient cervical dilatation in female carriers. * Contiguous gene syndromes have to be ruled out. |
| **Ultrastructure** | Small or only rudimental keratohyaline granules | Retained corneodesmosomes within the SC |
| **Special analyses** | Reduced or absent SG, reduced or negative filaggrin staining by antigen mapping | Absent steroid sulfatase (arylsulfatase-C) activity (leukocytes or fibroblasts), FISH test for STS deletion; elevated blood cholesterol sulfate levels (Fetal steroid sulfatase deficiency leads to low maternal serum/ urinary estriol levels. Therefore, RXLI may be detected in utero, when prenatal screening for Down syndrome and other disorders includes measurement of maternal estriol levels, as in the "triple screen" blood test.) |

*XR*, X-linked recessive; *SC*, stratum corneum; *SG*, stratum granulosum; *FISH*, florescent in situ-hybridization

* RXLI within the context of a contiguous gene syndrome (see Table II.2), e. g. in Kallmann syndrome, chondrodysplasia punctata (brachytelephalangic type) or ocular albinism type 1

Table 4

**Table IV.** Autosomal recessive congenital ichthyoses (ARCI): Summary of the clinical and morphologic findings

| | Harlequin ichthyosis (HI) | Lamellar ichthyosis (LI) | Congenital ichthyosiform erythroderma (CIE) |
|---|---|---|---|
| **Mode of inheritance** | AR | AR | AR |
| **Onset** | At birth, often preterm babies | At birth | At birth |
| **Initial clinical presentation** | Severe collodion membrane with armour-like membrane, extreme ectropion and eclabium, and contractures, broadened nose, synechiae of auricles, sometimes toes | Collodion membrane with ectropion and eclabium; less frequently congenital ichthyosiform erythroderma | Congenital ichthyosiform erythroderma or less frequently mild collodion membrane |
| **Disease course** | Development of an exfoliative / very scaling erythroderma similar to severe CIE with fine or large scales | Ranging from very mild to severe (probably never completely heals)<br>**Minor variants:**<br>- **Self-healing collodion baby (SHCB):** nearly complete resolution of scaling within the first three months of life (in ~10% of the cases)<br>- **Acral SHCB:** At birth only acral collodion membranes are observed that later on heal.<br>- **Bathing suit ichthyosis (BSI):** Collodion membrane at birth and development of LI or CIE. Then, within the first months of life, the skin predominantly of the extremities heals, but warmer skin areas, e. g. axillary region, scalp, (mid-)trunk, remain involved and show a localized form of LI. | Ranging from very mild to severe |
| **Cutaneous findings:** | | | |
| **Distribution of scaling** | Generalized | Generalized; focally pronounced scaling possible | Generalized; focally pronounced scaling possible |
| **Scaling type** | Coarse and large (plate-like) | Coarse and large (plate-like) | Fine |
| **Scaling color** | Grey or yellowish | Brownish or dark | White or grey |
| **Erythema** | Severe | Variable, less pronounced | Variable, often pronounced |
| **Palmoplantar involvement** | Yes, possibly with synechia of digits | **NIPAL4*: pronounced keratoderma; *ALOX12B* and *CYP4F22*: pronounced lichenification and mild keratoderma; *ALOXE2*: Ichthyosis vulgaris-like; *TGM1*: frequent palmoplantar involvement | |
| **Hypohidrosis** | Severe temperature dysregulation | Moderate to severe | Moderate to severe |
| **Scalp abnormalities** | Scarring alopecia | Scarring alopecia possible (often with *TGM1*) | Scarring alopecia possible |
| **Other skin findings** | Prone to skin infections | - | - |
| **Extracutaneous involvement** | Contractures; failure to thrive; short stature | Short stature (if severe) | Failure to thrive, short stature (if severe) |
| **Risk of death** | Very high during neonatal period | Elevated during neonatal period | Present during neonatal period |
| **Skin ultrastructure** | Vesicular lamellar body ghosts; paucity of secreted lamellar structures in SC | *ABCA12*=absence of LB content; **NIPAL4*= weak correlation with vesicular complexes, defective LB, perinuclear membranes within the SG in the glutaraldehyde fixation; *TGM1*: thin cornified envelope and disorganization of lamellar bilayers (with glutaraldehyde fixation: polygonal clefts within corneocytes) | |
| **Other analyses** | None | In situ monitoring of TGase-1 activity in cryosections, 'SDS heating test' of scales | |

*AR*, autosomal recessive; *LB*, lamellar body; *SC*, stratum corneum; *SG*, stratum granulosum; *SHCB*, self-healing collodion baby; *TGase-1*, transglutaminase-1
**NIPAL4* also known as *ICHTHYIN*

