Volume Two

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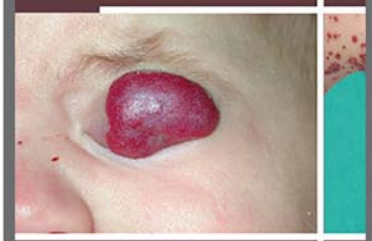

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Volume One

5th Edition

Schachner and Hansen's

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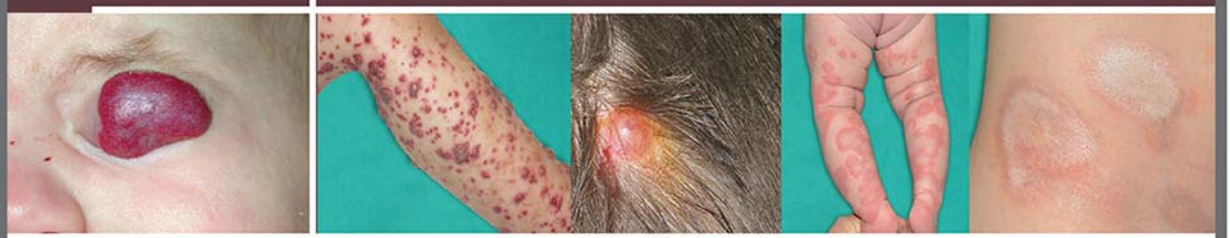

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SECTION

Genetic Diseases of the Skin in Children

CHAPTER

4.1

Disorders of Cornification

Qisi Sun, Nareh V Marukian, Keith A Choate

INTRODUCTION

A variety of disorders stem from abnormal epidermal differentiation and desquamation or defects of the epidermal permeability barrier. These disorders of cornification (DOC) are historically separated into several large groups including the ichthyoses, erythrokeratodermas, and palmoplantar keratodermas that comprise >24 well-defined entities.[1–3] Genetic advances have disclosed the cause of many of these disorders, and thus our system for their classification has changed. In this chapter, we will discuss most of the classical mendelian DOCs (MeDOCs) and the diseases classically considered as "ichthyoses". Also, several other DOCs will be reviewed and updated at the end of the chapter. In other chapters of this section 4, the readers will find other genetic skin diseases that were formerly included in the DOC headline such as the palmoplantar keratodermas, disorders of keratinocyte junctions, and others.

PART 1: THE ICHTHYOSES

INTRODUCTION

The term "ichthyosis" is derived from the Greek root "ichthys" meaning fish, which implies that there is scaling and/or hyperkeratosis of the skin. The group of ichthyoses is both clinically and etiologically heterogeneous which results in considerable difficulties in their classification. In principle, ichthyoses can be inherited or acquired presenting at birth or later in life can be limited to the skin or be an element of a multisystem disorder (**Table 1**). Severity and extent can cover a tremendous range from dry skin in ichthyosis vulgaris to syndromic disorders such as Netherton syndrome.

It is important to establish an exact diagnosis in a patient or family with ichthyosis because of ramifications for prognosis, therapy, and genetic counseling. Diagnostic criteria include age of onset, quality and distribution of scale, and presence or absence of erythroderma, blistering, associated abnormalities of skin adnexae, or other organ systems. Histopathological and ultrastructural features are largely unrevealing but can be helpful to recognize some disorders such as epidermolytic ichthyosis (EI). The inheritance pattern of an ichthyosis within a family often assists in establishing a clinical diagnosis. The examination of both parents of a sporadic case may reveal valuable diagnostic hints such as mosaic presentation (e.g., EI) or minor symptoms in carriers [e.g., X-linked recessive ichthyosis (XLRI/RXLI)]. Although sporadic cases are usually indicative of recessive ichthyoses, in particular when the parents are consanguineous, they may also represent spontaneously occurring new mutations with autosomal dominant inheritance which has important implications for genetic counseling. Applying these diagnostic guidelines, several but by far not all types of ichthyoses can be distinguished and diagnosed based on their key features (**Table 2**).

The ichthyoses were first discussed in the dermatological literature in 1808[4] and they still pose a diagnostic challenge. The ichthyoses are rare diseases and it is therefore difficult to delineate the full phenotypic spectrum of each type. Furthermore, new classification systems are being created according to the scientific advances. The schemes have been based on clinical[5-7] and histopathological and kinetic features,[8,9] inheritance,[2,3] biochemical, pathophysiological[9-12] and ultrastructural[13-18] criteria, or combinations of them,[1,19] which makes it difficult to correlate them with each other. Moreover, the nosology of ichthyoses is laden with descriptive names, eponyms, and synonyms like few other dermatoses. However, advances in cell and molecular biology of the skin over the past 15 years have provided us with new means for establishing a refined classification that includes the molecular causes and the underlying pathomechanisms of disease (**Table 3**). Global efforts are underway by an international group of clinicians and researchers to unify the nomenclature and classification of ichthyoses and other DOC, to incorporate their molecular causes, and to gain functional understanding of disease pathogenesis.[20-22] The terms used in this chapter reflect designations from the most recent consensus conference, though continued refinement is expected as new disorders are identified and genotyping becomes standard of care in clinical practice.[22]

TABLE 1 **Disorders of cornification.**

Types	Alternate names
Nonsyndromic ichthyoses:	
Ichthyosis vulgaris	
X-linked ichthyosis	Steroid sulfatase deficiency
Keratinopathic ichthyosis:	
Epidermolytic ichthyosis (EI)	Bullous congenital ichthyosiform erythroderma of Brocq; bullous ichthyosis; epidermolytic hyperkeratosis
Mosaic EI	Epidermal nevus of epidermolytic type
Superficial epidermolytic ichthyosis (SEI)	Ichthyosis bullosa of Siemens and exfoliative ichthyosis
Ichthyosis Curth–Macklin (ICM)	Ichthyosis hystrix
Ichthyosis with confetti (IWC)	Ichthyosis variegata and congenital reticular ichthyosiform erythroderma
Autosomal recessive congenital ichthyosis (ARCI):	
Congenital ichthyosiform erythroderma (CIE)	Nonbullous CIE and ichthyosis congenita type 1
Lamellar ichthyosis (LI)	Ichthyosis congenita type 2
Harlequin ichthyosis	
Others:	
Autosomal dominant ARCI-LI/CIE	
Peeling skin syndrome type A	Keratolysis exfoliativa congenita and continual skin peeling
Syndromic ichthyoses:	
Netherton syndrome/ ichthyosis linearis circumflexa	Comèl–Netherton syndrome
Sjögren–Larsson syndrome	
Chanarin–Dorfman syndrome	Neutral lipid storage disease, triglyceride storage disease with impaired long-chain fatty acid oxidation, and ichthyosiform erythroderma with leukocyte vacuolization
Refsum disease	Heredopathia atactica polyneuritiformis
Trichothiodystrophy	Tay syndrome and (P)IBIDS syndrome (photosensitivity-ichthyosis-brittle hair-impaired intelligence-decreased fertility-short stature syndrome)
Infantile Gaucher disease	Gaucher disease type II-GD II and Gaucher disease of the acute neuronopathic type

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Types	Alternate names
Neu–Laxova syndrome (NLS)	
CHIME syndrome	Zunich neuroectodermal syndrome and CHIME syndrome: ocular coloboma, congenital heart disease, early-onset ichthyosiform dermatosis, mental retardation and ear anomalies (conductive hearing loss), and epilepsy
Chondrodysplasia punctata, X-linked dominant	Conradi–Hünermann–Happle syndrome
Rhizomelic chondrodysplasia punctata (RCDP1)	Rhizomelic chondrodysplasia type 1; chondrodystrophia calcificans punctata, and autosomal recessive type
Cardiofaciocutaneous syndrome (CFC)	
Restrictive dermopathy	Tight skin-contracture syndrome and fetal hypokinesia sequence due to restrictive dermopathy
Multiple sulfatase deficiency	
Related disorders:	
KID syndrome	Keratitis-ichthyosis-like-deafness syndrome, ichthyosiform erythroderma, corneal involvement and deafness, and autosomal dominant
CHILD syndrome	
Mutilating keratoderma with ichthyosis	Loricrin keratoderma
KLICK syndrome	Keratosis linearis with ichthyosis congenita and sclerosing keratoderma
Keratosis spinulosa decalvans	
IFAP syndrome	Ichthyosis follicularis, atrichia, and photophobia syndrome
Migratory ichthyosis with diabetes mellitus	
Ichthyosis, hepatosplenomegaly, and cerebellar degeneration	
Ichthyosis-mental retardation syndrome with large keratohyalin granules in the skin	
Desmons syndrome	Ichthyosiform erythroderma, corneal involvement, and deafness; autosomal recessive
Acquired ichthyosis	

TABLE 2 **Features of selected ichthyoses.**

Diagnosis	Gene	Inheritance	Incidence	Onset	Clinical features	Associated features	Diagnostic clues
Ichthyosis vulgaris	*FLG*	Autosomal dominant	1:250	Infancy or childhood	Fine, adherent scale on extremities and trunk with sparing of flexures; larger scale on lower legs; hyper-linear palms/soles, and furrowed heels	Keratosis pilaris and atopic diathesis	Clinical and diminished/absent stratum granulosum
X-linked recessive ichthyosis	*STS*		1:2,000–1:6,000 males	Infancy	Fine to large, dark, adherent scale on extremities, trunk, neck, and lateral face; occasional palm/sole involvement	Corneal opacities on posterior capsule; increased electrophoretic mobility of beta-lipoproteins; and cryptorchidism. Female carriers: corneal opacities and prolonged birth with affected child	Lipoprotein electrophoresis; plasma cholesterol sulfate increased; steroid sulfatase activity in leukocytes; and molecular testing
Autosomal recessive congenital ichthyosis (ARCI)-lamellar ichthyosis (LI) phenotype	*TGM1* *ABCA12* *CYP4F22* *SULT2B1*	Autosomal recessive	1:300,000	Birth	Frequently collodion membrane at birth; large, thick, plate-like brown scale in generalized distribution; larger scale on lower legs; absent, or mild erythroderma	Heat intolerance; scarring alopecia; ectropion; and eclabium	Clinic, electron microscopy; in situ transglutaminase-1 expression and activity assay; and molecular testing
ARCI-congenital ichthyosiform erythroderma (CIE)	*ALOX12B* *ABHD5* *TGM1* *ALOXE3* *NIPAL4* *PNPLA1*	Autosomal recessive	1:100,000–1:200,000	Birth	Frequently collodion membrane at birth; fine, white scale in generalized distribution; and variable erythroderma	Heat intolerance, scarring alopecia; and rarely ectropion	Clinic, electron microscopy; in situ transglutaminase-1 expression and activity assay; and molecular testing
Autosomal dominant ARCI-LI/ARCI-CIE	Unknown	Autosomal dominant	Rare	Birth	Clinically variable; occasionally collodion membrane at birth; either generalized large, dark scale with absent or minimal erythroderma (LI type) or fine, whitish scale with variable erythroderma (CIE type); and pruritus	Ectropion possible	Clinic and pedigree analysis
Epidermolytic ichthyosis (EI) [bullous congenital ichthyosiform erythroderma (BCIE) brocq]	*KRT1* *KRT10*	Autosomal dominant	1:300,000	Birth	At birth erythroderma, blistering, and erosions; later clinically heterogeneous; hyperkeratosis with verrucous, cobblestone, or ridged pattern most prominent over joints; generalized or localized types; variable degree of erythroderma, palm/sole involvement; and blistering	Frequent skin infections; malodor; gait and posture abnormalities	Clinic, histopathology; and molecular testing

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Diagnosis	Gene	Inheritance	Incidence	Onset	Clinical features	Associated features	Diagnostic clues
Mosaic epidermolytic ichthyosis	*KRT1, KRT10*		Rare	Birth/early infancy	Localized hyperkeratosis with rough, verrucous surface arranged in linear patterns following the lines of Blaschko; and unilateral or bilateral		Clinic and histopathology
Superficial epidermolytic ichthyosis	*KRT2*	Autosomal dominant	Rare	Birth	Erythroderma and blistering at birth; later hyperkeratosis with accentuation of flexures and "molting" of the skin; palms, and soles spared		Clinic, histopathology; and molecular testing
Harlequin ichthyosis	*ABCA12*	Autosomal recessive	Rare	Birth	Very thick, yellow-brown plates of scale that tightly encase the neonate; large, deep, bright red and oozing cracks and fissures; extreme ectropion, eclabium, and ear deformities	Premature delivery; demise early postpartum or within days to weeks; sepsis; temperature, fluid and electrolyte imbalance; and variable other organ abnormalities	Clinic
Netherton syndrome	*SPINK5*	Autosomal recessive	1:300,000–1:50,000	Birth/infancy	Occasionally collodion membrane at birth; two principal phenotypes: ichthyosis linearis circumflexa and generalized, CIE-like ichthyosis; pruritus, and eczematous plaques are common	Trichorrhexis invaginata and other hair shaft abnormalities; highly elevated serum IgE; neonatal temperature and electrolyte imbalance, failure to thrive; recurrent infections; food and other allergies; and often unspecific aminoaciduria	Clinic, psoriasiform histopathology; light microscopic hair shaft analysis; serum IgE; electron microscopy (ruthenium tetroxide); and molecular testing
Sjögren–Larsson syndrome	*FALDH*	Autosomal recessive	1:250,000	Birth	Generalized coarse hyperkeratosis with ridged pattern in flexures and pruritus	Spastic di- and tetraplegia; mental retardation; parifoveal glistening white dots; and white matter disease of the brain	Fatty aldehyde dehydrogenase activity assay in cultured fibroblasts and molecular testing
Chanarin–Dorfman syndrome	*ABHD5*	Autosomal recessive	Rare	Birth	Generalized fine and white scale with variable erythema	Lipid-containing vacuoles in leukocytes; cataract; hearing impairment; myopathy; hepatomegaly; and developmental delay	Peripheral blood smear to detect lipid vacuoles (oil stains on frozen skin biopsy material)
Trichothiodystrophy	*ERCC2 ERCC3 GTF2H5 TTDN1*	Autosomal recessive	Rare	Birth	Occasionally collodion membrane at birth; generalized scaling with absent or minimal erythroderma; and flexures may be spared	Ichthyosis; brittle hair and nails; intellectual impairment; decreased fertility; short stature; lack of subcutaneous fatty tissue with ensuing progeria-like facies; and photosensitivity	Clinic; light microscopic hair shaft analysis under polarizing light
Refsum disease	*PAHX*	Autosomal recessive	Rare	Early childhood/ichthyosis in adulthood	Fine, white scale over trunk and extremities resembling ichthyosis vulgaris	Peripheral neuropathy; cranial nerve dysfunction (deafness, anosmia); cerebellar ataxia; retinitis pigmentosa; cardiomyopathy; and epiphyseal dysplasia	Plasma level of phytanic acid increased; phytanoyl-CoA hydroxylase activity assay in cultured fibroblasts; and molecular testing

