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Ichthyoses in everyday practice: management of a rare group of diseases

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Summary

Ichthyoses comprise a heterogeneous group of hereditary disorders of keratinization characterized by a highly varied clinical picture. A distinction is made between common hereditary ichthyoses (ichthyosis vulgaris and X-linked ichthyosis), which usually manifest themselves in the first year of life, and rare, sometimes severe congenital ichthyoses. Patients with very mild symptoms often do not even realize they have ichthyosis. The diagnosis is usually based on clinical evaluation. Molecular genetic testing as well as histological and electron microscopic studies may aid in confirming the diagnosis. Mapping a family tree is also diagnostically useful. Besides skin manifestations, important aspects of the clinical examination and history include disease onset, presence of a collodion membrane at birth as well as the presence of hair anomalies and extracutaneous signs and symptoms.

Rigorous hydration of the skin (several times a day) and balneotherapy are the mainstay of ichthyosis treatment. For patients with severe disease, systemic acitretin treatment should be considered on a case-by-case basis. While ichthyoses are generally limited to the skin, there are syndromic forms that may affect other organs and that require interdisciplinarity cooperation. Although ichthyoses remain incurable, they can be managed well with symptomatic treatment. However, such treatment is frequently time consuming and expensive. In the future, novel therapeutic approaches might include enzyme replacement and gene therapies as well as antiinflammatory drugs.

Objectives

The goal of the present CME article on ichthyoses is to familiarize the reader with the very heterogeneous clinical presentations associated with this group of disorders. Thereafter, the reader should be able to distinguish common forms of ichthyosis from rare variants, and know when to contact disease experts and other medical specialties. In addition, the article is intended to convey basic principles of adequate topical treatment and to provide information on how to thoroughly counsel affected patients and their families. The ichthyosis forms described herein are generally considered to be orphan diseases, with the exception of ichthyosis vulgaris.

This CME article is aimed at dermatology residents as well as board-certified dermatologists who would like to refresh their knowledge in this particular field.

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Introduction

Ichthyoses are a clinically heterogeneous group of hereditary disorders of keratinization.

Ichthyoses comprise a group of hereditary disorders of keratinization. Mutations in more than 50 different genes have been described as the cause of the various forms of ichthyosis [1, 2]. Phenotypically, ichthyoses are characterized by increased keratinization, scaly dry skin, and a varying degree of erythroderma [3].

Whenever there is clinical suspicion of ichthyosis, it is essential to determine whether the patient has a non-syndromic or a syndromic form. Non-syndromic disease variants primarily affect the skin, whereas syndromic ichthyoses may also be associated with extracutaneous involvement, including ocular, ear, skeletal and CNS manifestations as well as olfactory impairment. The Chanarin-Dorfman syndrome (synonym: neutral lipid storage disease [NLSD] with ichthyosis) can affect the liver and the striated muscles. Lymphocyte anomalies may also occur (Jordans anomaly) [3].

A distinction is made between common hereditary ichthyoses (IV and XLI), which usually manifest themselves within the first year of life, and rare, sometimes severe congenital ichthyoses, including ARCI. Patients with very mild symptoms (e.g., IV) frequently do not even realize they have a genetic disorder.

Ichthyoses can also be divided into common forms (ichthyosis vulgaris [IV] and X-linked ichthyosis [XLI]) and rare variants such as autosomal recessive congenital ichthyosis (ARCI). The term ARCI describes a group of disorders that includes harlequin ichthyosis (HI), lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE). These entities must be distinguished from acquired ichthyoses, such as in patients with a paraneoplastic syndrome and underlying malignancy. Syndromic ichthyoses include Netherton-syndrome (NTS) or Sjögren-Larsson syndrome (SLS); the latter is associated with mental retardation and neurological abnormalities [4].