1 **Table V.** Keratinopathic ichthyoses (KPI) and CRIE: Summary of the clinical and morphologic findings

| | Epidermolytic ichthyosis (EI) | Superficial epidermolytic ichthyosis (SEI) | Ichthyosis Curth Macklin (ICM) | Congenital reticular ichthyosiform erythroderma (CRIE)* |
|---|---|---|---|---|
| **Mode of inheritance** | AD or rarely AR (*KRT10*)<br>**Annular type:** AD | AD | AD | AD (?) (isolated cases) |
| **Onset** | At birth | At birth | Early childhood | At birth |
| **Initial clinical presentation** | Large erosions, mild scaling, erythroderma at birth | Erythroderma, widespread blistering | Striate or diffuse palmoplantar keratoderma | Exfoliative CIE, larger areas forming a reticular pattern predominantly on the extremities |
| **Disease course** | Resolution of erosions replaced by hyperkeratosis in the first months<br>**Annular type:** development of numerous annular, polycyclic, erythematous, scaly plaques on the trunk and extremities that enlarge slowly, and then resolve (intermittent presentations of EI) | Within weeks development of hyperkeratosis particularly over extensor sides of joints | Progressive worsening of PPK and development of hyperkeratotic plaques over joints and/or hyperkeratotic papules on the trunk and extremities | During childhood and puberty a characteristic patchy pattern starts to evolve |
| **Cutaneous findings:** | | | | |
| **Distribution of scaling** | Generalized, or predilection of friction areas, over joints | Friction areas | Palms and soles, large joints, rarely extremities and/or trunk | Generalized, later reticular ichthyosiform pattern |
| **Scaling type** | Adherent, moderate | Adherent, fine to moderate | Thick, spiky hyperkeratosis | Fine |
| **Scaling color** | White-brown | Brown ("Mauserung/molting") | Yellow-brown hyperkeratoses | Yellow-brown |
| **Erythema** | Frequent | Initially, fades | Erythroderma possible | Pronounced |
| **Palmoplantar involvement** | *KRT1*: epidermolytic PPK<br>*KRT10*: palms and soles are spared (exceptions possible) | Usually no | Massive PPK leading to deep, bleeding and painful fissures, flexural contractures, constriction bands | Yes |
| **Hypohidrosis** | Possible | Possible | None | - |
| **Scalp abnormalities** | Scaling | - | None | Scaling |
| **Other skin findings** | Pruritus, Blisters after minor trauma, proneness to skin infections / impetigo | Pruritus, bullae may occur after minor mechanical trauma ( often in summer) | - | - |
| **Extracutaneous involvement** | Growth failure with some severe phenotypes | | Gangrene and loss of digits | Growth failure with some severe phenotypes |
| **Risk of death** | Elevated during neonatal period | - | - | Elevated during neonatal period |
| **Skin ultrastructure** | EHK, aggregations and clumping of keratin filaments in suprabasal cells; partly cytolysis, lamellar body accumulation | Superficial EHK, cytolysis in granular cells of affected body areas; no keratin clumping | Binuclear cells, particular concentric perinuclear "shells" of aberrant - putatively - keratin material | Vacuolization of superficial granular cells and (often?) so far unidentified filamentous material in vacuolated cells |
| **Special analyses** | - | - | - | - |

*AD,* autosomal dominant; *AR*, autosomal recessive; *EHK,* epidermolytic hyperkeratosis; *PPK*, palmoplantar keratoderma *SC*, stratum corneum; *SG*, stratum granulosum
*also known as 'Ichthyosis variegata' and 'Ichthyosis en confettis'