TABLE 3 **Etiological classification of disorders of cornification.**

	System	Genes	Disorder	Mechanism
Structural protein defects	Keratin disorders	*KRT1* and *KRT10*	Epidermolytic ichthyosis	Mutations in epithelial keratin genes predominantly affect the boundaries of the alpha helical rod domain and dominantly interfere with alignment and assembly of keratin intermediate filament (KIF). As a result, the KIF cytoskeleton is weakened and fragile, and may collapse under mechanical stress leading to cytolysis
		KRT2	Superficial Epidermolytic ichthyosis	
		KRT9	Epidermolytic palmoplantar keratoderma	
		KRT10 and *KRT1*	Mosaic EI/epidermal nevus of the epidermolytic type	
		KRT6A and *KRT6B*	Pachyonychia congenita I	
		KRT16 and *KRT17*	Pachyonychia congenita II	
		KRT16	Focal nonepidermolytic palmoplantar keratoderma	Keratin mutations affecting the end domains of keratin-1, dominantly disturbing interaction with KIF associated proteins and cytoplasmic KIF organization
		hHb1 and *hHb6*	Monilethrix	
		KRT4 and *KRT13*	White sponge nevus	
		KRT3 and *KRT12*	Meesmann corneal dystrophy	
		KRT1	Diffuse nonepidermolytic palmoplantar keratoderma Ichthyosis hystrix	
		KRT1	Curth–Macklin	
Disorders of the cornified cell envelope		*LOR*	Mutilating keratoderma with ichthyosis (loricrin type)	Frameshift mutations transform the tail domain of loricrin, impair formation of the cornified cell envelope and result in intranuclear accumulation of loricrin
		LOR	Progressive symmetric erythro-keratoderma (loricrin type)	
Desmosomal disorders		*DSP* and *DSG1*	Striate palmoplantar keratoderma	Dominant mutations in desmoglein-1 and desmoplakin impair desmosomal cell adhesion and interaction with KIF (haploinsufficiency)
		DSP and *JUP*	Naxos disease	Recessive mutations in plakoglobin disrupt interactions of desmosomal proteins with KIF and weaken desmosomes and adherens junctions, thereby disturbing integrity of cells in skin, hair, and myocardium
Enzyme defects	Disorders of lipid metabolism	*TGM1* *TGM1*	ARCI-lamellar ichthyosis ARCI-CIE phenotype	Recessive transglutaminase-1 mutations result in enzyme deficiency which severely impairs protein cross-linking and esterification of epidermis-specific ceramides during formation of the protein and lipid envelope of corneocytes, and perturbs the skin barrier function
		ALOXE3	ARCI-congenital ichthyosiform erythroderma (nonbullous)	These two enzymes belong to the lipoxygenase family of nonheme, iron-containing dioxygenases and are highly expressed in suprabasal epidermis, trachea, lung, tongue, brain, and testis. LOXs catalyze oxygenation of free and esterified polyunsaturated fatty acids, phospholipids and triglycerides, and, thus, are involved in establishing the epidermal lipid barrier
		ALOX12B	ARCI-congenital ichthyosiform erythroderma (nonbullous)	
		FALDH	Sjögren–Larsson syndrome	Recessive mutations inactivate fatty aldehyde dehydrogenase which catalyzes the oxidation of long-chain aliphatic aldehydes to fatty acids. As a result, the synthesis of epidermal lipids and the catabolism of either phospholipids and sphingolipids in the brain are impaired

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	System	Genes	Disorder	Mechanism
Enzyme defects	Disorders of lipid metabolism	*STS*	X-linked recessive ichthyosis and other sulfatase deficiencies	Steroid sulfatase deficiency results in impaired hydrolysis of cholesterol sulfate leading to accumulation of cholesterol-3 sulfate in the epidermis
		EPB	X-linked dominant chondrodysplasia punctata	Mutations in delta 8-delta 7 sterol isomerase (emopamil binding protein) impair postsqualene cholesterol biosynthesis resulting in depletion of cholesterol and accumulation of intermediates. Cholesterol is a major structural element of plasma membranes and a precursor for the synthesis of steroids and bile acids. Sterol toxicity probably interferes with lipid biosynthesis
		NSDHL	CHILD syndrome	Mutations in NSDHL impair postsqualene biosynthesis upstream to delta 8-delta 7 sterol isomerase
		ABHD5	Chanarin-Dorfman syndrome	ABHD5 is a lipid droplet-associated lipase cofactor, and defects in the gene lead to impaired triglyceride degradation, resulting in triglyceride inclusions in the lamellar bodies. A defect in the degradation of endogenously produced diacylgycerols to phospholipids results in widespread tissue deposition of neutral lipids
Disorders of protein catabolism		*SPINK5*	Netherton syndrome	Recessive mutations in activate the serine proteinase inhibitor KAZAL type 5. Exact pathomechanisms remain to be elucidated
		CTSC	Papillon–Lefèvre syndrome	Allelic disorders caused by deficiency of the lysosomal proteinase cathepsin C (dipeptidyl aminopeptidase I) which is expressed in skin, gingiva, and a variety of immune cells. Exact pathomechanisms remain to be elucidated
		CTSC	Haim–Munk syndrome	
Disorders of amino acid metabolism		*TAT*	Richner–Hanhart syndrome	Tyrosine aminotransferase deficiency results in elevated serum tyrosine and deposition of tyrosine crystals in various tissues and body fluids
Peroxisomal disorders		*PEX7*	Rhizomelic chondrodysplasia punctata type 1	Peroxisomal import disorder. Recessive mutations inactivate an import receptor for type 2 peroxisomal targeting sequences (PTS2). Several proteins depending on this pathway fail to be imported from the cytosol into the peroxisomes, resulting in deficient plasmalogen biosynthesis, and phytanic acid oxidation while very long-chain fatty acid oxidation is normal
		PAHX	Refsum disease	Recessive mutations inactivate the peroxisomal enzyme phytanoyl-CoA hydroxylase and impair degradation of phytanic acid which subsequently accumulates in tissues and body fluids
Regulatory defects	Disorders of calcium homeostasis	*ATP2A2*	Darier disease	Dominant mutations inactivate intracellular calcium pumps and thereby disturb calcium homeostasis of the epidermis
		ATP2C1	Hailey–Hailey disease	
	Connexin disorders	*GJB3*; *GJB4*, and *GJA1*	Erythrokeratoderma variabilis	Dominant mutations in several epidermal connexin genes dominantly interfere with the formation or function of gap junctional intercellular channels implicated in cell-cell signaling
		GJB2	Diffuse palmoplantar keratoderma associated with hearing impairment	
		GJB2	Vohwinkel syndrome	
	Disorder of nucleotide excision repair	*ERCC2* *ERCC3*	Trichothiodystrophy	Recessive mutations inactivate two helicase subunits of the transcription/repair vector TFIIH, thereby impairing excision repair of UV-induced DNA damage

PATHOGENESIS OF DISORDERS OF CORNIFICATION

The skin is the body barrier to the environment. The epidermal barrier protects the organism from water loss and physical, chemical, and mechanical insults. The process of keratinization, a highly organized and tightly controlled one, is designed to maintain constanttly this barrier. Accordingly, epidermal keratinocytes undergo terminal differentiation and migration to the skin surface to form the stratum corneum, the main component of the skin barrier. Keratin proteins are the major constituents of keratinocytes, representing 85% of the cellular protein.[23] Keratins are a large family of over 20 proteins expressed in tissue and differentiation specific patterns. They form keratin intermediate filaments (KIF) and build an elaborate cytoskeleton which provides structural stability and flexibility for epithelial cells.[24] Keratins of two types, the acidic (type I) and basic (type II), are encoded by genes clustered on chromosomes 17q12–q21 and 12q11–q13. They are expressed in pairs composed of one acidic and one basic keratin (heterodimers). Keratin monomers contain a central, alpha-helical rod domain which is flanked by variable, nonhelical head and tail domains. Heterodimers polymerize in heterotetramers and then assemble into KIF. Short, highly conserved regions at the boundaries of the rod segment, designated helix initiation motif (1A) and helix termination motif (2B), have been recognized as zones of overlap between aligned keratin proteins and are crucial for their proper assembly to KIF.[25,26] In the epidermis, basal keratinocytes predominantly express keratins 5 and 14 while cells in the upper epidermis switch to the expression of the differentiation-specific keratins 1 and 10. Cells of the granular layers also produce keratin 2 which might assemble with keratin 10. Other site-specific suprabasal keratins include keratin 9 found exclusively in palms and soles, and keratins 6, 16, and 17 which are expressed when the epidermis is stressed. Pathogenic mutations in 25 different keratin genes are responsible for a wide range of genodermatoses affecting skin, mucous membranes, hair, nails, and sebaceous glands (K5, K14, K1, K10, K9, K16, K6c, K6b, K6a, K2, K81, K83, K86, K74, K85, K13, K12, K8, K18, K19, K25, K71, K74, K17, and K75). These mutations primarily cluster at mutational "hot spots" at the beginning and end of the central rod domain and disturb KIF assembly, resulting in perinuclear clumping of fragmented KIF and cell fragility, the hallmarks of keratin disorders.

In analogy to a brick wall built from bricks and mortar, the stratum corneum contains two principal elements: protein-rich corneocytes (bricks) and a lipid-enriched extracellular matrix (mortar). The barrier function of the skin is accomplished by formation of the cornified cell envelope, an 8–15 nm structure that replaces the plasma membrane in terminally differentiating keratinocytes. It is a highly insoluble and tough polymer of proteins (protein envelope) and lipids (lipid envelope). The protein envelope results from sequential cross-linking of specialized precursor proteins, such as involucrin, small proline-rich proteins, elafin, cystatin A, and loricrin with KIF and desmosomal proteins facilitated by epidermal transglutaminases.[27] It confers chemical and mechanical resilience as well as water retention of corneocytes. The lipid envelope is formed by a monolayer of long-chain omega-hydroxyceramides which are covalently attached to the outer surface of the protein envelope by ester bonds, a process which is again mediated by membrane-bound transglutaminase.[28] These protein-linked ceramides coat the corneocytes and intervene with intercellular lipids in a comb-like fashion.

The lipid composition of the stratum corneum is markedly different from the lower epidermis. Instead of phospholipids, the stratum corneum contains large amounts of neutral lipids such as cholesterol and free fatty acids, as well as polar lipids such as ceramides and epidermis-specific ω-hydroxy and ω-hydroxyacylceramides. These lipids are synthesized in the spinous layers of the epidermis where they are stored and transported as stacks of laminar sheets in lamellar bodies (**Fig. 1**). One of the first events in the formation of the cornified cell envelope is the fusion of lamellar bodies with apical cell membranes in granular cells and extrusion of their contents into the intracellular space. Hydrolytic enzymes of the lamellar bodies transform glycolipids and phospholipids into free fatty acids and ceramides, respectively. Using the corneocyte lipid envelope as template, discharged lipids reorganize into intercellular lipid lamellae, which form broad double bilayers connecting with each other through intervening lipid monolayers. This arrangement results in the characteristic pattern of alternating electron dense and electron lucent bands visible by transmission electron microscopy with ruthenium tetroxide fixation. Together, lipid envelopes and intercellular lipid lamellae "glue" corneocytes together and impede water loss through the skin. In a normal stratum corneum, 15–20 layers of corneocytes are stacked on top of each other. They are also held together by corneodesmosomes which are successively degraded by proteolytic lamellar body enzymes to reduce their cohesiveness and allow desquamation of the outermost cells.

Desquamation is a continuous, inconspicuous process by which individual corneocytes or small clumps of them are separated and exfoliated through frictional forces. The human body sheds approximately 2 billion corneocytes during the course of a day, illustrating the striking magnitude of this imperceptible process. Visible scaling as seen in ichthyosis is produced by exfoliation of clumps of 100–500 or more adherent corneocytes. Normal desquamation is an orderly process of loss of corneocyte adhesion by proteolytic degradation of corneodesmosomes which connect the corneocytes. This process mandates a delicate balance between several different proteases, their inhibitors, and the pH milieu.[20] Under normal conditions, epidermal cell proliferation and desquamation are in a steady-state. Any exogenous or endogenous process that disturbs this homeostasis is bound to impair the barrier function of the skin which can eventually result in disease. Hyperkeratosis of the stratum corneum can stem from an increased number of cells produced by the epidermis (hyperproliferative ichthyosis), from delayed desquamation (retention hyperkeratosis), or a combination of both mechanisms.

Stratum corneum formation is controlled by several important factors. Intracellular calcium plays a key regulatory role in epidermal differentiation. The amount of intracellular calcium increases as cells migrate upward in the epidermis.[29]

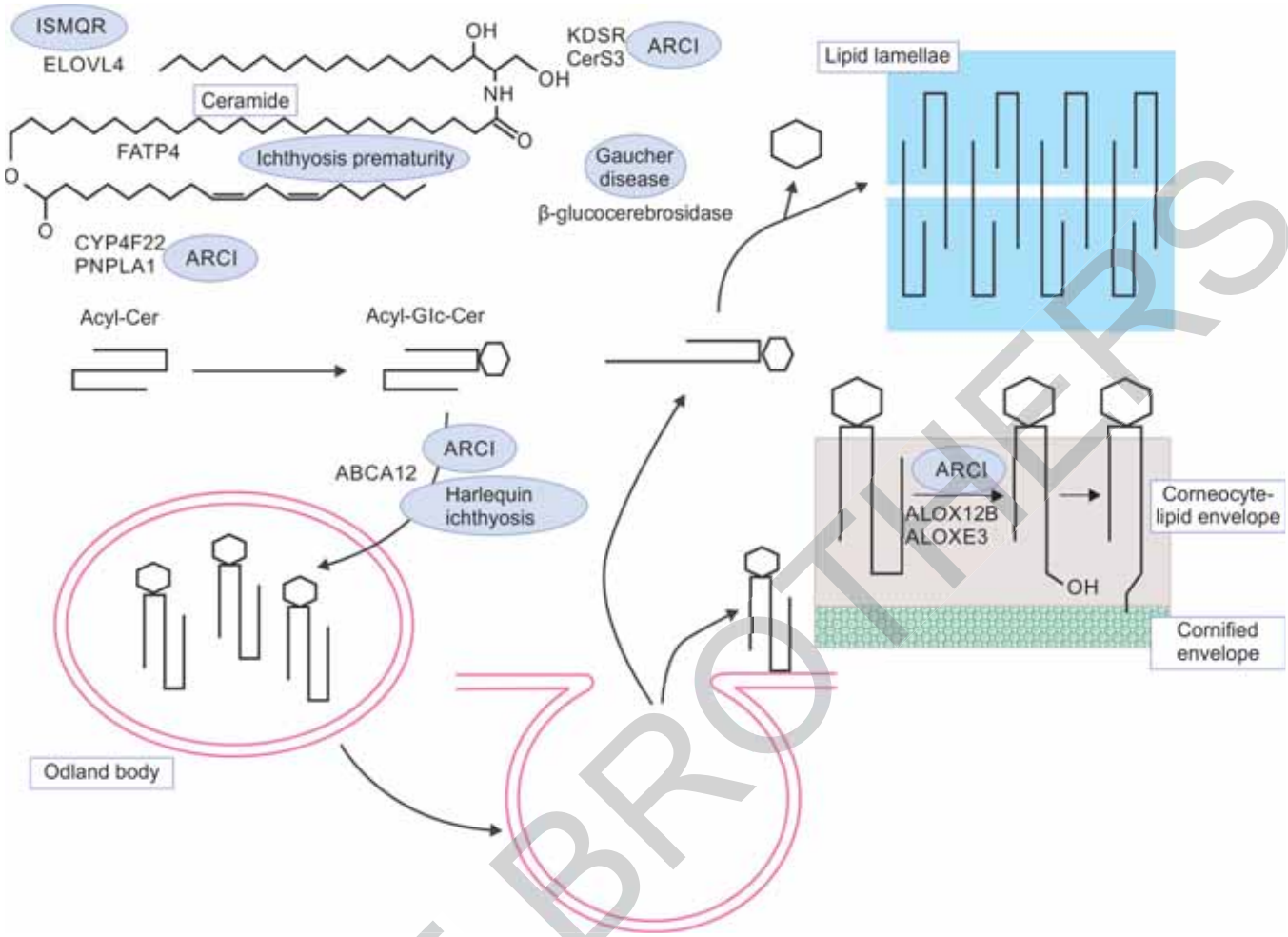


FIG. 1: Lipid processing in the epidermis and proteins related to ichthyoses. The de novo ceramide pathway enzymes lead to synthesis of the ceramide scaffold. KDSR (3-keto-dihidrosphingosine reductase) and CerS3 (ceramide synthase 3) are involved in skin ceramide synthesis. Elongation of the fatty acid chain of ceramide involves the availability of fatty acids by FATP4 and enzymes called elongases, including ELOVL4. The addition of further lipids, specially, esterified ω-hydroxy fatty acids, to form functionally active acylceramides involves CYP4F22 and PNPLA1. Acylceramides are then glycosylated and transported into Odland bodies by ABCA12. During keratinization, Odland bodies in the stratum granulosum are extruded and their content is released to the extracellular space. A part of glycosylated acylceramides is deglycosylated by β-glucocerebrosidase, and resulting lipids are arranged in bilayers (lamellae) in the intercellular space at the stratum corneum. Another part is incorporated to the corneocyte plasma membrane, to form the corneocyte-lipid envelope. In this process, lipoxygenases such as ALOXE3 and ALOX12B allow the final binding of ceramides to the cornified envelope of the keratinocyte. All these enzymes and proteins are cause of different types of ichthyosis.