There are many symptomatic treatments available. In everyday clinical practice, appropriate topical therapies are essential to prevent complications and sequelae such as infection, fissures, contractures or a feeling of stigmatization. In addition, it is very important to counsel family members on aspects of heredity and prognosis. Parents confronted with ichthyosis in their new-born child frequently experience considerable uncertainty and fear. Given the rarity of these disorders, medical personnel too may often feel a sense of uncertainty. It is therefore crucial to establish the correct diagnosis as early as possible and to offer comprehensive information about the disease. Affected families should also be informed about patient support groups. Early access to such groups (e.g., Selbsthilfegruppe Ichthyose e. V. in Germany) can be very helpful, as it ensures the exchange of information among families affected by the same rare disorder. Patient support groups are highly experienced in educating those affected on how to cope with the disease in everyday life, and they can provide information on other places families may turn to for help. Contact with other affected families can also be very useful in that if allows them to see how other children with ichthyosis thrive and manage their everyday life [3].

If ichthyosis is clinically suspected, it is essential to take a detailed history, which ought to include the family history as well as questions about consanguinity, delivery, preterm births, prolonged labor, complications during pregnancy, development after birth, and the time of disease onset. Extracutaneous manifestations and abnormalities in adnexal structures should also be noted. The initial onset of cutaneous manifestations should be inquired to narrow down the type of ichthyosis. Other important aspects of the clinical examination and history include the presence of blisters, erythroderma, hair anomalies, ear and eye deformities and the presence of a collodion membrane at birth. The hands and feet can also be helpful in narrowing down the differential diagnoses (palmoplantar hyperlinearity as a sign of IV, or palmoplantar keratoderma in cases of *KRT1* mutations) [2, 3].

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Pathomechanisms

Impaired barrier function and pathological keratinization are common features of all types of ichthyosis. The genes involved in ichthyosis encode epidermal proteins that play a key role in the formation of cell contacts (cornified envelope) and the cytoskeleton as well as in lipid metabolism.

As a result, hyperkeratosis, increased scaling, inflammation and, in some cases, blistering may occur.

Some of the proteins involved are not only expressed in the skin but can also be found in other tissues; some syndromic forms of ichthyosis are caused by dysfunction in these proteins.

The physiological defects underlying ichthyoses are numerous and highly varied. As it is impossible to offer a single, comprehensive explanation, we will discuss the various relevant pathomechanisms associated with the ichthyosis forms described herein in more detail.

Impaired barrier function and pathological keratinization are common features of all types of ichthyosis. The genes involved in ichthyosis encode epidermal proteins that play a key role in the formation of cell contacts (cornified envelope) and the cytoskeleton as well as in lipid metabolism. As a result, hyperkeratosis, increased scaling, inflammation and, in some cases, blistering may occur. Some of the proteins involved are not only expressed in the skin but can also be found in other tissues; some syndromic forms of ichthyosis are caused by dysfunction in these proteins.

In healthy skin, corneocytes are linked by cell contacts (including corneodesmosomes) that are degraded by proteolytic enzymes (serine proteases such as kallikrein 5 and 7) during normal desquamation. The antagonists of serine proteases are referred to as serine protease inhibitors (e.g., LEKTI) [1]. The proteins and lipids required for normal barrier function are produced during terminal differentiation of keratinocytes. Various types of lipids are stored in lamellar bodies (also known as Odland bodies) and then secreted into the intercellular space. During the differentiation process, keratinocytes change their shape; they become flatter and take on a polygonal form in the stratum spinosum. One of the factors governing the differentiation process is skin pH [4].

Ichthyosis vulgaris is characterized by a mutation in the *filaggrin* gene (*FLG*), which codes for profilaggrin. Filaggrin (FLG) binds to keratin filaments in the upper epidermis and thus stabilizes the cytoskeleton. In addition, substances produced during filaggrin degradation constitute a natural moisturizing factor and have UV-protective effects. Profilaggrin is contained in the keratohyalin granules in the stratum granulosum. In the upper granular layer, the cell membrane of keratinocytes is supported by the cornified envelope, which consists of structural proteins such as loricrin and involucrin that are cross-linked by transglutaminases. Lamellar ichthyosis has been shown to be caused by decreased transglutaminase 1 (TG1) activity.