Table 6

**Table VI.** Other non-syndromic ichthyosis forms: Summary of the clinical and morphologic findings

| | Loricrin keratoderma (LK) | Erythrokeratodermia variabilis (EKV) | Keratosis linearis, ichthyosis congenita, keratoderma (KLICK) | Peeling skin disease (PSD) |
|---|---|---|---|---|
| **Mode of inheritance** | AD | AD | AR | AR |
| **Onset** | At birth | At birth or within first year of life | At birth | At birth (or first weeks of life) |
| **Initial clinical presentation** | CIE or collodion baby | Co-occurrence of transient, migratory erythematous patches and hyperkeratosis limited to geographic outlined plaques or generalized | Congenital ichthyosis | Ichthyosiform erythroderma (IE), atopic dermatitis-like lesions |
| **Disease course** | Improvement and development of PPK | Relapsing-remitting, erythema are fleeting (hours-days), hyperkeratosis more stable (months to years) | Mild | Mild to moderate, spontaneous remissions, and relapses |
| **Cutaneous findings:** | | | | |
| **Skin distribution** | Generalized mild scaling with accentuated hyperkeratosis over joints, flexural areas | Generalized or focally accented hyperkeratosis, predominantly on extremities, buttocks | Generalized, accentuated linear keratoses in skin folds, (sclerosing) PPK | Generalized (to be differentiated from acral PSS) |
| **Scaling type** | Fine | Rough, thickened skin, possibly hystrix skin; occasionally peeling | | Large peeling scales |
| **Scaling color** | White | White to grey, yellow or brown | White-Brown | White |
| **Erythema** | Uncommon | Focal migratory | Uncommon | Varying from mild to moderate, may improve with age |
| **Palmoplantar involvement** | Non-inflammatory diffuse PPK with honeycomb pattern, mild digital constriction, brown hyperkeratosis, knuckle pads over dorsal aspects | Diffuse PPK present in about 50% of patients | Yes | Yes |
| **Hypohidrosis** | - | No | Yes | No |
| **Scalp abnormalities** | No | No | No | No hair abnormalities |
| **Other skin findings** | Keratoderma (thickening), pseudo-ainhum or (mild) linear constrictions | No | Linear keratosis | Pruritus |
| **Extracutaneous involvement** | - | None | None | Associated atopic diathesis, short stature (single cases) |
| **Risk of death** | - | No | Normal | Elevated during neonatal period |
| **Skin ultrastructure** | Electron dense intranuclear granules in granular cells, thin CE in lower SC, abnormal extracellular lamellae | Mostly non specific changes with various degrees of deviations or suppression of keratinization and reduction of LB in the SG | Hypergranulosis and abnormally big keratohyaline granules | Superficial exfoliation, separation directly above SG or within SC, either between adjacent or within corneocytes |
| **Other analyses** | Histology: Parakeratosis, and hypergranulosis | - | - | Immunohistochemistry: LEKTI is normal or even elevated |

*AD*, autosomal dominant; *AR*, autosomal recessive; *LB*, lamellar body; *PPK*, palmoplantar keratoderma; *SC*, stratum corneum; *SG*, stratum granulosum

Table 7

**Table VII.** X-linked ichthyosis syndromes (for RXLI see Table III): Summary of the clinical and morphologic findings

| | Ichthyosis follicularis alopecia photophobia (IFAP) syndrome | Conradi-Hünermann-Happle syndrome (CDPX2) |
|---|---|---|
| **Mode of inheritance** | XR* | XD |
| **Onset** | At birth | At birth |
| **Initial clinical presentation** | Mild collodion skin, congenital atrichia | Ichthyosiform erythroderma may be severe |
| **Disease course** | Development of generalized follicular keratosis that can be severe or improves during the first year of life | CIE clears up after a few months, lifelong hyperkeratosis distributed in a linear, blotchy pattern, follicular atrophoderma |
| **Cutaneous findings:** | | |
| **Distribution of scaling** | Generalized (mosaic in carriers) | Generalized or mosaic pattern of skin lesions |
| **Scaling type** | Mild to moderate | Discrete IV-like scaling |
| **Scaling color** | Whitish | Variable |
| **Erythema** | Mild | Resolving after birth |
| **Palmoplantar involvement** | Inflammatory focal to diffuse (also possible in carriers) | Unusual |
| **Hypohidrosis** | Mild | No |
| **Scalp abnormalities** | Follicular keratoses, atrichia, occasionally some sparse and thin hair may be present | Patchy areas of cicatricial alopecia |
| **Other skin findings** | Disturbed nail growth (possible), proneness to infections | Sparse eyelashes and eyebrows, nail anomalies |
| **Extracutaneous involvement** | Severe photophobia (vascularizing keratitis or anomalies in Bowman's membrane), retarded psychomotor development, in some cases: cerebral atrophy, temporal lobe malformation, hypoplasia of corpus callosum, failure to thrive, atopic manifestations, inguinal hernia, aganglionic megacolon, testicular or renal anomalies | Stippled calcifications of enchondral bone formation, chondrodysplasia punctata, short stature, asymmetric shortening of legs, kyphoscoliosis, dysplasia of hip joints, sectorial cataracts, asymmetric facial appearance due to unilateral hypoplasia, flattened nose bridge |
| **Risk of death** | Present during neonatal period | Present during neonatal period |
| **Skin ultrastructure** | Non-epidermolytic hyperkeratosis | Cytoplasmic vacuoles of keratinocytes in the SG |
| **Other analyses** | Histology: Numerous atrophic hair follicles and absence of sebaceous glands | Histology: Calcification in follicular keratoses (in neonates); roentgenographic examination; serum GC-MS for high 8-DHC and cholestenol level |