(ARCI: autosomal recessive congenital ichthyosis; ISQMR: ichthyosis, spastic quadriplegia, and mental retardation)

High intracellular calcium concentrations are critical for the expression and processing of differentiation-specific proteins such as keratin-1, keratin-10, profilaggrin, loricrin, involucrin, and others as well as for the action of transglutaminases. Increased transepidermal water loss with ensuing changes in pH and ion concentration, in particular calcium and potassium, is thought to trigger factors for release of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-8, IL-10, interferon-γ, transforming growth factor (TGF)-α and -β as well as the adhesion molecule and intercellular adhesion molecule-1 (ICAM1). These molecules can elicit a host of different homeostatic responses including secretion of preformed lamellar bodies, increase lipid and lamellar body synthesis, stimulation of deoxyribonucleic acid (DNA) synthesis to generate more corneocytes, and epidermal inflammation.[30,31] Other modulators of terminal differentiation include retinoic acid, vitamin D, protein kinase C, urokinase, and transcription factors all of which are still under investigation.

In the last 20 years, genetic tools have been successfully applied to uncover the molecular basis of a large number of heritable disorders of the skin and its appendages, leading to identification of >300 disease genes.[32] This knowledge substantially advanced our understanding of the process of cornification itself as well as the pathobiology of DOC.

It is now possible to categorize ichthyoses and DOC, at least in part, on the basis of their underlying genetic defects and pathogenesis. These may affect: (1) structural (scaffolding) proteins of the epidermis including keratins, desmosomal proteins, and proteins of the cornified cell envelope; (2) proteins involved in lipid metabolism and transport;

(3) proteins involved in protein and amino acid metabolism; and (4) regulatory molecules controlling cornification such as calcium and connexins (**Table 3**). Keratin disorders, such as EI, superficial epidermolytic ichthyosis (SEI), and epidermolytic palmoplantar keratoderma result from fragility of the KIF network of keratinocytes with ensuing epidermolysis. However, faulty KIF may also directly interfere with the secretory function of lamellar bodies and other differentiation-specific proteins, thus impairing the permeability barrier of the skin. An increasing number of inherited congenital ichthyoses have been associated with defects in the lipid metabolism of the skin, hindering formation of the lipid envelope, and intercellular lipid lamellae. For example, the lipid transporter protein encoded by the *ABCA12* gene plays a pivotal role for maintaining the lipid balance in the epidermis, for transfer of epidermal lipids into lamellar bodies, and efflux of multiple lipids including cholesterol. If missing, as in patients with Harlequin ichthyosis [a form of autosomal recessive congenital ichthyosis (ARCI)] due to detrimental *ABCA12* mutations, no lipid barrier is formed, the permeability barrier of the skin is completely deficient, and there is a lack of desquamation. Several other forms of ARCI stem from a lack of proteins that are directly involved in a common metabolic pathway catabolizing leukotriene derivates of arachidonic acid to 12(*R*)-hepoxilin A3 and other hydroxyepoxyalcohol end products (hepoxilin pathway). Phytanoyl-CoA hydroxylase deficiency in Refsum disease impedes the normal synthesis of ceramides while fatty aldehyde dehydrogenase (FALDH) deficiency in Sjögren–Larsson syndrome (SLS) imparis synthesis of fatty acids. Loss of transglutaminase-1 activity in the ARCI phenotypes lamellar ichthyosis (LI)/congenital ichthyosiform erythroderma (CIE) has profound effects on the cornified cell envelopes. The dual impairment of protein-protein cross-linkage as well as attachment of ceramides and formation of the lipid envelope leads to severe diminution of the skin barrier and hyperkeratosis. The basic defect in XLRI is steroid sulfatase deficiency causing impaired hydrolysis of cholesterol sulfate and accumulation of cholesterol-3 sulfate in the epidermis. High levels of this metabolite inhibit the normal function of transglutaminase-1 thus explaining the partial phenotypic overlap between XLRI and LI, and underscoring the pivotal role of transglutaminase-1 in the cornified envelope formation and normal functioning of the stratum corneum.

Disorders of cornification may also arise from genetic defects involving important regulators of epidermal differentiation. In case of Hailey–Hailey disease and Darier disease, a partially reduced function of intracellular calcium pumps negatively affects the calcium homeostasis of the epidermis and response to intercellular signaling. Connexin disorders are thought to arise from impaired gap junctional intercellular communication between keratinocytes and/or from ATP release through connexin hemichannels with ensuing effects on transport of ions such as calcium and cyclic nucleotides.

The etiologic classification of ichthyoses and DOC based on the underlying genetic defects, though still preliminary and incomplete, is advancing the traditional nosology. Efforts to identify specific mutations and genotype-phenotype correlations will help us to increase our diagnostic abilities and will permit an accurate genetic counseling with the opportunity to achieve reliable and early prenatal diagnosis. Also, we expect that targeted therapies for these disorders will be developed in the future.

This chapter will comprehensively review these forms of ichthyosis. Patient advocacy organizations such as the Foundation for Ichthyosis and Related Skin Types [FIRST; (800) 5453286; e-mail: info@firstskinfoundation.org; http://www.firstskinfoundation.org] and the National Organization for Rare Disorders [NORD; (800) 999 6673; e-mail: orphan@rarediseases.org; http://www.rarediseases.org/] offer valuable information material, facilitate personal contacts with other affected families, and support patients and their families.

THE NONSYNDROMIC ICHTHYOSES

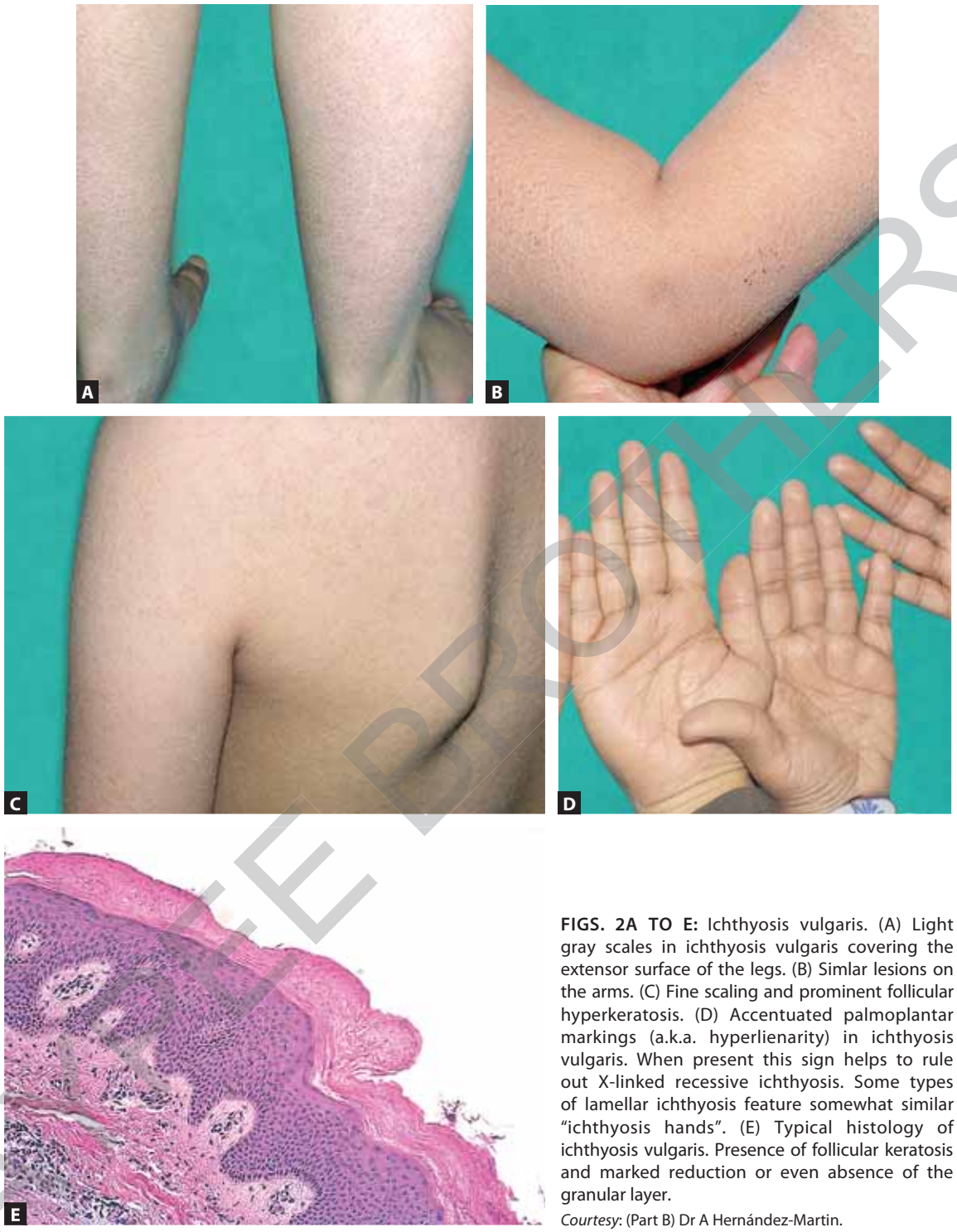
Ichthyosis Vulgaris

Ichthyosis vulgaris is the most common disorder of keratinization, characterized by light white to gray scales mainly involving the extensor surfaces of the extremities and the trunk (**Figs. 2A to E**). Wells and Kerr studied 6061 pupils and predicted a frequency of four in 1,000 in the general population.[33] An incidence of 12.6 per 1,000 was found in another study of school-aged children.[34]

Pathophysiology

In 2006, Smith *et al.* showed that ichthyosis vulgaris was inherited in an autosomal semidominant pattern with a more severe, classical phenotype in homozygotes, and a milder (and occasionally absent) phenotype in heterozygotes due to loss-of-function mutations in the *FLG* gene which encodes the protein profilaggrin.[35] Profilagrin is maintained as an inactive proprotein in the keratohyalin granules of the granular layer and subsequently is proteolytically cleaved to produce between 10 and 12 filaggrin polypeptide repeats. Filaggrin is responsible for keratin filament aggregation, adds to skin barrier function, and also hydration of the stratum corneum via its breakdown products. Filaggrin mutations are highly population-specific; e.g., in the European and Japanese populations, the two best studied populations to date, several recurrent mutations are seen, but the recurrent European mutations are not seen in the Japanese population and vice versa.[36,37] Thus, several founder mutations are likely to account for prevalent *FLG* mutations in many discrete populations, making mutation detection challenging. Furthermore, there are no particular highly mutated regions or "mutation hot spots", as each mutation detected to date is either a missense mutation encoding a premature termination codon or an insertion/deletion that leads to a downstream premature termination codon. The position of the mutation does not appear to have an effect on the disease given that any mutation upstream of the carboxy terminal appears to prevent full post-translational processing of profilaggrin into functional filaggrin repeats.[38]

Given the high cumulative population prevalence of filaggrin mutations in European populations of almost 10%, the possibility of these mutations modifying the expression of other



FIGS. 2A TO E: Ichthyosis vulgaris. (A) Light gray scales in ichthyosis vulgaris covering the extensor surface of the legs. (B) Simlar lesions on the arms. (C) Fine scaling and prominent follicular hyperkeratosis. (D) Accentuated palmoplantar markings (a.k.a. hyperlienarity) in ichthyosis vulgaris. When present this sign helps to rule out X-linked recessive ichthyosis. Some types of lamellar ichthyosis feature somewhat similar "ichthyosis hands". (E) Typical histology of ichthyosis vulgaris. Presence of follicular keratosis and marked reduction or even absence of the granular layer.

Courtesy: (Part B) Dr A Hernández-Martin.

ichthyotic disorders has been considered. It has been shown in one family that carriage of a *FLG* loss of function mutation modifies the clinical severity of X-linked ichthyosis.[39] Null mutations in FLG have also been associated with increased severity in patients with alopecia areata.[40]

The autosomal recessive mutation flaky tail (ft) mouse provides an interesting animal model for ichthyosis vulgaris. Flaky tail mice have been shown to be null for filaggrin expression and to carry homozygous mutations in the murine filaggrin gene.[41] Interestingly, they also are highly susceptible to transcutaneous allergen priming and allergic inflammation.[41] Indeed, patients with icthyosis vulgaris are at an increased risk for allergies, atopic dermatitis, and asthma. This increased risk is thought to be due to disruption of the skin's normal barrier function which allows for increased penetration of the epidermis by allergens.[42]

Clinical Features

Signs of ichthyosis vulgaris are not present at birth but usually develop during the first months of life. Typical cutaneous features include light white to gray scales covering mainly the extensor surfaces of the extremities and the trunk (**Figs. 2A** to **E**). The groin and major flexures are always spared. Follicular keratoses projecting above the skin surface are a further characteristic sign of the disease, present in most affected children. According to Mevorah *et al.,*[43] keratosis pilaris occurs in 75% of all ichthyosis vulgaris patients compared with 42% of the general population; Brown's study found keratosis pilaris in 100% of patients with marked IV compared with 30% of the normal population.[34] Accentuated palmoplantar markings (hyperlinearity) are a further hallmark of ichthyosis vulgaris and are found in 100% of patients homozygous for *FLG* mutations and 75% of those heterozygous for *FLG* null alleles.[34] If the accentuation is marked, it may be of considerable diagnostic help (**Figs. 2A** to **E**) but evaluation of accentuated palmoplantar creases may prove difficult if this sign is only mildly expressed, as is seen in many heterozygotes.[36] Ichthyosis vulgaris is often associated with atopic dermatitis and carries an increased risk of associated asthma and food allergies.[44]

In some cases, it is difficult to make a clear-cut distinction between XLRI and ichthyosis vulgaris. A recent survey showed that an accurate clinical diagnosis was achieved only in about 50% of the cases.[45] In the author's experience, the presence of palmar hyperlinearity and marked keratosis pilaris is often helpful. For a definite diagnosis, a detailed family history (including obstetric history of prolonged labor) and additional diagnostic measures, for example demonstration in a skin specimen of reduced filaggrin expression in IV or performing biochemical or genetic tests to exclude XLRI, should be considered.