Other essential components contributing to the stability of the cytoskeleton include keratins, which are produced by keratinocytes and subsequently form intermediate filaments. Basal keratinocytes primarily produce keratin 14 and 5; those in the stratum spinosum, keratin (KRT) 1 and 10. Keratin expression can be therapeutically modified by retinoids. Keratinopathic ichthyoses are characterized by mutations in the *KRT1, KRT2* or *KRT10* genes. Histologically, these ichthyosis variants are associated with epidermolytic hyperkeratosis [4].

Deficiency in certain proteins of lipid metabolism are also involved in the pathogenesis of ichthyoses, as is the case in XLI. The disease is characterized by accumulation of cholesterol sulfate due to a lack of steroid sulfatase. Other genes affected in certain ARCI forms include those that code for ATP-binding cassette transporters (involved in lipid transport) or epidermal lipoxygenase. Some syndromic ichthyoses too present with alterations in lipid metabolism (Table 1) [2, 3]. Decreased activity of these proteins is associated with impaired formation of the cornified envelope as well as abnormal epidermal differentiation and proliferation.

Many forms of ichthyosis are characterized by hyperkeratosis and scaling. A humanized mouse model has shown that the thickened corneal layer in animals with LI reduces transepidermal water loss and thus prevents dehydration.

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Table 1 Summary of the various types of ichthyoses, including affected genes, pattern of inheritance, clinical characteristics and diagnostic procedures [1, 2].

		Ichthyosis	*Gene* (Gene product on the protein level) (inheritance pattern)	Clinical features	Diagnostic procedures
Non-syndromic ichthyoses	Common ichthyoses	Ichthyosis vulgaris	*FLG* (filaggrin) (autosomal semi-dominant)	– Fine scaling – Palmoplantar hyperlinearity – Atopy – Keratosis pilaris	– Histology – Immunohistology (antigen mapping, FLG) – Electron microscopy – Molecular genetic analysis
		X-linked ichthyosis	*STS* (steroid sulfatase) (XR)	– Rhomboid scaling; sparing of the flexor surfaces – Improvement in the summer – Cryptorchidism – Autism and/or ADHS – Prolonged labor	– Histology – Electron microscopy – Enzyme activity analysis (EDTA blood) – FISH analysis – Lipoprotein electrophoresis – Molecular genetic analysis
	ARCI and keratinopathic ichthyoses	Harlequin ichthyosis	*ABCA12* (ATP-binding cassette transporter 12) (AR)	– Scales with an armor plate-like appearance at birth – Massive ectropion – Eclabium – Severe erythroderma	– Histology – Electron microscopy – Molecular genetic analysis
		Lamellar ichthyosis, congenital ichthyosiform erythroderma	*TGM1* (transglutaminase 1 [TG1]); *ALOX12B* (epidermal lipoxygenase 12B); *ALOXE3* (epidermal lipoxygenase E3); *CYP4F22* (cytochrome P450 polypeptide); *NIPAL4 (ichthyin)* *ABCA12* *(AR)*	– Collodion baby – Coarse scales (LI) – Erythroderma with whitish scaling (CIE) – Palmoplantar hyperlinearity (*ALOXE3*) – Diffuse yellowish palmoplantar keratoderma (*NIPAL4*) – Decreased ability to sweat	– Histology – Immunohistology (antigen mapping, TG1) – Enzyme activity analysis (frozen sections, TG1) – Electron microscopy – Molecular genetic analysis
		Bathing suit ichthyosis	*TGM1* (AR)	– Coarse scales, especially on the trunk – Heat intolerance	– Histology – Enzyme activity analysis – Electron microscopy – Molecular genetic analysis
		Self-improving congenital ichthyosis	*TGM1;* *ALOX12B;* *ALOXE3* (AR)	– Resolves within the first year of life	– Histology – Immunohistology (TG1) – Electron microscopy – Molecular genetic analysis