*Female carriers may present with a linear pattern of mild follicular ichthyosis, mild atrophoderma, hypotrichosis, and hypohidrosis (X-chromosomal lyonization effect).
*8-DHC*, 8-dehydrocholesterol; *CDPX2*, chondrodysplasia punctata type 2; *CIE*, congenital ichthyosiform erythroderma; *GC-MS*, gas chromatography-mass spectrometry; *KG*, keratohyaline granules; *LB*, lamellar body; *PPK*, palmoplantar keratoderma; *RXLI*, recessive X-linked ichthyosis, *SG*, stratum granulosum; *XD*, X-linked dominant; *XR*, X-linked recessive

**Table VIII.1.** Autosomal ichthyosis syndromes with prominent hair abnormalities: Summary of clinical and morphologic findings

| | Netherton syndrome (NTS) | Ichthyosis with hypotrichosis (IHS) | Ichthyosis-hypotrichosis-sclerosing cholangitis (IHSC) syndrome[1] |
|---|---|---|---|
| **Mode of inheritance** | AR | AR | AR |
| **Onset** | At birth (or later) | at birth | At birth (or shortly after) |
| **Initial clinical presentation** | CIE in most of cases, collodion membrane rare, Ichthyosis linearis circumflexa (ILC), atopic dermatitis like lesions | Lamellar ichthyosis, severe hypotrichosis, absent eyebrows and eyelashes | Mild scaling, neonatal jaundice with hepatomegaly, frontal alopecia in early childhood |
| **Disease course** | Mild to severe, spontaneous remissions, and relapses | Over time, scalp hair growth and appearance / color may improve | Mild ichthyosis, liver involvement variable |
| **Cutaneous findings:** | | | |
| **Skin distribution** | Localized (ILC-type) or generalized (CIE-type) | Generalized, including the scalp, face may be unaffected | Predominant on trunk |
| **Scaling type** | Fine or large, double edged scales (ILC) | Coarse, plate-like, adherent | Fine to polygonal, thin |
| **Scaling color** | White | Brown to dark | Normal |
| **Erythema** | Frequent, varying from moderate to severe, may improve with age | Unusual | Unusual |
| **Palmoplantar involvement** | Possible | No | No |
| **Hypohidrosis** | No | Yes | No |
| **Scalp abnormalities** | Short, fragile and brittle hair, alopecia (hair, lashes and eyebrows); spontaneous remissions and relapses | Hypotrichosis in youth, sparse, unruly hair in adolescence, recessing frontal hair line in adults | Major criterion: coarse thick hair, fronto-temporal scarring alopecia; hypotrichosis, curly/woolly hair |
| **Other skin findings** | Severe pruritus, prone to bacterial and viral (HPV) skin infections | Follicular atrophoderma | |
| **Extracutaneous involvement** | Hair shaft (HS) abnormalities, failure to thrive, severe atopic diathesis, increased IgE level and eosinophilia, frequent skin infections (Staphylococcus aureus or HPV) | Sparse and curly eyebrows, occasionally photophobia and pingueculum | Major criterion: Sclerosing cholangitis or congenital paucity of bile ducts[2] |
| **Risk of death** | Life threatening neonatal hypernatremic dehydration, and sepsis | Normal | Not observed, but theoretically possible from liver involvement |
| **Skin ultrastructure** | Suppressed keratinization, thin or absent SC & SG, reduction of corneodesmosomes, intercorneal clefts | High presence of intact corneo-desmosomes in the upper SC, residues of membranous structures in the SC | Splitting of desmosomal anchoring plaques in the SG |
| **Other analyses** | Trichorrhexis invaginata: highly diagnostic (usually after 1 year), but inconsistent; skin immunochemistry: absent or reduced expression of LEKTI | Hair microscopy may reveal dysplastic hair, pili torti or pili bifurcate | Liver function tests, cholangiography, liver biopsy |

*AR*, autosomal recessive; *CIE*, congenital ichthyosiforme erythroderma, *ILC*, ichthyosis linearis circumflexa, *SC*, stratum corneum, *SG*, stratum granulosum

[1] also known as neonatal ichthyosis-sclerosing cholangitis (NISCH) or ILVASC syndrome

[2] previously described leukocyte vacuoles are probably an artifact and are no longer a diagnostic criteria