Pathology

A reduced granular layer, which may be completely lacking in parts of the biopsy, is the most outstanding histologic feature of ichthyosis vulgaris (**Figs. 2A to E**). The stratum corneum usually displays a mild but compact orthohyperkeratosis. A reduced rete-papillae pattern, occasional prominent follicular keratosis, and reduction in the number of the sebaceous glands are further features of ichthyosis vulgaris.[19] At the ultrastructural level, the diminished granular layer is reflected by reduced and abnormal keratohyalin granules which exhibit a crumbly and spongy appearance.[46]

Therapeutics

Usually ichthyosis vulgaris responds well to topical products containing urea, lactic acid, or NaCl. Urea should not be used on large body areas before the age of 1 year and ichthyosis vulgaris should not be treated by ointments containing salicylate because this can cause life-threatening poisoning due to percutaneous absorption.[47] Salicylate intoxication is characterized by tinnitus, vomiting, wheezing, and hyperventilation associated with metabolic acidosis and an anion gap. Therefore, in affected children total body treatment with salicylic acid should be avoided.[19]

Recessive X-linked Ichthyosis

X-linked recessive ichthyosis is the second most common type of ichthyosis. Population genetics studies disclosed a minimum prevalence in the male population of 1 to 6,390 in southern England 33 and 1 in 9,855 males in Japan.[48] Routine screening of pregnancies in Denmark showed that the incidence of RXLI was 1 in 2,000 males.[49]

Pathophysiology

X-linked recessive ichthyosis was one of the first genetic skin diseases that was mapped by classic linkage analysis, namely a close linkage with the Xg-blood group to the X-chromosome.[50] A family tree may help to make the diagnosis, especially if a maternal grandfather and other maternal male relatives are affected with sparing of female carriers (indicating an X-linked recessive mode of inheritance) (**Figs. 3A** to **D**).

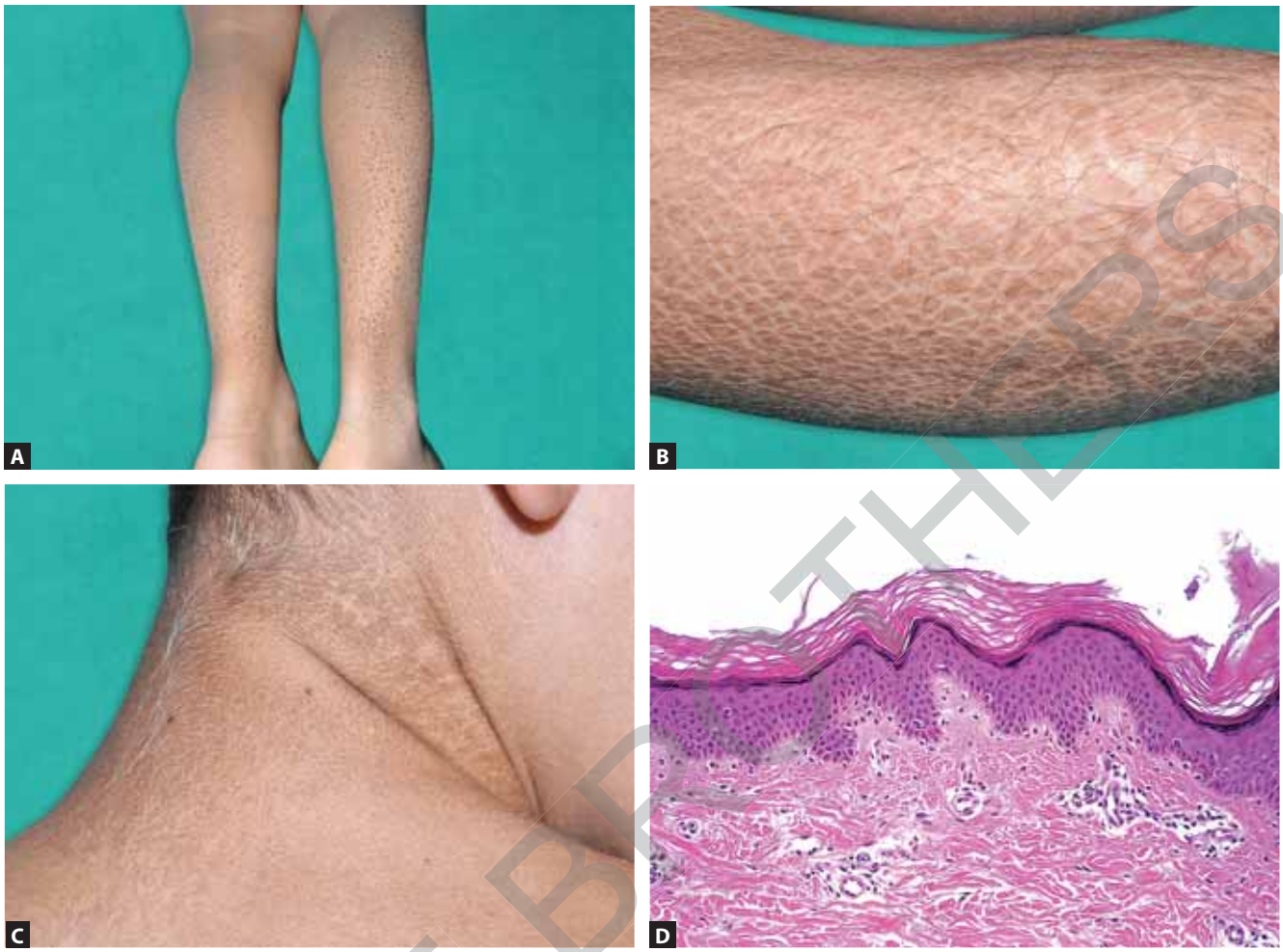
In 1978, Webster *et al.* discovered that fibroblasts in X-linked ichthyosis lacked steroid sulfatase which is encoded by the *STS* gene which is located at the distal end of the X-chromosome in a region that escapes X-inactivation. This means that fibroblast enzyme activity in female carriers is similar to that of healthy men.[3,51] However, the expression of steroid sulfatase is variable among cells and does not always correlate with the number of X-chromosomes.[52] Female carriers can be detected by fluorescent in situ hybridization (FISH) on metaphase blood cells; about 90% of all patients have a large deletion (2–3 megabases) on the short arm of the X-chromosome.[53]

Diagnosis can be performed via genetic testing including FISH, chromosome microarray, and gene-level sequencing, and these approaches have largely replaced biochemical tests such as assays of steroid sulfatase activity or elevated serum cholesterol sulfate levels.[54]

The development of scaling in RXLI has been attributed to the perturbed epidermal cholesterol sulfate cycle and the accumulation of cholesterol sulfate. Increased cholesterol sulfate inhibits epidermal serine proteases such as kallikreins.[55] This results in retained corneodesmosomes and consequently in decreased and delayed desquamation of corneocytes and the features of a "retention hyperkeratosis".

Clinical Features

X-linked recessive ichthyosis is the cutaneous manifestation of steroid sulfatase deficiency. Noncutaneous manifestations of this enzyme defect include birth complications, cryptorchidism, and corneal opacities.[56,57] The whole course of the disease has been traced from birth, thanks to prenatal diagnosis of placental sulfatase deficiency. Of 21 boys prenatally diagnosed in Denmark, 19 showed general peeling of the skin at 1–3 weeks of life with generalized large, light, and loosely attached scales.[58] During the following weeks, this fine scaling was replaced by the typical polygonal dark and firmly attached scales of RXLI. The fine scaling in early life is not very striking, however, and usually escapes the attention of parents or nurses. When the patients or their parents are asked about the onset of the disease they usually say that it started at the age of 2–6 months.



FIGS. 3A TO D: X-linked recessive ichthyosis. (A) Typical rhombic yellow-brown hyperkeratosis in older children. (B) A detail of the small, dark, polygonal scales. (C) Typical scales on the sides of the neck and retroauricular areas. (D) Histology shows with prominent granular layer and orthohyperkeratosis.

Courtesy: (Part A to C) Dr A Hernández-Martin.

At that time, normally large thick dark-brown to yellow-brown hyperkeratoses cover the trunk, the extremities, and the neck (**Figs. 3A to D**). The face is spared, except for preauricular scaling, and palms and soles are normal, which is of considerable clinical help in the differential diagnosis from ichthyosis vulgaris. The dark hyperkeratoses are especially prominent over the lateral aspects of the trunk and the back of the neck resulting in "a dirty look" which is a further typical feature of RXLI and usually not seen in ichthyosis vulgaris. Axillae and antecubital and popliteal fossae may be involved in some patients but are often spared. This criterion therefore should not be used to separate the disease from ichthyosis vulgaris which usually spares the antecubital and popliteal fossae completely. About 30% of the patients do not have the classic dark-brown hyperkeratoses, but rather large and light-gray hyperkeratoses. This occurs most commonly in younger boys, although brothers sharing the same mutation may show the classic yellow-brown hyperkeratoses in one and the other may show light-gray scaling. These latter patients are often erroneously thought to have ichthyosis vulgaris. Follicular keratosis (keratosis pilaris) is absent in RXLI clinically, although it may be seen occasionally in histopathological examinations. Female carriers of the disease gene may display a fine, silver-light scaling on the lower leg,[59] but concomitant ichthyosis vulgaris must be ruled out in these cases.

Obstetric manifestations of steroid sulfatase deficiency include insufficient cervical dilatation which may result in prolonged labor (failure to progress), necessitating cesarean section or forceps delivery. About 30% of boys postnatally diagnosed as having RXLI had a history of perinatal complications.[57,60] Gonadal abnormalities are unusual but include cryptorchidism (undescended testicles), which may be associated with decreased fertility, and in extreme cases with hypogenitalism. Rarely, testicular cancer (but not cryptorchidism) has been described. At risk pregnancies are detected by finding low maternal serum estriol on prenatal screening.[61]

Rarely, patients with RXLI present with additional systemic clinical manifestations due to a contiguous gene deletion. Examples include mental retardation, as well as Kallmann syndrome, which is a form of hypogonadotrophic hypogonadism characterized by impaired sense of smell, delayed or absent puberty, chondrodysplasia punctata, as well as hypertrophic pyloric stenosis, and unilateral renal aplasia in rare cases.[62] An increased incidence of epilepsy and attention deficit hyperactivity disorder (ADHD) has been suggested in RXLI patients.[63]

Pathology

Biopsied skin of patients with RXLI shows nonspecific epidermal hyperplasia (**Fig. 3D**), usually associated with a prominent granular layer and orthohyperkeratosis.[64,65] Biopsy does not allow RXLI to be distinguish from mild forms of ARCI (see below).

Therapeutics

Therapeutic approaches vary considerably depending on availability and teaching. Keratolytic agents such as 12% ammonium lactate are used to facilitate the release of retained corneocytes, and topical preparations containing urea, glycolic acid, and glycerol have become available as over the counter products.

Keratinopathic Ichthyoses

Epidermolytic ichthyosis (EI) and superficial EI (SEI)
Synonyms: bullous congenital ichthyosiform erythroderma of Brocq (BCIE), epidermolytic hyperkeratosis, bullous ichthyosis, and ichthyosis exfoliativa.

As early as 1897, Nikolski recognized the characteristic histopathology of the bullous form of congenital ichthyosis.[66] In 1902, Brocq first differentiated between dry (nonbullous) and wet (bullous) forms of CIE.[7] The term "epidermolytic hyperkeratosis" was coined by Frost and Van Scott in 1965 for the autosomal dominant blistering form of congenital ichthyosis which is named for the distinctive histopathologic features of vacuolar degeneration and hyperkeratosis of the epidermis.[9] Ichthyosis bullosa of Siemens was first decribed as a distinct type of EI with a milder phenotype and sparing of palms and soles in 1937.[67] In recognition of the underlying keratin gene mutations in this group of disorders, the international group of experts in the ichthyoses proposed renaming this group of keratin disorders "keratinopathic ichthyoses" with subgroups of EI (KRT1/KRT10 mutations) and SEI (KRT2), respectively. EI is a rare disorder with an estimated incidence of 1 in 200,000 to 1 in 300,000 individuals.

Pathophysiology

Epidermolytic ichthyosis and SEI are autosomal dominant disorders with complete penetrance but extensive clinical variability. Both genders are affected equally and an affected person faces in each pregnancy a 50% risk of transmitting the disorder to the offspring. EI is caused by heterozygous mutations in the genes encoding keratin 1 and keratin 10 (*KRT1* and *KRT10*), which are expressed in the differentiated layers of the epidermis. Mutations in a minor keratin expressed in the outermost spinous and granular layers of the epidermis, *KRT2*, are associated with SEI, which has a milder phenotype then EI.

Different approaches including genetic linkage analysis, ultrastructural examination, and mouse models of EI led almost simultaneously to the discovery of mutations in *KRT1* and *KRT10* as the molecular basis of EI.[68-70] *KRT1* and *KRT10* localize on chromosomes 17q12–q21 and 12q11–q13, respectively. Keratins 1, 2 (type II), and 10 (type I) are the principal, differentiation-specific keratins in the upper epidermis. Their expression pattern correlates with fragility and cytolysis of the superficial epidermis in EI and SEI, while the basal expression of keratins 5 and 14 represents the site of disease pathology in epidermolysis bullosa simplex.

To date, at least 180 distinct pathogenic mutations have been identified in KRT1 and KRT10 in EI, while at least 35 unique KRT2 mutations have been reported in SEI. The mutations are nonrandomly distributed and >90% cluster at the 1A and 2B boundaries of the rod domains representing mutational "hot spots".[71-73] Despite the presence of these mutational "hot spots", recessive EI is ultimately caused by loss of K10 expression, regardless of mutation location.[74] The most common mutations, present in >30% of all EI patients, affect the arginine codon 156 in KRT10, which contains a methylated and hypermutable CpG dinucleotide.[71] In KRT2, mutations often alter glutamic acid codon 487 (E487K) in the helix termination motif. In vivo and in vitro studies demonstrated that these mutations perturb proper keratin alignment, and thereby oligomerization, filament assembly, and integrity. As a result, the KIF network is fragile, disrupted, and less resistant to stress, thus compromising mechanical strength and cell integrity of the epidermis and leading to cytolysis and blistering. Compensatory overexpression of the alternate (hyperproliferative) keratins 6 and 16 in affected skin might contribute to the improvement of skin fragility with age.