		Keratinopathic ichthyoses	EI	*KRT1* (keratin 1); *KRT10* (keratin 10) (AD, rarely AR [*KRT10* mutations])	– Blistering and erosions – "Scalded child" appearance in some cases – Verruciform palmoplantar keratoderma in some cases (*KRT1*)	– Histology – Immunohistology – Electron microscopy – Molecular genetic analysis
			SEI	*KRT2* (Keratin 2) (AD)		
		Other KPI variant	CRIE	*KRT1* *KRT10* (AD) Special feature: loss of *KRT* mutations due to recombination → replacement of keratinopathic component → partial "healing" of the skin	– Erythroderma at birth, over the years increasing occurrence of whitish patches (look like healed areas, "confetti" ichthyosis) – Palmoplantar keratoderma	
Other non-syndromic ichthyosis		Peeling skin disorder		*CDSN* corneodesmosin) (AR)	– Peeling of the upper epidermis – Erythroderma in some cases – Pruritus	– Histology – Electron microscopy – Immunohistology (antigen mapping, CDSN) – Molecular genetic analysis
Syndromic ichthyoses		Netherton syndrome		*SPINK5* (LEKTI) (AR)	– Erythroderma – Trichorrhexis invaginata – Atopy, food allergies – Laboratory findings: high IgE levels, eosinophilia – Failure to thrive – Pruritus – Susceptible to severe infections	– Histology – Immunohistology (antigen mapping, LEKTI) – Hair analysis using trichoscopy (trichorrhexis invaginata) – Molecular genetic analysis
		Sjögren-Larsson syndrome		*ALDH3A2* (fatty aldehyde dehydrogenase) (AR)	– Yellowish velvety keratosis – Mild erythroderma – Severe pruritus – Neurological abnormalities (spasticity) – Mental retardation	– Histology – Molecular genetic analysis

Continued

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Table 1 Continued.

	Conradi-Hünermann-Happle syndrome	*EBP* (delta-8 delta-7 sterol isomerase emopamil-binding protein) (XD)	– Collodion baby in some cases – Congenital ichthyosiform erythroderma – Atrophoderma – Skin lesions frequently follow Blaschko lines – Alopecia with patchy scarring – Epiphyseal calcification – Scoliosis	– Histology – Molecular genetic analysis
	Dorfman-Chanarin syndrome	*ABHD5* (adipocyte-triglyceride lipase) (AR)	– Mild collodion membrane in some cases – Ichthyosis (similar to congenital ichthyosiform erythroderma) – Hepatosplenomegaly – Myopathy – Cataracts – Hearing impairment – Vacuolization of white blood cells (Jordans anomaly)	– Histology – Molecular genetic analysis – Blood smear – Laboratory: liver function tests – Liver ultrasound – Ophthalmological examination
	KID syndrome	*GJB2* (connexin 26); *GJB6* (connexin 30) (AD)	– Spiny, velvety, brown hyperkeratosis with erythroderma – Sensorineural hearing loss since birth – Scarring alopecia in some cases	– Histology – Immunohistology – Molecular genetic analysis
	Trichothiodystrophy syndrome	Associated with *C7Orf11, ERCC2/XPD* and *ERCC3/XPB* (proteins involved in DNA transcription/repair) (AR)	– Collodion baby in some cases – Ichthyosis with palmoplantar keratoderma – Sparse, brittle hair with longitudinal splitting – Atopy – Nail dystrophy – Psychomotor retardation – Immune deficiency – Cataracts	– Hair analysis (tiger tail banding under polarizing microscopy; sulfur deficiency) – Molecular genetic analysis

Abbr.: AD, autosomal dominant; AR, autosomal recessive; ARCI, autosomal recessive congenital ichthyosis; CIE, congenital ichthyosiform erythroderma; CRIE, congenital reticular ichthyosiform erythroderma; EI, epidermolytic ichthyosis; FISH, fluorescence in situ hybridization; KID, keratitis-ichthyosis-deafness syndrome; KPI, keratinopathic ichthyosis; LI, lamellar ichthyosis; LEKTI, Lympho-epithelial Kazal-type-related inhibitor; SEI, superficial epidermolytic ichthyosis; TG1, transglutaminase 1; XD, X-linked dominant; XR, X-linked recessive.
References: [3, 4, 7].