**Table VIII.2.** Autosomal ichthyosis syndromes with prominent hair abnormalities and/or neurologic signs: Summary of clinical and morphologic findings

| | Trichothiodystrophy (TTD) | TTD (not associated with CI) | Sjögren-Larsson syndrome (SLS) | Refsum syndrome (HMSN4) | MEDNIK* syndrome |
|---|---|---|---|---|---|
| **Mode of inheritance** | AR | AR | AR | AR | AR |
| **Onset** | At birth | Childhood or late adulthood | At birth | Childhood or late adulthood | At birth or within first weeks of life |
| **Initial clinical presentation** | Collodion baby, CIE | Xerosis, scaling, IV-like | CI of mild type, focal accentuation of hyperkeratosis on scalp & neck | Xerosis, Scaling | Erythematous rashes, similar to EKV |
| **Disease course** | Post neonatal improvement in most cases, mild LI possible | Progressive | Mild to moderate | Progressive | Progressive |
| **Cutaneous findings:** | | | | | |
| **Distribution of scaling** | Generalized | Generalized | Generalized but more severe on the trunk & neck | Generalized | Generalized, |
| **Scaling type** | Fine, rarely lamellar | Fine or light | Velvet-like, fine scaling | Fine or light | EKV-like |
| **Scaling color** | White, grey | White-grey | Grayish | White-grey | " |
| **Erythema** | Due to photosensitivity | Absent | Yes | Absent | " |
| **Palmoplantar involvement** | Possible palmoplantar keratoderma | Accentuated palmoplantar markings | Yes | Accentuated palmoplantar markings | Not specifically |
| **Hypohidrosis** | No | No | Yes | Unusual | ? |
| **Scalp abnormalities** | Hair fragility, variable | Hair fragility, variable | - | Absent | Not specifically |
| **Other skin findings** | Photosensitivity, atopic dermatitis | - | Pruritus | - | nail thickening, mucous membrane affected |
| **Extracutaneous involvement** | Growth and developmental delay, short stature, recurrent infections, cataracts | | Spastic paraplegia, mental retardation, ocular involvement | Development of night blindness (retinitis pigmentosa), anosmia, progressive deafness, peripheral neuropathy, cerebellar ataxia | Congenital sensorineural deafness, peripheral neuropathy, psychomotor and growth retardation, chronic diarrhea, mental retardation |
| **Risk of death** | High risk of death in childhood due to infection | | Increased | Without treatment present | Life threatening congenital diarrhea |
| **Skin ultrastructure** | Limited studies: perinuclear vacuoles in the cytoplasm of keratinocytes, irregularly arranged bundles of tonofilaments (?) | | Not specific: abnormal LB, cytoplasmic lipid vacuoles and lamellar/nonlamellar phase separations layers | Mostly non specific: lipid vacuoles in melanocytes, basal keratinocytes and dermal cells | Histology: hyperkeratosis with hypergranulosis |
| **Other analyses** | Hair shafts with alternating light & dark bands under polarizing microscopy and structural abnormalities such as trichochisis, low-sulfur hair content | | Eye examination; increased fatty alcohols (blood); reduced aldehyde dehydrogenase or fatty alcohol NAD oxidoreductase (leucocytes) | Increased phytanic acid levels (blood) | Elevation of VLCFAs (blood) |

*AR*, autosomal recessive; *CI*, congential ichthyosis; *IV*, ichthyosis vulgairs; *SG*, stratum granulosum; *SC*, stratum corneum, *LB*, lamellar body; *EKV*, erythrokeratodermia variabilis
**MEDNIK*, Mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratodermia (~erythrokeratodermia variabilis 3, Kamouraska type)

**Table VIII.3.** Autosomal recessive ichthyosis syndromes with fatal disease course: Summary of clinical and morphologic findings