The etiology of acanthosis and hyperkeratosis in EI/SEI is not as well understood and probably includes hyperproliferation of the epidermis combined with decreased desquamation and other factors.[75] Experimental studies have demonstrated that keratin 10 normally inhibits proliferation and cell cycle progression of keratinocytes, while loss of keratin 10 leads to increased keratinocyte turnover.[76]

Keratin 1 or 10 mutations also have a deleterious effect on the permeability barrier function of the epidermis, as becomes evident in mice completely deficient in keratin 10, which have an eight-fold increase in transepidermal water loss compared to normal mice while heterozygous animals exhibit a delay in barrier repair and reduced hydration of the stratum corneum. Although the stratum corneum in EI appears ultrastructurally normal, its lipid composition is significantly altered with a decreased ratio of ceramides to total lipids due to reduced activity of acid sphingomyelinase.[75,77] Biochemical and ultrastructural studies in patients with EI largely confirmed these observations and revealed incomplete lamellar body secretion as evident by decreased delivery of acid lipase to the stratum corneum. This secretion deficiency is likely a direct effect of altered KIF structure and interaction with lamellar bodies (rather than increased fragility of corneocytes or an abnormal cornified cell envelope).[78]

Because KIF formation in suprabasal keratinocytes requires the presence of both keratin 1 and keratin 10, mutations in either gene may produce a similar phenotype and marked clinical and genetic heterogeneity has been identified in subjects with EI. Nevertheless, *KRT1* mutations are usually associated with severe palmoplantar keratoderma whereas mutations in *KRT10* typically result in EI with no or mild involvement of palms and soles.[79] This difference is explained by the limited expression of KRT10 in palmoplantar epidermis, where KRT9 is an alternate expression partner for KRT1.

Almost half of all cases of EI occur sporadically and represent new mutations, which explains why the parents in such cases are clinically unaffected. However, germline mosaicism cannot be excluded as it is possible that a parent of a patient with EI has a somatic mutation that has arisen postzygotically during early embryogenesis, resulting in a mosaic form of EI following the lines of Blaschko (aka nevoid EI and linear epidermolytic epidermal nevus).[80,81] Epidermal nevi of the epidermolytic icthyosis type represent a mosaic form of EI due to postzygotic, somatic mutations in KRT1, KRT2, and KRT10 that occur during embryogenesis. Paller et al.[81] studied a family in which the parent of a child with generalized EI had mosaic skin involvement following Blaschko's lines. Mutation analysis in cultured keratinocytes from the affected skin of the parent identified a heterozygous mutation in KRT10, which was absent in keratinocytes from normal skin but identical to the mutation of the affected child. Extensive unilateral or bilateral mosaic involvement with massive hyperkeratosis has also been described as "ichthyosis hystrix". In the case of epidermal mosaicism, it is possible that the somatic mutation also involves gonadal cells and, therefore, can be transmitted from the germline to the offspring, resulting in generalized disease in the offspring.[82,83] In this case, a parent with linear epidermolytic epidermal nevi can have offspring with generalized EI, thus underscoring the importance of thorough clinical examination of parents of an affected proband, and need for appropriate genetic counseling. If a parent has mosaic involvement, the offspring has an increased risk of developing generalized EI (up to 50%).

Several variants of EI have been recognized and characterized on a molecular level. Patients with "cyclic ichthyosis with epidermolytic hyperkeratosis" or "annular epidermolytic ichthyosis" typically have episodic flares of annular polycyclic plaques with scale which coalesce to involve most of the body surface. Episodes may persist for several weeks or months and the skin may be normal between flares. While the clinical features may closely resemble erythrokeratoderma variabilis, the histological and ultrastructural features are characteristic for EI. These EI variants are caused by mutations that alter the conserved end domain (2B) of the keratin 1 and keratin 10 rod, respectively.[84-87] Such mutations outside of the immediate helix boundaries are rare and generally tend to be associated with a milder phenotype.

Ichthyosis (hystrix) Curth–Macklin (IHCM) is a rare autosomal dominant disorder of cornification that may clinically mimic EI but displays no skin fragility. Since the first description in 1954, only a few families and sporadic cases of IHCM have been reported. The clinical expression varies not only in-between but also within families and ranges from palmoplantar keratoderma, which may be severe and mutilating, to generalized skin involvement with dramatic hystrix-like verruciform hyperkeratosis. Ichthyosis Curth–Macklin (ICM) can be differentiated from EI by its peculiar ultrastructural abnormalities of the KIF cytoskeleton in differentiating keratinocytes. KIFs are not arranged in thick bundles but instead form a shell-like, interspersed network of tangled filaments often associated with perinuclear vacuolization and formation of binucleated cells. In contrast to EI, there is no evidence for epidermolysis or keratin clumping. IHCM is another KRT1 disorder. However, mutations are located outside the typical hot spot regions and introduce a frameshift that drastically alters the keratin 1 tail in its composition, chemical character, structure and properties, thereby interfering with supramolecular organization of KIF and their interactions with other differentiation-specific proteins such as loricrin.[88-90]

Almost all patients with EI/SEI and diagnostic findings of epidermolysis, hypergranulosis, and hyperkeratosis on histopathologic examination have a disease-causing mutation in either the keratin 1, 2, or keratin 10 gene (*KRT1*, *KRT2*, and *KRT10*), which can be identified by DNA sequencing. DNA sequence analysis or other methods of mutation detection have been successfully performed from chorionic villus sampling (CVS) or amniocentesis, which allows prenatal diagnosis as early as the 10th to 12th week of gestation.[91]

Clinical Features

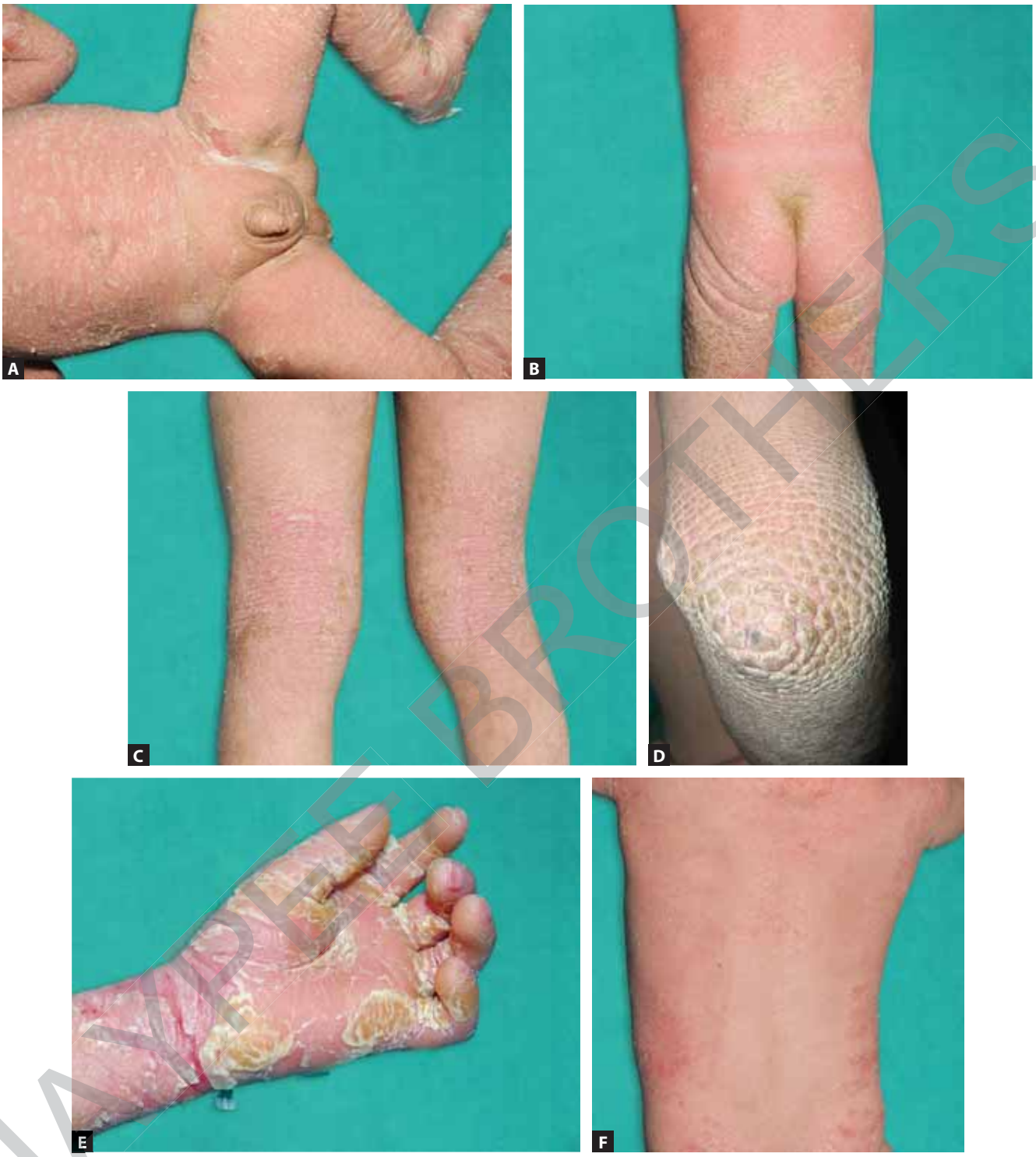
Epidermolytic ichthyosis usually presents at birth with erosions and widespread areas of denuded skin and erythroderma, which stem from increased epidermal fragility and are provoked by the frictional trauma during passage through the birth canal. Overtime, blistering diminishes while hyperkeratosis develops.

In the neonatal period, infants show erythema, large erosions, peeling, and widespread areas of denuded skin reminiscent of epidermolysis bullosa, although focal areas of hyperkeratosis may already be present (**Figs. 4A** to **K**). Later during infancy and childhood, the bullous component becomes less prominent while severe hyperkeratosis prevails.

The clinical presentation of EI is extremely variable, although it tends to be consistent within a family. The thickened, yellow to dark brown, dirty-appearing skin has a verrucous surface or sharp, protruding spines, which has been described as ichthyosis hystrix (**Figs. 4A** to **K**). The extremities over the joints, back, areas around umbilicus and areolae, and the scalp are most severely affected. While the hyperkeratosis usually forms a linear and ridged pattern in flexural areas, it has a cobblestone appearance over the extensor surface of the joints (**Figs. 4A** to **K**). The face is relatively spared.

In general, focal episodes of blistering are common and often triggered by secondary infections and trauma or friction. Patients shed the thickened, hard superficial epidermis in large plates, most likely due to intraepidermal blistering, thereby revealing a tender, erythematous base, or erosions.

Severe scalp involvement with encasement of the hair shafts is a common feature of EI. Lips, eyes, mucous membranes, and teeth are normal but linear arrayed hyperkeratosis in the corners of the mouth is not uncommon.



FIGS. 4A TO K: *Continued*

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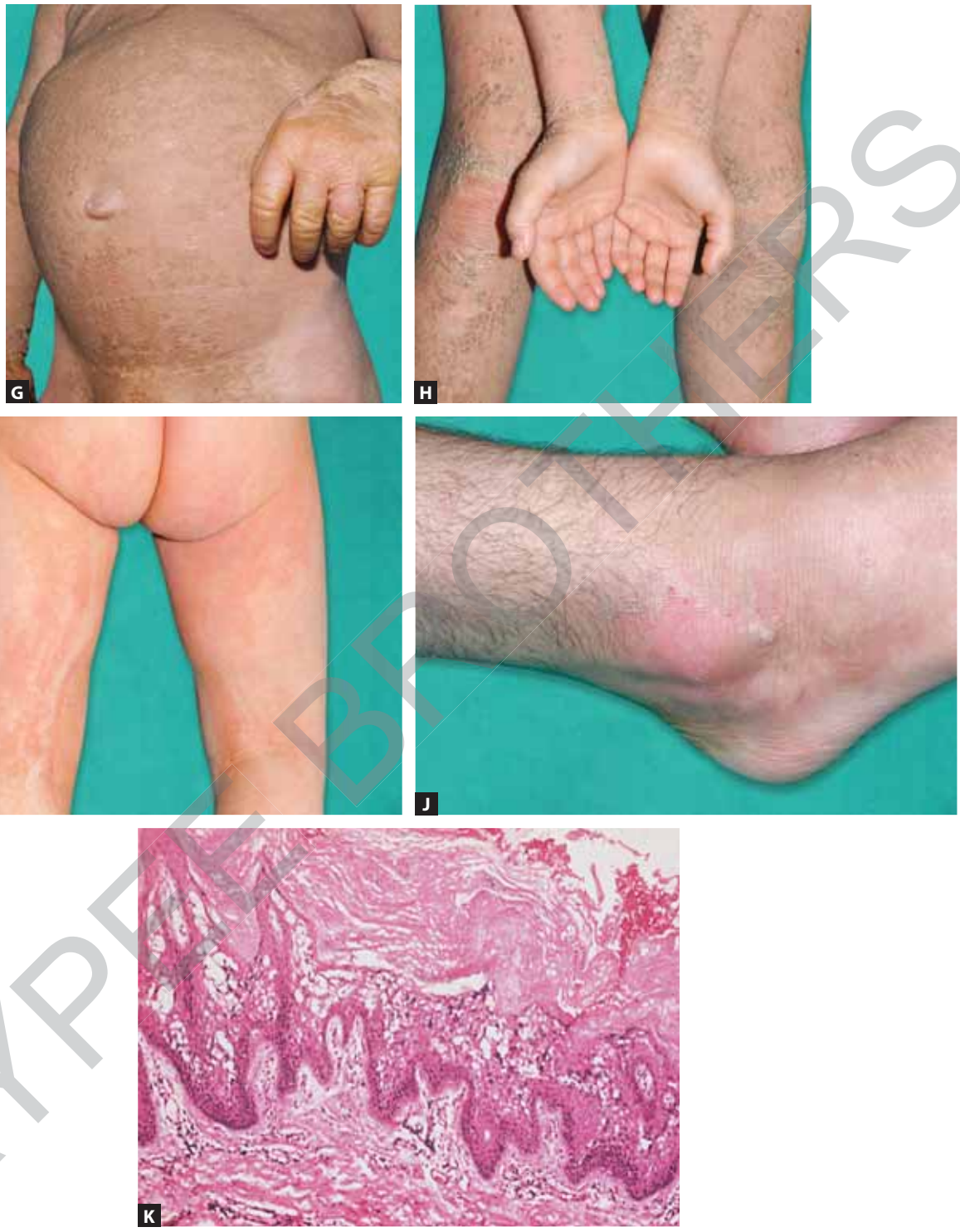


FIGS. 4A TO K: Keratinopathic ichthyoses. (A) Generalized erythroderma, scaling, and peeling in an infant with K1 mutation. (B) Diffuse erythroderma with thick, brown, verrucous hyperkeratosis in a child with mutant K1. (C) Erythema and thick scaling, with a ridged pattern in the knee folds. (D) Severe hyperkeratosis with cobblestone surface pattern over the extensor surface of the elbow. (E) Severe palmoplantar hyperkeratosis is a typical feature in K1 mutations. (F) Erythroderma and widespread superficial peeling in an infant with a K10 mutation. (G) With time, erythema becomes less conspicuous and extensive hyperkeratrosis predominates. (H) Sparing of the hands in spite of severe generalized hyperkeratosis in a child with K10 mutation. (I) Mosaic epidermolytic ichthyosis with very extensive blaschkolinear involvement; these patients have an increased risk of transmission to offspring because of gonadal mosaicism. (J) Superficial epidermolytic ichthyosis (EI) (ichthyosis bullosa of Siemens): mild hyperkeratosis, accentuated skin folds, and superficial blistering of the skin. (K) Characteristic histopathologic features of EI. Massive hyperkeratosis and vacuolar degeneration of the upper spinous layers of the acanthotic and papillomatous epidermis.