Hyperkeratosis may thus be considered a repair process aimed at preventing transepidermal water loss [4–6]. Ichthyosis-related hyperkeratosis may be based on the following mechanisms: epidermal hyperproliferation, increased corneocyte adhesion and decreased desquamation of the upper skin layers. In addition, some forms of ichthyosis are characterized by an inflammatory component, with increased release of cytokines [1, 4].

Common hereditary ichthyoses

Ichthyosis vulgaris (IV) is the most common form of ichthyosis, with a prevalence of about 1 : 100 to 1 : 250. X-linked ichthyosis is the second most common type (prevalence about 1 : 2,000 to 1 : 4,000). While the onset of symptoms is usually a few months after birth, newborns with XLI may present as collodion baby (CB).

Ichthyosis vulgaris

Ichthyosis vulgaris (Figure 1a, b) is caused by a mutation in the *FLG* gene and inherited in a semi-dominant manner. Filaggrin plays a key role in skin barrier maintenance and also acts as natural moisturizing factor. Mutations in the *FLG* gene may also be involved in the pathogenesis of atopic dermatitis. Phenotypically, IV is characterized by fine gray scaling on the extremities and trunk, xerosis cutis as well as palmoplantar hyperlinearity (Figure 1a). Scaling is especially prominent on the extensor surfaces of the extremities. Some patients also present with keratosis pilaris on the upper arms and thighs. More than 50 % of patients also have atopic dermatitis [3]. Ichthyosis vulgaris symptoms may be so mild that they are hardly detectable during clinical examination. Patients frequently do not even realize they have IV. Histology plays an essential role in the diagnosis of ichthyoses, particularly for narrowing down differential diagnoses. Reduction or complete lack of the stratum granulosum is a typical feature of ichthyosis vulgaris. This histological criterion can only be found in a limited number of other forms of ichthyosis such as HI, acquired ichthyoses or the Conradi-Hünermann-Happle syndrome. Immunohistochemical staining may provide evidence of filaggrin deficiency [3, 4].

Ichthyosis vulgaris is the most common form of ichthyosis. It is caused by filaggrin deficiency. Characteristic findings include fine scaling and palmoplantar hyperlinearity.

X-linked ichthyosis

X-linked ichthyosis is the second most common form of ichthyosis.

X-linked ichthyosis (XLI) (Figure 1c–e) is the second most common form of ichthyosis. Given the inheritance pattern, the disease almost exclusively affects male newborns. Their mothers are heterozygous carriers of the gene defect. There have been isolated cases of affected females (homozygous carriers or X0 karyotype). X-linked ichthyosis is caused by deficiency in or complete lack of steroid sulfatase (STS), which hydrolyzes cholesterol sulfate to yield cholesterol. Deficiency in STS causes cholesterol sulfate accumulation and thus inhibits epidermal serine proteases. This leads to decreased desquamation and retention hyperkeratosis. Histologically, the granular layer is more prominent than in patients with IV. Clinically, XLI presents with fine or coarse, frequently brownish scales on the extremities and trunk (Figure 1d). There is frequently prominent involvement of the nape of the neck. In everyday practice, it may at times be difficult to distinguish XLI and IV. It has recently been shown that XLI may also be associated with an atopic disposition, and that XLI patients have an increased prevalence of *FLG* mutations. In male patients suspected of having IV, XLI should therefore always be considered in the differential diagnosis [7, 8]. Some patients with XLI also present with extracutaneous manifestations such as cryptorchidism, a tendency for hyperactivity and/

Clinically, XLI presents with fine or coarse, frequently brownish scales on the extremities and trunk. There is frequently prominent involvement of the nape of the neck.