| | Gaucher syndrome type 2 | Multiple sulfatase syndrome | Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma (CEDNIK) syndrome | Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome |
|---|---|---|---|---|
| **Mode of inheritance** | AR | AR | AR | AR |
| **Onset** | At birth, or later | At birth, or later | After 5-11 months | At birth, can sometimes be late |
| **Initial clinical presentation** | CIE or less frequently mild collodion membrane | Prevailing neurological symptoms, skin similar to RXLI | Until up to one year of age, normal skin; thereafter LI type | Xerosis and scaling within a few days of birth |
| **Disease course** | Ranging from mild to moderate | Fatal | Fatal | Fatal |
| **Cutaneous findings:** | | | | |
| **Distribution of scaling** | Generalized | Generalized, sparing of body folds | Generalized with sparing of skin folds | Generalized with sparing of skin folds |
| **Scaling type** | Fine or moderate; scaling may resolve after neonatal period | Large rhomboid scales or fine scaling | Coarse and large (plate-like) | Fine or platelike (extensor sites) |
| **Scaling color** | White or grey or brown | Dark-brown or light-grey | Whitish | White or brownish |
| **Erythema** | Unusual | Absent | Absent | Absent |
| **Palmoplantar involvement** | - | - | Yes | Spared |
| **Hypohidrosis** | Yes | - | Not studied (no heat stroke) | Not studied |
| **Scalp abnormalities** | - | Absent | Fine, sparse hair | Mild scarring alopecia |
| **Other skin findings** | - | Possible | None | Ectropion |
| **Extracutaneous involvement** | Hydrops fetalis; progressive neurological deterioration; hepatosplenomegaly, hypotonia, respiratory distress, arthrogryposis, facial anomalies | Metachromatic leukodystrophy, mucopolysaccharidoses, progressive psychomotor deterioration | Sensorineural deafness; cerebral dysgenesis; neuropathy; microcephaly; neurogenic muscle atrophy; optic nerve atrophy; cachexia | Arthrogryposis (wrist, knee or hip); intrahepatic bile duct hypoplasia with cholestasis; renal tubular degeneration; metabolic acidosis; abnormal platelet function; cerebral malformation |
| **Risk of death** | Death often by two years of age | Death within the first year of life | Lethal within the first decade | Lethal within first year of life |
| **Skin ultrastructure** | Lamellar/non-lamellar phase separations in SC | Same ultrastructural features as RXLI | Impaired lipid loading onto LB and defective LB secretion | Defective LB secretion |
| **Special analyses** | Liver function tests; decreased beta-glucocerebrosidase activity (leukocytes); Gaucher cells (bone marrow); increased acid phosphatase (serum) | Diagnostic urinary metabolites | Absent RAB protein on immunohistochemistry, MRI | Liver and renal biopsy |

*AR*, autosomal recessive; *CIE*, congenital ichthyosiform erythroderma; *IV*, ichthyosis vulgairs; *LB*, lamellar body; RXLI, *recessive X-linked ichthyosis*; *SC*, stratum corneum

**VIII.4.** Autosomal ichthyosis syndromes with other associated signs: Summary of clinical and morphologic findings.

| | **Keratitis ichthyosis deafness (KID) syndrome**[1] | **Neutral lipid storage disease with ichthyosis** | **Ichthyosis prematurity syndrome (IPS)**[2] |
|---|---|---|---|
| **Mode of inheritance** | AD | AR | AR |
| **Onset** | At birth or within the first year of life | At birth, or shortly after | At birth (polyhydramnion, prematurity, >6 weeks) |
| **Initial clinical presentation** | Severe generalized (or localized) (erythro)keratoderma with spiky, hyperkertosis, PPK, keratitis, ectropion, nail dystrophy | Congenital ichthyosiform erythroderma, EKV-like changes or less frequently mild collodion membrane | Respiratory distress, generalized skin hyperkeratosis with focal accentuation on scalp, eyebrows |
| **Disease course** | Lethal in neonatal period in some cases, progressive hyperkeratosis, PPK and keratitis in some, improvement in others | Ranging from mild to moderate | Severe at birth, spontaneous improvement |
| **Cutaneous findings:** | | | |
| **Distribution of scaling** | Generalized or focally accented hyperkeratosis | Generalized | Focal accentuation (see above) |
| **Scaling type** | Hystrix or cobblestone | Fine or moderate | Caseous (vernix caseosa-like) |
| **Scaling color** | Brown-yellow-grey | White or grey or brown | Whitish |
| **Erythema** | Generalized-focal | Unusual | Mild to moderate |
| **Palmoplantar involvement** | Diffuse PPK with grainy surface, very common | Yes | Yes, initially |
| **Hypohidrosis** | No | Yes | No |
| **Scalp abnormalities** | Hypotrichosis possible, scarring alopecia in association with follicular occlusion syndrome | - | Extensive at birth |
| **Other skin findings** | Recurrent fungal, bacterial and viral infections, Association with follicular occlusion syndrome (e. g. hidradenitis suppurativa ), mucocutaneous squamous cell carcinoma in 10-20% of patients | Rhomboid lichenification of nuchal skin | Follicular keratosis ("toad skin"), atopic eczema, asthma, eosinophilia |
| **Extracutaneous involvement** | Photophobia, keratitis, variable degree of SNHL (mostly bilateral), absence of corpus callosum and shortened heel cords possible | Jordan's anomaly, variable hepatosplenomegaly, mild myopathy, cataract; occ: developmental delay, short stature | Pulmonary involvement and asphyxia at birth, later on atopic asthma, eosinophilia, and occasionally hyper IgE |
| **Risk of death** | Lethal in some severe congenital presentations (e.g. in case of G45E mutation) | Normal | Perinatally potentially fatal due to respiratory asphyxia; otherwise normal |
| **Skin ultrastructure** | Limited studies: abnormal KG and tonofilaments | Keratinocytes with lipid droplets, abnormal LB | Deposits of trilamellar membranous curved lamellae in swollen corneocytes and perinuclearly in edematous granular cells |
| **Other analyses** | None | Abnormal liver function tests; increased CPK, fasting test (reduced lipolysis), lipid vacuoles within polymorphonuclear leukocytes and monocytes ('Jordan's anomaly') | Blood cell count (eosinophilia) |