Courtesy: (Part A to C and E to I) Dr A Hernández-Martin.

There has been one case of self-healing autosomal recessive EI. Although the patient presented with congenital erythroderma and superficial blistering, by one year of age, the patient witnessed nearly complete resolution of her skin. Mild scaling with superficial erosions after scratching were the only clinical signs that remained. The researchers concluded that despite two novel heterozygous *KRT10* variants predicting null-mutations, one of the variants induced a splice site that allowed production of KRT10 polypeptide, leading to "self-improving" ichthyosis.[92]

In SEI, erythroderma and blistering become apparent at birth or during early infancy and subsequently subside, while hyperkeratosis develops with predilection to flexures, over joints, and on the dorsa of hands and feet. The skin surface may appear ridged, shiny, or lichenified. Characteristics are superficially denuded areas with collarette-like borders described as "molting" or "Mauserung", which develop due to superficial blistering and shedding of the stratum corneum.[71] The clinical features of SEI and EI overlap widely, and *KRT2* mutations have been reported in patients previously misdiagnosed as having EI (**Figs. 4A** to **K**).[93,94]

Although EI affects primarily the skin, there is perinatal morbidity and potential mortality in affected infants due to sepsis, as well as fluid and electrolyte imbalance. Posture and gait abnormalities are not infrequent and might be a result from pain in the skin overlying joints. EI is accompanied by a very distinct, pungent body odor, which is disturbing to patients and their families and impairs their social life.

Pathology

Epidermolytic ichthyosis is characterized by distinct structural and ultrastructural abnormalities that separate EI from other congenital ichthyoses (**Fig. 4K**). A strikingly acanthotic epidermis with hypergranulosis is covered by a massive thickened, dense, and orthokeratotic stratum corneum with focal parakeratosis. Keratinocytes of the suprabasal and granular layers exhibit marked intracellular vacuolization and dense clumps of KIF which may appear as unusual dyskeratosis.[95] Cytolysis may lead to formation of small intraepidermal blisters with a cleavage plane in the middle or upper spinous layers. A mild perivascular lymphohistiocytic infiltrate is usually present in the upper dermis. Collectively, these histopathological changes are described as "epidermolytic hyperkeratosis". In patients with EI, these changes are present continuously throughout the spinous/granular layers, while a focal involvement is found in patients with mosaic EI.[96] The pathological changes in SEI are similar but limited to the uppermost and granular cell layers which express keratin 2.

Ultrastructural analysis in EI reveals fragmented, clumped KIF in the lower, and perinuclear KIF shells in the upper epidermal layers. The assembly of the cornified cell envelope is altered but keratohyalin granules appear normal. Collapse of the cytoskeleton also impairs association of KIF with desmosomal proteins, thus resulting in cell fragility, acantholysis, and cytolysis. Despite the massive hyperkeratosis, the barrier function of the skin is markedly disturbed leading to increased transepidermal water loss[97] and bacterial colonization of the stratum corneum, in particular with *Staphylococcus aureus*. Epidermal proliferation in EI is markedly increased.[98]

Differential Diagnosis

Widespread blistering and denuded skin in a neonate with EI are difficult to distinguish clinically from different forms of epidermolysis bullosa, staphylococcal scalded skin syndrome, and toxic epidermal necrolysis. Light and electron microscopic examination of frozen skin biopsy material obtained from the margin of a fresh blister and bacterial cultures usually lead to the diagnosis. If epidermolysis bullosa is suspected, immunomapping and/or ultrastructural analysis are necessary to determine the specific subtype. Neonates with ankyloblepharon-ectodermal defects-cleft (AEC) syndrome (Hay–Wells syndrome) may present with erosions and collodion membrane but have also ankyloblepharon, hair and nail dystrophy, and cleft lip/cleft palate (**Table 4**). Incontinentia pigmenti can be discriminated by the blaschkoid distribution of vesicles and different histopathology. In addition, one should consider mastocytosis, congenital syphilis, and herpes simplex.

Later during infancy and childhood, EI is readily distinguished from congenital recessive ichthyoses clinically because of generalized blistering at birth and occurrence of focal blisters thereafter. These clinical impressions can be confirmed by skin biopsy revealing the distinctive light microscopic features of epidermolytic hyperkeratosis. Similar histologic findings may be also seen in the epidermolytic form of palmoplantar keratoderma (type Vörner), which is clinically characterized by isolated, diffuse palmoplantar keratoderma with a striking red margin. This autosomal dominant genodermatosis is very similar to peeling skin type 1 (see below) but is caused by mutations in the *KRT9* gene that is predominantly expressed in the suprabasal epidermis of palms and soles.[71,99]

TABLE 4 **Disorders with collodion membrane presentation.**

Disorder	Frequency
ARCI-lamellar	Common
ARCI-CIE	Common
ARCI-CIE/ARCI-LI intermediate phenotypes	Common
ARCI-Harlequin ichthyosis	Common
Autosomal dominant ARCI-lamellar/CIE	Rare
Self-healing/self-improving collodion baby	Always
Sjögren–Larsson syndrome	Rare
Infantile Gaucher disease	Rare
Hay–Wells syndrome	Rare
Trichothiodystrophy	Rare
Netherton syndrome	Rare
Congenital hypothyroidism	Rare
Conradi–Hünermann–Happle syndrome	Rare
Dorfman–Chanarin syndrome	Rare
Ichthyosis vulgaris	Rare
Ichthyosis with confetti	Rare

(ARCI: autosomal recessive congenital ichthyosis; CIE: congenital ichthyosiform erythroderma; LI: lamellar ichthyosis)

Superficial epidermolytic ichthyosis can be distinguished from EI by the absence of erythroderma, the characteristic molting of the outer layer of the epidermis (Mauserung) as well as by the very superficial epidermolysis of the granular cell layers seen on light microscopy. The different site of skin pathology (granular vs. spinous cell layers of the epidermis) is paralleled by the distinct expression pattern of keratin 2, which is structurally altered due to dominant mutations in the *KRT2* gene.[71,93]

Ichthyosis Curth–Macklin may closely resemble EI with ridged, verrucous hyperkeratosis over joints, and flexures in some patients while others have only limited hyperkeratosis restricted to palms and soles. In contrast to EI, there is no clinical or histological evidence for blister formation and epidermolysis. Instead, ultrastructural analysis reveals cytoplasmic shells of fine, tangled KIF in the upper differentiated cell layers of the epidermis associated with perinuclear vacuolization and binucleated cells.[89,90]

Therapeutics

Infants with erythema, blistering, widespread erosions, and denuded skin require management in a neonatal intensive care nursery. They should be handled gently to avoid further trauma to the skin and blistering, and placed in protective isolation and monitored for development of sepsis. In some patients, treatment with broad-spectrum antibiotics may be necessary. Dehydration and electrolyte imbalances are not uncommon and have to be treated accordingly. Erosions and denuded skin generally heal rapidly which can be supported by use of lubricants and protective padding.

The treatment for EI, like other congenital ichthyoses, is symptomatic and often difficult. It should be tailored to the specific needs of the patient depending on the acute clinical presentation at the time of consultation. It is important to avoid mechanical trauma to the skin because of the increased skin fragility (e.g., comfortable clothing and shoe wear). Extensive, thick, hard hyperkeratosis requires hydration, lubrication, and keratolytic treatment. Recurrent and long bathing are suitable to moisten the skin and facilitate mechanical abrasion of the thickened stratum corneum (gentle scrubbing with a soft brush, sponges, etc.). Additional use of antiseptics such as antibacterial soaps, chlorhexidine, or dilute bleach in the bathwater may help control bacterial colonization and bicarbonate addition can aid in scale removal.[85] The use of lubricants and emollients at least twice daily is recommended, but specific agents and formulations may be selected based on individual preferences of the patient. Many commercially available keratolytic creams and lotions containing urea, salicylic acid, alpha-hydroxy acids, or propylene glycol are effective to diminish and remove scale, and to soften the skin. However, they are often not well tolerated, especially in children, because of burning and stinging when the skin is fissured or denuded. Occlusion may enhance the effect but should be used with care in children or patients with heat intolerance. Widespread topical application of salicylic and lactic acid should be avoided because of the risk of systemic absorption. Topical tretinoin and vitamin D preparations are effective but costly and may cause skin irritation. A therapeutic option is treatment of the exposed skin areas only, rendering the visible parts more acceptable.[100,101] Bacterial skin infections are common in EI and often trigger blistering, thus requiring topical treatment with antibiotic ointments or even courses of oral antibiotics.[102]

Synthetic oral retinoids may be very effective in decreasing hyperkeratosis and frequency of infections in patients with generalized EI. Nevertheless, these drugs augment the epidermal fragility of EI and may lead to exacerbation of blistering.[103] It is advisable to start therapy at very low doses with the aim to reach the lowest possible maintenance dose and carefully monitor patients.[104,105] Although oral antibiotics are helpful during episodes of blistering and bacterial superinfections, continuous preventive therapy (oral or topical antibiotics) should be avoided because of the risk of development of resistant bacterial strains.

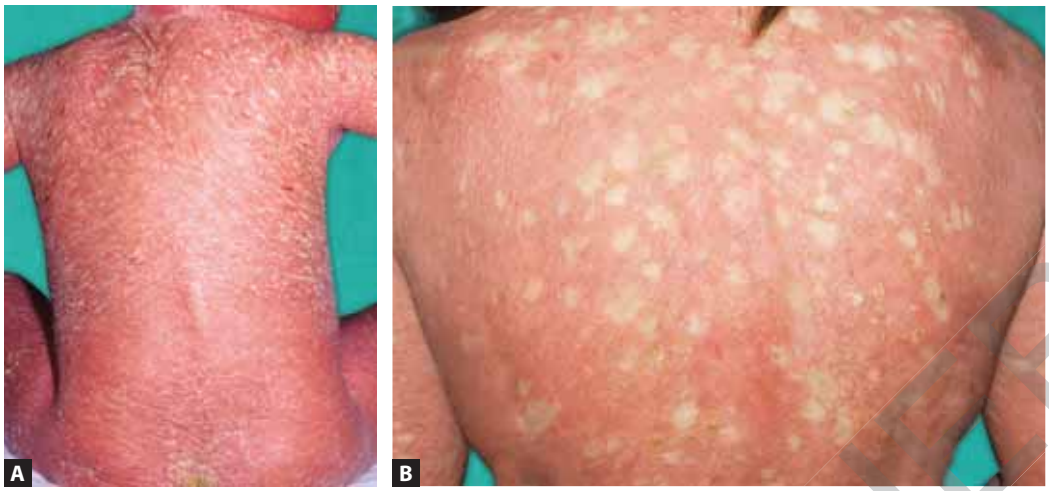
Severe neonatal blistering rapidly improves and most children exhibit only focal blistering in response to trauma or secondary infection. Adult patients may experience little to no blistering. The hyperkeratosis progresses during childhood and persists throughout life but occasionally may improve. Clinical type and course of EI are relatively consistent within families. The acrid body odor and disfigurement in EI may pose social problems and can harm the psychosocial development of children and should be addressed. Bleach baths or shower gels that contain bleach may be helpful, if odor is a problem.

Ichthyosis with Confetti

This autosomal-dominant congential ichthyosis is characterized by erythema and scaling at birth, typically without a collodion presentation.[106] In childhood, white spots appear which have normal histology. Affected skin shows hyperkeratosis and brown macules can be present within red skin and white spots (**Figs. 5A** and **B**). Pathognomonic ultrastructural changes consist of perinuclear shells composed of interdigitating filaments. Choate et al. identified frameshift mutations in *KRT10* and *KRT1* which cause this disorder and found that white spots manifest due to revertant mosaicism in which the affected allele is lost via mitotic recombination.[107,108] In contrast to the mutations which cause EI and occur primarily in the rod domains of K1 and K10, the mutations which cause ichthyosis with confetti (IWC) affect in the tail domain of these proteins, giving rise to a unique phenotype. There have been reported cases of squamous cell carcinoma arising at a young age and patients should receive regular skin cancer screening examination.[109] Therapeutic approaches parallel those for EI.

Autosomal Recessive Congenital Ichthyoses

The ARCI form a rare, clinically, and genetically heterogeneous group of disorders with generalized excessive scaling of the skin from birth. They occur worldwide with an estimated prevalence of 1 in 200,000 persons, but are more common in inbred populations.[110] Terminology and nosology of these disorders have continuously evolved, resulting in much confusion. More than 100 years ago, the all-comprising group of "ichthyosis congenita" was separated into harlequin ichthyosis and a bullous and a nonbullous form of CIE.[7] Frost and Van Scott[9] fortified this distinction and proposed the descriptive terms "LI" for all autosomal recessive forms and, based on distinctive histopathological features, "epidermolytic" hyperkeratosis

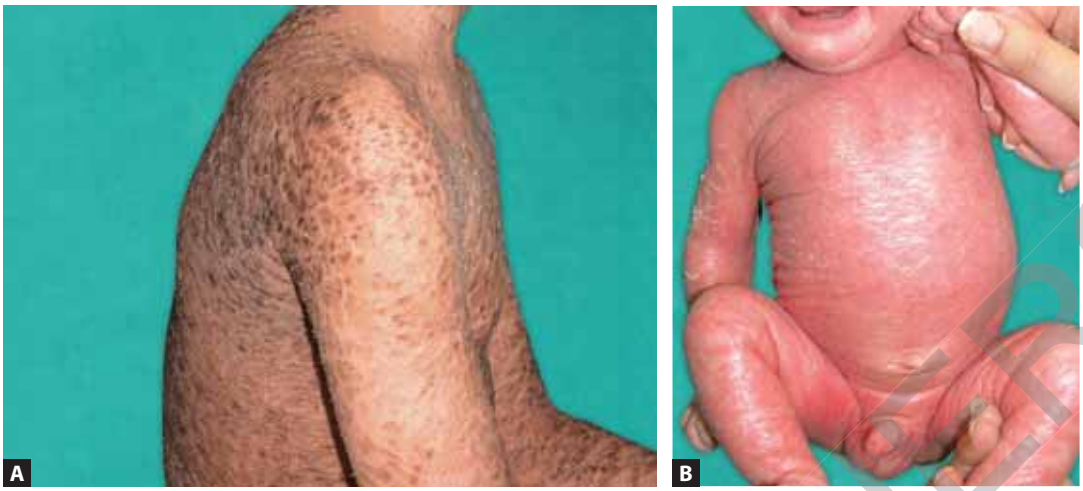


FIGS. 5A AND B: Ichthyosis with confetti. (A) a patient with ichthyosiform erythroderma in infancy. (B) Same patient with erythroderma and irregular white spots of healthy skin on the upper back.

for the autosomal dominant form of congenital ichthyosis. Subsequently, Traupe et al.[111] identified a rare autosomal dominant form of congenital ichthyosis with clinical features indistinguishable from the recessive forms. The considerable clinical heterogeneity of autosomal recessive ichthyoses both prompted and limited arduous attempts to further refine their distinction using clinical, histological, biochemical, and ultrastructural markers which were further hampered by the limited number of patients available for study. Bernhardt and Baden[112] recognized four subtypes predominantly based on severity of disease, while Bergers et al.[113] used discrepancies in the activity of hydrolytic enzymes in the scale of patients to differentiate between an erythrodermic and nonerythrodermic form of autosomal recessive LI. Based predominantly on ultrastructural abnormalities of the stratum corneum, Anton–Lamprecht and others identified three major types of congenital autosomal recessive ichthyoses including the accumulation of lipid droplets in type I, formation of "cholesterol" clefts in type II, and lamellated membrane structures in type III.[13,15,17,114] However, these correlate only loosely with the clinical subtypes of ichthyoses. Clinical scrutiny together with the incorporation of up-to-date knowledge on ichthyoses led Traupe[19] to define LI as an isolated congenital ichthyosis with three forms: erythrodermic, nonerythrodermic, and autosomal dominant LI. Using clinical, biochemical, and histologic criteria combined with differences in the epidermal proliferation rate,[11] Williams and Elias[12] further discriminated the two distinct phenotypes among the recessive forms of nonbullous congenital ichthyoses, distinguishing between LI and (nonbullous) CIE. However, we now appreciate that genotype alone does not determine whether the phenotype will be LI or CIE. While the clinical presentation of ARCI can represent an end of the spectrum between LI and CIE, there is a significant amount of overlap, and it is difficult to predict from the genotype where in this spectrum the phenotype will fall.[115] In its classic form, LI usually presents at birth with collodion membrane and is characterized by large, dark, plate-like scale with variable presence of ectropion, eclabium, and scarring alopecia (**Figs. 6A** and **B**). CIE classically presented with generalized redness and fine white scaling. In many patients, however, the skin disorder demonstrates intermediate phenotypes with variable degrees of erythema and scaling.

Although work to further categorize these disorders by biochemical and histological differences have not yet produced a reliable method for classification, much progress has been achieved in elucidation the genetic basis of ARCI and identifying additional genes that result in this phenotypically diverse group of disorders. So far, mutations in 12 different genes have been found to lead to ARCI: *TGM1*, *ALOX12B*, *ALOXE3*, *NIPAL4*, *CYP4F22*, *ABCA12*, *PNPLA1*, *CERS3*, *SDR9C7*, *SULT2B1*, *KDSR*, and *SDR9C7*. Mutations in some of these genes have recently been identified and reveal new mechanisms of disease in humans. For example, in 2012, Grall et al. discovered mutations in PNPLA1 (patatin-like phospholipase domain-containing protein 1 gene) that result in ARCI.[116] *PNPLA1* encodes a protein with a key role in lipid metabolism. The finding came out of the observation of high rates of ichthyosis in Golden Retrievers. Selective breeding of dogs to create pure breed results in the accumulation of desired traits, as well as the propagation of disease-causing mutations. In a study of Golden Retrievers, Grall et al. were able to identify homozygous mutations in PNPLA1 in 20 Retrievers with ichthyosis. This was applied to the analysis of 46 consanguineous families with ARCI with no mutations in known genes which identified two different mutations in PNPLA in two families. Heniz et al. found that mutation in *SULT2B1* which encodes sulfotransferase family 2B member 1, and is central to the synthesis of cholesterol sulfate cause a lamellar phenotype with large scales in six individuals from three unrelated families.[117] This enzyme converts cholesterol into cholesterol sulfate, a reverse reaction to steroid sulfatase; interstingly, mutations in enzymes with antagonic functions cause two skin phenotypes with similar manifestations.

Mutations in the *KDSR* gene, encoding the enzyme 3-keto-dihydrosphinosine reductase, have also been found to cause a spectrum of DOC ranging from a phenotype similar to progressive symmetric erythrokeratoderma (PSEK) to a Harlequin ichthyosis-like phenotype. *KDSR* is an enzyme in



FIGS. 6A AND B: Autosomal recessive congenital ichthyosis (ARCI). The polar forms of a spectrum. (A) Classical lamellar ichthyosis phenotype: large, brown, and plate-like scales. (B) Classical congenital ichthyosiform erythroderma phenotype with intense erythroderma and fine white scale.

the de novo ceramide synthesis pathway, which plays a crucial role in keratinocyte differentiation and creation of a functional epidermal barrier.[118,119] Loss-of-function mutations in *KDSR* disrupt this de novo pathway but do not affect the two alternate ceramide-producing routes: the sphingomyelinase and salvage pathways.[118] Boyden et al. initially described loss of function mutations in *KDSR*, in kindreds with fixed, erythematous, and hyperkeratotic plaques on the face, buttocks, and groin.[118] The subjects had variations of thickened, erythematous skin at birth, after which the erythema was replaced by clearly demarcated, thickened, scaly lesions and erythema, and thickening of the palms and soles.[118] These features resolved nearly completely in two subjects who received isotretinoin, a systemic retinoic acid derivative that targets the sphingomyelinase pathway and increases ceramide compounds through sphingosine N-acylation.[120] Subsequently, Takeichi et al. reporteded four additional individuals compound heterozygous for *KDSR* mutations, with a spectrium of phenotypes.[121] While two had palmoplantar and perianal keratoderma similar to those in Boyden *et al.*, two had Harlequin-like ichthyosis and all four were thrombocytopenic.[120] Bariana *et al.* report another kindred compound heterozygous for *KDSR* mutations in which the index case and his affected sister were thrombocytopenic, but had a minimal skin phenotype aside from mild axillary keratoderma in the affected sister that self-resolved.[122]

Finally, Hotz *et al.* identified seven patients with ARCI with mutations in *SDR9C7*, all of whom manifested a relatively mild phenotype with generalized scale and mild or localized erythema. *SDR9C7* encodes a short chain dehydrogenase/reductase thought central to retinoid metabolism.[123]

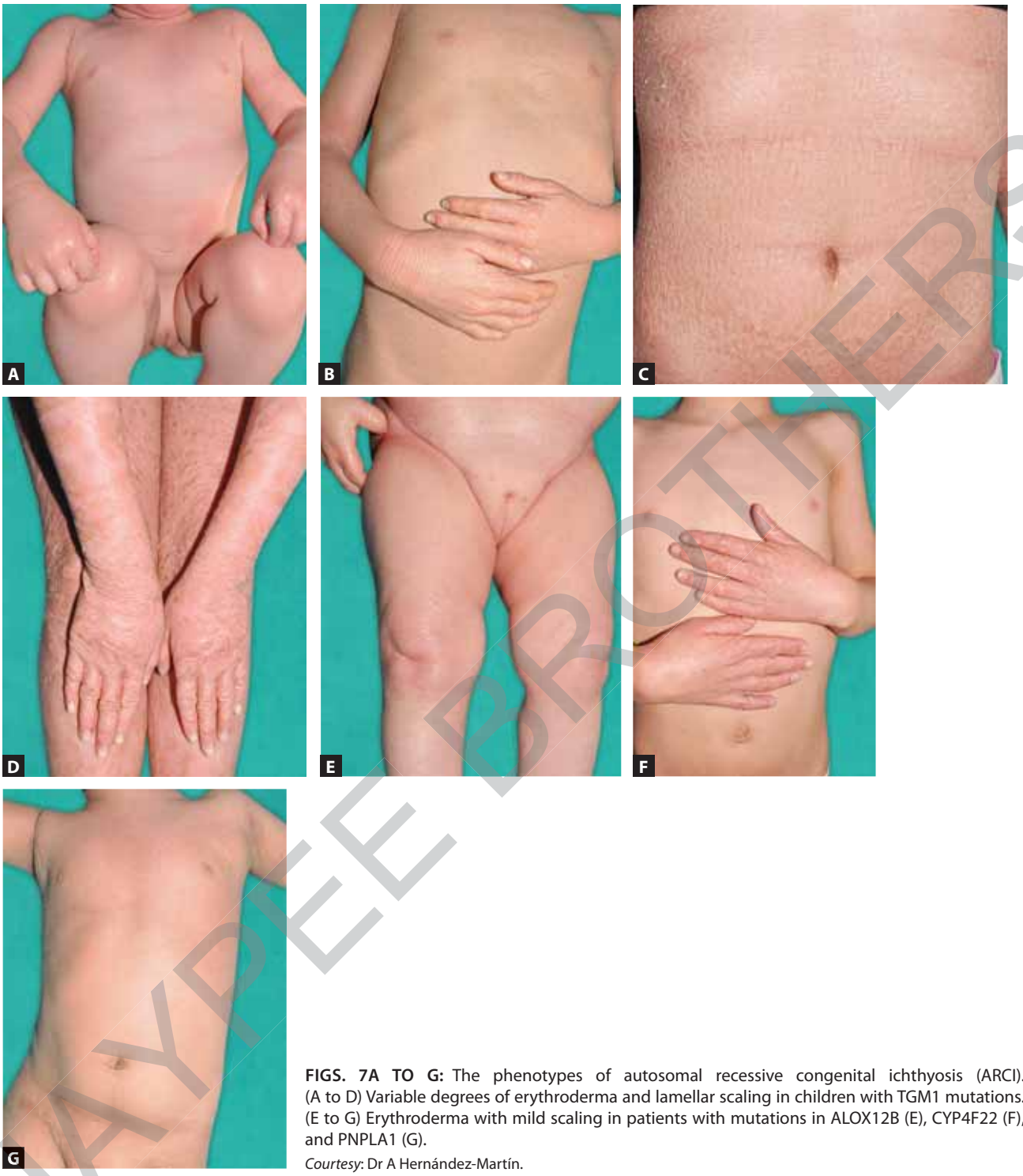
Lamellar Ichthyosis Phenotype

As discussed above, LI and CIE encompass a phenotypic spectrum within the umbrella term of ARCI, and mutations in many genes can lead to either phenotype. Although the true incidence is unknown, LI is estimated to occur in 1 in 200,000 to 1 in 300,000 live births. Both genders are affected equally. It has been observed worldwide without ethnic clustering, although it is more common in certain regions such as Norway (1 in 91,000), or in inbred populations with a high degree of consanguinity.

Pathophysiology

Both LI and CIE are inherited in an autosomal recessive pattern and families with an affected child face a recurrence risk of 25% for each pregnancy. Mutations in *TGM1* are classically implicated in causing the LI phenotype, associated with the characteristic presentation with large, plate-like scale. *TGM1* encodes transglutaminase-1 (TGM1), located on chromosome 14q1. Mutations in *TGM1* are also the leading cause of ARCI, accounting for ARCI in ~55% of patients in the US.[124] In patients with the classic LI phenotype, the mutation detection rate is much higher between 65–90%.[124-127] However, mutations in *TGM1* have been also reported in patients with ARCI with a phenotype more consistent with CIE, including mild to moderate erythroderma, and white or gray small scales.[124,125,128,129] A genotype-phenotype comparison in a large cohort of 104 patients with ARCI predicts that individuals born with a collodion membrane with plate-like scale, ectropion and/or alopecia are four times more likely to have TGM1 mutations than patients without one or more of these features.[124]

In addition to causing generalized ARCI (which encompasses both LI and CIE phenotypes), mutations in TGM1 have been shown to cause bathing suit ichthyosis (BSI) which is a rare form of LI characterized by restriction of the scaling to the trunk, with sparing of the central face, buttocks, and limbs (**Figs. 7A** to **G**). It has been shown that the specific mutations in *TGM1* that cause BSI lead to a temperature-sensitive variant of transglutaminase, with markedly decreased enzyme activity at higher temperature but relatively improved activity at lower temperatures.[130] This temperature-sensitivity explains the differential scaling, with greater scaling at sites of higher temperature such as the trunk. More recently, studies have elucidated the specific mutations that lead to a temperature-sensitive transglutaminase, furthering the genetic understanding of BSI and allowing for better prognostication for patients with mutations in *TGM1*.[131,132] Mutations in



FIGS. 7A TO G: The phenotypes of autosomal recessive congenital ichthyosis (ARCI). (A to D) Variable degrees of erythroderma and lamellar scaling in children with TGM1 mutations. (E to G) Erythroderma with mild scaling in patients with mutations in ALOX12B (E), CYP4F22 (F), and PNPLA1 (G).

Courtesy: Dr A Hernández-Martín.

TGM1 have also been shown to cause self-healing ichthyosis, a rare form of ARCI characterized by the presence of a collodion membrane at birth with spontaneous resolution of the phenotype within the first few weeks. In this rare form of ARCI, the collodion membrane may spontaneously resolve leaving normal skin or very mild generalized (erythrodermic) ichthyosis. This variant may be caused by mutations in either *TGM1* or *ALOX12B* which were shown to be fully inactivating only in utero but not after birth.[133,134] Therefore, it has been speculated that self-healing collodion baby is a dynamic phenotype that, similar to BSI, is dependent on environmental conditions that influence the stability of the mutant protein.

TGM1 is essential to the crosslinking of proteins during the formation of the cornified envelope. Transglutaminases catalyze the calcium-dependent cross-linking of proteins through the formation of N(epsilon)-(gammaglutamyl) lysine isopeptide bonds widely expressed throughout the body. In the epidermis, *TGM1* (together with *TGM3*) is expressed in the upper, most differentiated keratinocytes of the epidermis, where its gene product transglutaminase-1 serves a dual role

during the cornification. The enzyme facilitates the formation of the insoluble protein envelope by cross-linking numerous structural proteins such as involucrin, small proline-rich proteins, loricrin, KIF, and desmosomal proteins.[27] In addition, it is paramount for the ester linkage of epidermis-specific omega-hydroxyceramides to the plasma membrane and formation of the lipid envelope.[28] *TGM1* mutations resulting in lack of transglutaminase-1 expression and/or diminished function[135-137] therefore hinder the formation of the protein envelope as well as the lipid envelope and perturb the normal process of cornification and desquamation.[17,135,138,139]

Over 100 distinct mutations have been identified in *TGM1,*[124] most of which are scattered across the gene and either truncate the gene product (39% nonsense, frameshift, and splice site mutations) or impair its function in the epidermis (61% missense mutations), thus resulting in functional null alleles. Due to a founder effect, the splice site mutation c.877-2 A to G (IVS5-2 A to G), which results in alternative splicing of the *TGM1* message, is the most common *TGM1* mutation detected on 28% of disease alleles. It accounts for the majority of mutant alleles in patients of northern European descent and probably originates from a German predecessor.[124,128,140] However, LI is genetically heterogeneous and other genes have been implicated in its pathoetiology. Individuals from nine families with LI of Northern African descent (Morocco, Mali, and Algeria) were found to have missense mutations in the *ABCA12* gene on chromosome 2q35.[141] Mutations seem to alter the first nucleotide-binding fold of this ABC transporter that is responsible for the energy-dependent transport of lipid substrates across membranes, especially in lamellar bodies of keratinocytes. Mutations in the *CYP4F22* gene on chromosome 19p13.12, which encodes a cytochrome P450 enzyme thought to function in lipoxygenase pathways, were reported in patients with LI associated with hyperlinear palms (but without collodion membrane) from 12 consanguineous families from Algeria, France, Italy, and Lebanon.[142] In addition, exceedingly rare forms of autosomal dominant congenital ichthyosis with LI or CIE features have been reported,[119,143] which has important implications for genetic counseling.