*AR*, autosomal recessive; *LB*, lamellar body; *PPK*, palmoplantar keratoderma; *SC*, stratum corneum, *SG*, stratum granulosum; *SNHL*, Sensorineural hearing loss

[1] May overlap with Clouston syndrome in rare cases

[2] To be differentiated from self-healing collodion baby (see Table IV)

**Table IX.** Overview of the molecular basis and pathophysiologic aspects of inherited ichthyoses and related MEDOC (Refer to the chapter 'Modern pathophysiologic view').

| Primary defect | Pathophysiologic aspects of the epidermis | Affected gene(s) | Diseases |
|---|---|---|---|
| **1.) *Disorders of keratinocyte proteins ('bricks')*** | | | |
| **Cytoskeleton** | | | |
| Keratin intermediate filament (KIF) disorder | Weakening or collapse of cytoskeleton and decreased mechanical stability of epidermis; affecting LB secretion resulting in paucity of SC lamellar material & CDSN retention | *KRT1 / 10*<br>*KRT1*<br>*KRT2* | Epidermolytic ichthyosis<br>Ichthyosis Curth-Macklin<br>Superficial epidermolytic ichthyosis |
| **Cornified lipid/cell envelope** | | | |
| TGase-1 deficiency | Weak cornified cell envelope with reduced lamellar membrane and NLPS | *TGM1* | Lamellar ichthyosis, CIE, SHCB, BSI |
| Loricrin disorder | Weak cornified cell envelope with reduced lamellar membrane and NLPS. Possible cytotoxic effect through gain of function of mutant loricrin molecules | *LOR* | Loricrin keratoderma |
| **Protease/protease-inhibitors** | | | |
| LEKTI deficiency | Increased serine protease activity with premature loss of CDSN and induction of inflammation | *SPINK5* | Netherton syndrome |
| Matriptase deficiency | Defective filaggrin processing | *ST14* | IHS |
| Cathepsin C deficiency | Impaired innate immune response & desquamation | *CTSC* | Papillon-Lefèvre syndrome |
| **Keratohyaline** | | | |
| Filaggrin deficiency | Decreased corneocyte hydration due to low natural moisturizing factor (NMF). High SC pH resulting in increased protease activity | *FLG* | Ichthyosis vulgaris |
| **2.) *Disorders of lipid metabolism, assembly and/or transport ('mortar')*** | | | |
| **Lipid synthesis/ modification** | | | |
| Hepoxilin pathway defect | Defect of different enzymes (or receptors) within the lipoxygenase pathway, impaired processing of profilaggrin to monomeric filaggrin (abnormal SC lipid composition likely) | *ALOX12B*<br>*ALOXE3*<br>*CYP4F22*<br>*NIPAL4* | Lamellar ichthyosis; Congenital ichthyosiform erythroderma |
| Steroid sulfatase deficiency | Abnormal SC lipid composition with lamellar/ NLPS; inhibition of proteases causes persistence of CDSN | *STS* | Recessive X-linked ichthyosis |
| Fatty acid transporter defect | Impaired transport and activation of fatty acids (critical fetal/neonatal period), defective SC lipid homeostasis | *SLC27A4* | Ichthyosis prematurity syndrome |
| **Lipid transport and secretion** | | | |
| Primary lamellar body (LB) defect | Disturbed transport of lipids as well as proteases, protease inhibitors, and antimicrobial peptides. Paucity of SC lamellar structures. | *ABCA12 (nonsense vs. missense)* | Harlequin ichthyosis; Lamellar ichthyosis/CIE |
| **Cholesterol biosynthesis and homeostasis disorders** | | | |
| 8-7 sterol isomerase | Defective "Kandutsch" pathway | *EBP* | CDPX2 |
| C3 sterol dehydrogenase | Interference with "sonic hedgehog" | *NSDHL* | CHILD syndrome |
| Zinc endopeptidase/site-2-protease defect | Impaired transcription factors (SREBF1&2) affect sterol/ER homeostasis and cell differentiation | *MBTPS2* | IFAP syndrome |
| **Triglyceride metabolism** | | | |
| Neutral lipid storage disease | Abnormal SC lipid composition with lamellar/non-lamellar phase separaions | *ABHD5* | Neutral lipid storage disease with ichthyosis |
| **Lysosomal storage** | | | |
| Glucocerebrosidase deficiency | Disturbance of the SC lipid composition of ceramides, cholesterol, and free fatty acids | *GBA* | Gaucher syndrome type 2 |
| **Peroxisomal hydroxylation** | | | |
| Phytanoyl-CoA hydroxylase deficiency | Phytanic acid excess disturbs cholesterol / cholesterol sulfate, or alters lipid degradation | *PHYH*<br>*PEX7* | Refsum syndrome |
| **Microsomal oxidation** | | | |
| Fatty aldehyde dehydrogenase deficiency | SC lamellar phase separation or NLPS | *ALDH3A2* | Sjögren-Larsson syndrome |
| **Intracellular membrane trafficking** | | | |
| Secretory (SNARE) pathway defects | Impaired LB function | *AP1S1*<br>*SNAP29*<br>*VPS33B* | MEDNIK syndrome<br>CEDNIK syndrome<br>ARC syndrome |
| **3.) *Disorders of cell-cell junctions*** | | | |
| **Gap junctions** | | | |
| Connexin disorders | (?) Increased sensitivity to apoptosis, reactive hyperproliferation, impaired calcium regulation | *GJB2 (GJB6)*<br>*GJB3/GJB4* | KID syndrome<br>EKV |
| **Tight junctions** | | | |
| Claudin disorders | (?) Impaired regulation of paracellular permeability, defective epithelial polarization | *CLDN1* | IHSC syndrome |
| **4.) *Disorders of DNA transcription/repair*** | | | |
| **Nucleus** | | | |
| Nucleotide excision repair defect | ? | C7Orf11<br>*ERCC2/XPD*<br>*ERCC3/XPB* | Trichothiodystrophies/ TFIIH related |
| Transcription defect (?) | ? | *C7Orf11* | TTD without CI |