Studies of mice deficient in transglutaminase-1 provided additional insight into the pathophysiology of LI.[144] The mice exhibit a phenotype similar to LI, including taut, erythrodermic, and scaling skin with impaired barrier function. The faulty cross-linking activity of transglutaminase-1 was shown to result in the complete loss of the cornified cell envelope, disturbed degradation of the nuclei, and keratohyalin granules as well as cytoplasmic accumulation of loricrin. The transepidermal water loss and percutaneous absorption rate were tremendously increased, indicative of a severely impaired skin barrier. These results strongly emphasize the essential role of transglutaminase-1 in the development and maturation of the stratum corneum and in the adaptation of the skin to a dry environment after birth.[144]

Lamellar ichthyosis has become a prototype for therapeutic cutaneous gene delivery. In the human skin/immunodeficient mouse xenograft model, Choate et al. succeeded in short-term correction of the molecular, histological, and functional abnormalities of LI skin in vivo.[145] Transglutaminase-1 deficient primary keratinocytes from LI patients were transduced with a retroviral vector driving the expression of transglutaminase-1 and then grafted onto the skin of nude mice. This bioengineered LI epidermis showed a transient normal expression of the enzyme as well as other differentiation markers and normal barrier function of the skin. However, keratinocytes retained the transglutaminase-1 gene only for a short period of time. Therefore, this and other approaches[146] are not yet practicable for use in human but demonstrate that in vivo functional correction of the primary defect as well as therapeutic gene delivery is feasible.

In families with identifiable mutations or known linkage to gene loci, prenatal diagnosis can be performed by mutation and/or genotype analysis from CVS or amniocentesis material at an early gestational age.[115,147] In addition, in families with a known genetic mutation, it has become possible to perform preimplantation genetic diagnosis, a practice which has become more common over the last 10 years.[13]

Clinical Features

Lamellar ichthyosis usually presents at birth by the presence of a collodion membrane which is a tight, shiny, and translucent covering encasing the newborn. Over the first few weeks of life, this thick membrane dries, cracks, and is gradually replaced by generalized scaling.

Lamellar ichthyosis is characterized by dark brown, large scales, which form a plate-like pattern and involve the entire body surface including the face, flexures, palms, and soles (**Figs. 7A** to **G**) The scales are centrally attached and often have raised borders leading to superficial fissures and form a mosaic or bark-like pattern. Severe tautness of facial skin commonly results in ectropion and eclabium as well as a significant hypoplasia of nasal and auricular cartilage. While an underlying erythroderma can usually be appreciated during infancy, children, and adults have minimal to no erythroderma. Palmoplantar keratoderma may vary, ranging from accentuated skin markings to severe thickening with cracking and fissuring.

Severe scarring alopecia, especially at the periphery of the scalp, is a common feature of LI.[148] Hair shafts emerging from the scalp are encased by the thickened stratum corneum and the taut skin exerts traction and compression. Inflammation of the nail folds may produce secondary nail dystrophy with thickening of the nail plates and ridging. The thickened, firm stratum corneum in LI also constricts the sweat ducts, often resulting in severe heat intolerance. Although lips and mucous membranes tend to be spared, severe ectropion may lead to madarosis, conjunctivitis, and incomplete lid closure with ensuing keratitis.

Lamellar ichthyosis is not primarily associated with systemic manifestations. Collodion babies have an increased incidence of premature birth with concomitant perinatal morbidity and mortality. They are at increased risk for sepsis, fluid, and electrolyte imbalance and particularly hypovolemic hypernatremia.[149]

Pathology

Ultrastructural and immunohistochemical studies of skin biopsies in at least half of all LI patients reveal thin or absent cornified cell envelops.[135,138] Biochemical in vitro assays of

cultured keratinocytes often demonstrate drastically reduced transglutaminase-1 activity,[137] although it can be normal due to genetic heterogeneity.[136,150] DNA-based molecular testing is commercially available for diagnostic and prenatal testing and carrier detection in LI.

The histological abnormalities in LI are nonspecific and include massive orthokeratotic hyperkeratosis with relatively mild acanthosis, regular papillomatosis, and dilated capillaries in the superficial dermis. In contrast to CIE, the epidermal proliferation rate is normal or only slightly elevated.[11] Elongated cholesterol clefts as well as a variable number of translucent lipid droplets in the stratum corneum and a thin or absent cornified cell envelope have been described as significant ultrastructural abnormalities in LI, although these findings widely overlap with those found in CIE.[125,135,151]

Differential Diagnosis

In the neonatal period, there is considerable clinical overlap with other congenital ichthyoses that may manifest as collodion baby, including CIE, Netherton syndrome, SLS, and trichothiodystrophy.

Therapeutics

As far as prognosis, LI is a severe disorder persisting throughout life. However, treatments are available to improve quality of life and decrease rates of associated comorbidities.

Autosomal recessive congenital ichthyosis is characterized by severe impairment of desquamation and barrier function of the skin resulting in substantial loss of water, ions, and proteins in the neonatal period. Sufficient dietary protein and fluid intake is required particularly during infancy and childhood to avoid or minimize growth failure.[152] Secondary hypohidrosis due to obstruction of eccrine sweat ducts results in heat intolerance, which is aggravated in a hot climate and may limit physical activity. External cooling by dousing with cool water and the use of air conditioning can ameliorate the symptoms. Accumulation of scale in the external ear canals often leads to occlusion and bacterial colonization with ensuing recurrent ear infections, which may be prevented by periodic scale removal and otologic care. Severe ectropion demands ophthalmologic follow-up and, if necessary, surgical repair to prevent irreversible corneal damage. Topical tazarotene may be useful in localized areas.

Autosomal recessive congenital ichthyosis is often severely disfiguring and poses a challenge to the development of a positive body image and hence, to normal psychosocial development. Families and patients need continuous support in dealing with psychosocial problems. Patient support organizations such as the Foundation for Ichthyosis and Related Skin Types (FIRST) and the National Organization for Rare Disorders (NORD) have been of tremendous benefit to patients and their families.

Congenital Ichthyosiform Erythroderma Phenotype

Synonym: Nonbullous congenital ichthyosiform erythroderma (NBCIE).

As discussed above, LI and CIE encompass a phenotypic spectrum within the umbrella term of ARCI with much overlap between the two ends of the spectrum. While CIE may be more common than LI, its incidence probably does not exceed 1 in 200,000. In contast to the LI phenotype which is characterized by the presence of large scales with or without erythroderma, the CIE phenotype features small scales on a background of erythroderma.

Pathophysiology

Congenital ichthyosiform erythroderma is clinically and genetically very heterogeneous and, in contrast to LI, only a small subset of patients with clinical features of CIE were found to carry inactivating *TGM1* mutations leading to transglutaminase-1 deficiency with ensuing abnormal formation of the cornified cell envelope and perturbed barrier function of the skin.[125,126,128] However, there is no obvious correlation between the specific location and nature of recessive *TGM1* mutations and their phenotypic expression as LI or CIE.[125] Mutations in the two related *ALOXE3* and *ALOX12B* genes on 17p13.1 account for approximately 12% of patients in whom *TGM1* mutations have been ruled out. 60% of these mutations were found in the *ALOX12B* gene and the remaining 40% in the *ALOXE3* gene.[153,154] *ALOX12B* and *ALOXE3* encode the lipoxygenases 12R-LOX (12R-lipoxygenase) and eLOX-3 (epidermis-type lipoxygenase 3), respectively. The consecutive action of these enzymes leads to the oxygenation of ceramides which are essential to the formation of the lipid barrier.[15] While 12R-LOX is responsible for generating fatty acid hydroperoxide, eLOX functions as hydroperoxide isomerase to generate epoxy alcohols. While most individuals with *ALOX* gene mutations were born with a collodion membrane and later showed mild to moderate CIE, a few individuals had mild LI or self-healing collodion baby presentation.[134,154] Autosomal recessive mutations in a gene named *NIPAL4* on chromosome 5q33.3 appear to be the leading cause of congenital ichthyosis in TGM1-negative Scandinavian patients (>90%) with specific ultrastructural features such as abnormal lamellar bodies in the stratum granulosum and perinuclear, elongated membranes.[155] Clinically, patients with *NIPAL4* mutations had a CIE phenotype but mostly lacked a collodion presentation at birth. Two missense mutations, A176D and G230R, accounted for approximately 90% of disease alleles in this cohort. In addition, several consanguineous families with *NIPAL4* mutations from the Mediterranean and South America have been reported.[156] *NIPAL4* is a transmembrane protein of poorly-recognized function with homologies to both transporters and G-protein coupled receptors which is hypothesized to represent a membrane receptor for ligands (trioxilins A3 and B3) from the hepoxilin pathway. It is highly expressed in brain, lung, stomach, leukocytes, and keratinocytes.[156] Finally, autosomal recessive *ABCA12* mutations have to be considered as a molecular cause of CIE. While *ABCA12* mutations typically present at birth as Harlequin ichthyosis, overlap with collodion membrane has been observed. Moreover, surviving children with Harlequin ichthyosis show a phenotypic shift and develop features of severe CIE often including alopecia, failure to thrive, and growth retardation. Therefore, *ABCA12* mutations should be taken into account for this phenotype (for details see next

section on "Harlequin ichthyosis"). Prenatal diagnosis based on molecular approaches is available for families carrying mutations in all genes known to cause CIE phenotypes.

Clinical Features

Similar to LI, most infants present at birth with a collodion membrane which subsequently evolves into generalized scaling and pronounced erythroderma.

The clinical manifestations of CIE are usually milder than in LI and demonstrate a greater variability in the intensity of erythema, size, and type of scale even within a family. Generally, scales are white, fine, and powdery (**Figs. 7A** to **G**), although they may become larger, darker, or plate-like on the extensor surface of the lower extremities. Severely affected patients show an intense red erythroderma and develop ectropion and scarring alopecia. Marked hyperkeratosis of palms and soles with cracks and deep fissures often contrasts the fine, translucent scale elsewhere on the body. Patients with milder disease exhibit less or minimal erythroderma but generalized scaling and variable palmoplantar involvement.

Scarring alopecia is less common than in patients with LI.[148] The impediment of sweat ducts and pores results in hypohidrosis and heat intolerance. Secondary nail dystrophy (thickened nail plates and ridging) and onychomycosis may develop while lips, mucous membranes, and teeth tend to be spared.

Congenital ichthyosiform erythroderma has no primary systemic manifestations. While most patients with CIE phenotypes show normal growth and development, severely erythrodermic children may show growth retardation, likely due to ample chronic loss of water and calories caused by a defective permeability barrier of the skin.[152] Adult patients anecdotally report joint pain, gait abnormalities, and flexural contractures associated with palmoplantar keratoderma. An increased incidence of nonmelanoma skin cancers has been reported in a few patients with ARCI including the development of multiple aggressive squamous cell carcinoma of the skin even during long-term low-dosage treatment with systemic retinoids.[157,158] Therefore, long-term follow up for adult patients with ARCI should include the consideration of skin cancer, even if a patient is treated with retinoids.

Pathology

The histopathological features of CIE are not diagnostic and do not allow a definite distinction from LI. However, they are valuable to exclude EI. Compared to LI, there is pronounced acanthosis of the epidermis with hypergranulosis, mild-to-moderate hyperkeratosis, and focal to extensive parakeratosis. The epidermal cell turnover rate in CIE is markedly increased indicative of epidermal hyperproliferation.[11]

Ultrastructural and biochemical abnormalities in CIE, although not very well correlated with the clinical phenotypes, are suggestive for abnormalities in the lamellar body secretory system. Electron microscopic examinations reveal abnormal and an increased number of lamellar bodies, many of which appear to be retained within corneocytes, thereby resulting in accumulation of lipid droplets in the stratum corneum.[13,15,135] Intercellular lipid lamellae of the stratum corneum, which derive from the secretion and reorganization of lamellar body contents, appear highly disorganized in CIE. These structural aberrations are accompanied by differences in the activity of lamellar body enzymes in the stratum corneum,[119] which may play a role in the abnormal persistence of desmosomes.[135] Collectively, these changes might result in a disturbed skin barrier function with increased transepidermal water loss, which in turn has been shown to stimulate epidermal hyperplasia.[30,159] Nevertheless, many ultrastructural features are not specific for CIE and have been observed in other hyperproliferative disorders.[135]

Differential Diagnosis

Severe forms of CIE and LI can be distinguished based on clinical, histological, and ultrastructural findings. CIE is defined by the presence of generalized, bright red erythema, and fine white scale. Patients with LI have generalized thick, plate-like scale with minimal to no erythroderma. Both disorders may present as collodion baby. Ectropion, eclabium, and scarring alopecia are more commonly seen in LI. Keratinocytes in LI show a normal granular layer, cell proliferation, and lamellar bodies but massively thickened stratum corneum without parakeratosis.[119,135] The presence of cholesterol clefts in the stratum corneum by electron microscopic examination is suggestive of LI, while a larger number of lipid droplets are more common in CIE.[13,15,17] The mitotic rate in CIE is increased as is the number of lamellar bodies and the stratum corneum is thickened with focal to complete parakeratosis. The distinction of LI and CIE based on elevated levels of N-alkanes in CIE has been refuted because they may originate from exogenous sources.

Other types of ichthyosis can be differentiated from CIE and LI based on specific clinical, histological, and biochemical parameters (**Table 2**). In contrast to ichthyosis vulgaris (which never presents as a collodion baby), skin involvement in LI, and CIE is typically generalized including all flexures, and results in taut facial skin with ensuing ectropion/eclabium and alopecia. However, the distinction between LI/CIE intermediate phenotypes and ichthyosis vulgaris may be difficult. XLRI can be excluded by biochemical testing. Chanarin–Dorfman syndrome (neutral lipid storage disease) can usually be identified by examining a peripheral blood smear. Skin findings in Netherton syndrome may closely resemble CIE, but this disorder is often associated with failure to thrive, recurrent or systemic infections, pruritus, highly elevated plasma immunoglobulin E (IgE) levels, and hair shaft abnormalities, and has a psoriasiform histopathology. Trichothiodystrophy can be eliminated by light and polarizing microscopy of hair. Finally, EI can be distinguished clinically based on the occurrence of blisters, flexural accentuation, and absence of ectropion as well as by its distinctive histopathology.

Therapeutics

Newborns with a collodion membrane are at risk for thermoinstability, hypernatremic dehydration, complications due to increased transcutaneous water loss, skin infections, and sepsis. They should be carefully monitored for temperature, fluid and electrolyte imbalances, and signs of pneumonia

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