*CDSN*; corneodesmosome; *CE*, cornified envelope; *ER*, endoplasmatic reticulum; *KIF*, Keratin intermediate filament; *LB*, lamellar body; *NLPS*, non-lamellar phase separations; *SC*, stratum corneum (for abbreviations of diseases see Table II.1-2.)

**Table X.** Examples of foundations, patient organizations and useful internet links

| **Foundations and registries:** | |
|---|---|
| US: Foundation for Ichthyosis and Related Skin Types (FIRST) (www.scalyskin.org), Registry for Ichthyosis and Related Disorders (www.skinregistry.org/) | |
| Germany (Europe): Network for Ichthyoses and Related Keratinization disorders (NIRK) (www.netzwerk-ichthyose.de/) | |
| Japan: registry for ARCI and KPI supported by the Health and Labor Science Research Grants, Research on Intractable Diseases, Ministry of Health, Labor and Welfare | |
| Austria: national registry for genodermatoses including ichthyoses | |
| **Patient organizations for ichthyosis:** | |
| Austria | www.selbsthilfe-tirol.at/Selbsthilfegruppen/Gruppen/Ichthyose.htm |
| Belgium | www.devidts.com/ichthyosis |
| Denmark | www.iktyosis.dk |
| Finland | www.iholiitto.fi/ |
| France | www.anips.net/ |
| Germany | www.ichthyose.de |
| Italy | www.ittiosi.it/ |
| Japan | www.gyorinsen.com |
| Monaco | www.aaimonaco.org |
| Spain | www.ictiosis.org |
| Sweden | www.iktyos.nu/ |
| Switzerland | www.ichthyose.ch |
| UK | www.ichthyosis.org.uk/ |
| US | www.scalyskin.org |
| **Other databases and internet links:** | |
| Web site hosted at NCBI: | www.genetests.org |
| Portal for rare diseases and orphan drugs: | www.orpha.net |
| Human intermediated filament database: | www.interfil.org |
| German guidelines for diagnosis and treatment of ichthyoses: | www.uni-duesseldorf.de/AWMF/ll/013-043.htm |

**Figure 1**
**Click here to download high resolution image**