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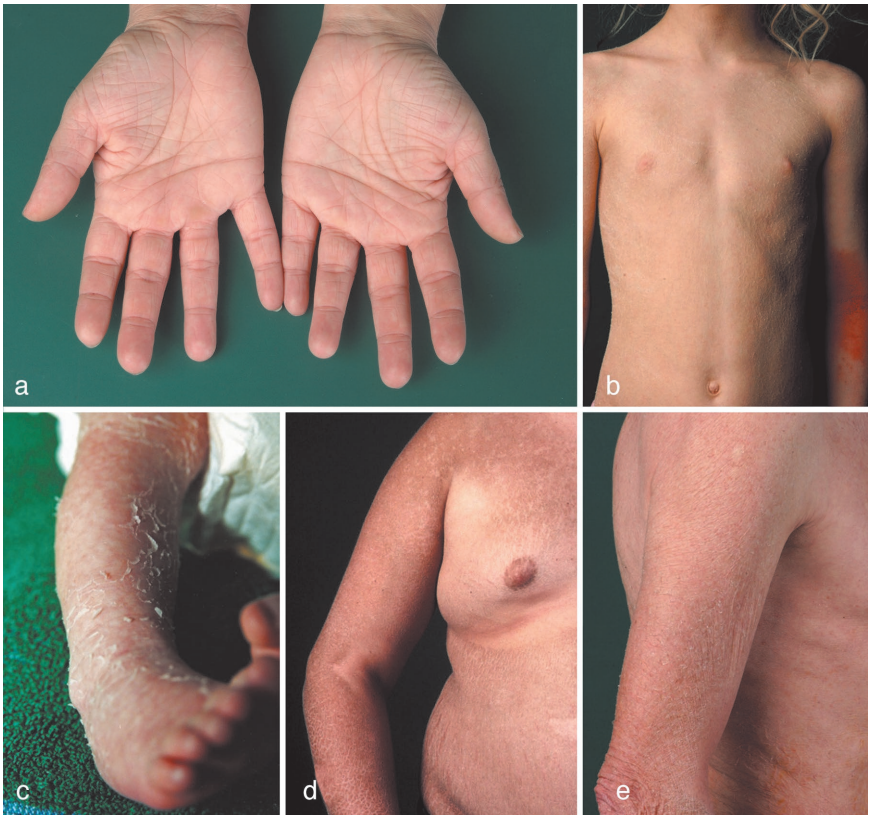

Figure 1 Clinical examples of common hereditary ichthyoses. Patient with X-linked ichthyosis (XLI) and additional *FLG* mutation showing palmoplantar hyperlinearity (a). Patient with ichthyosis vulgaris (IV) with fine scaling and coexisting atopic dermatitis (b). XLI (c–e) with significant scaling three weeks after birth (c); 14-year-old boy with brownish scales on the extensor aspects of the extremities (d); older patient with gray-white scaling (e).

Some patients with XLI also present with extracutaneous manifestations such as cryptorchidism, a tendency for hyperactivity and/or autism. Mothers of sons with steroid sulfatase deficiency frequently report difficult or prolonged labor.

or autism. Mothers of sons with steroid sulfatase deficiency frequently report prolonged labor. This might be caused by delayed cervical dilation. If adjacent genes are also affected, this may result in hypogonadotropic hypogonadism with anosmia (Kallmann syndrome). In such cases, the disease is referred to as a syndromic form of XLI. Steroid sulfatase deficiency may be associated with very severe disease during the winter season. Intermittent systemic acitretin treatment may be considered [4, 5].

Rare congenital ichthyoses

Some of the following forms of ichthyosis are extremely rare (prevalence 1 : 500,000 or even less common).

Autosomal recessive congenital ichthyoses

Autosomal recessive congenital ichthyosis (ARCI) describes a group of very heterogeneous ichthyoses, including harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosiform erythroderma. They are all inherited in an autosomal recessive manner.

Autosomal recessive congenital ichthyosis (ARCI) describes a group of very heterogeneous ichthyoses, including harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosiform erythroderma. They are all inherited in an autosomal recessive manner. There are also some milder disease variants such as pleomorphic ichthyosis or self-improving congenital ichthyosis (SICI). While these forms usually improve over the course of time, certain environmental factors may cause disease flares. To date, more than ten different genes have been identified that are known to cause ARCI [1].

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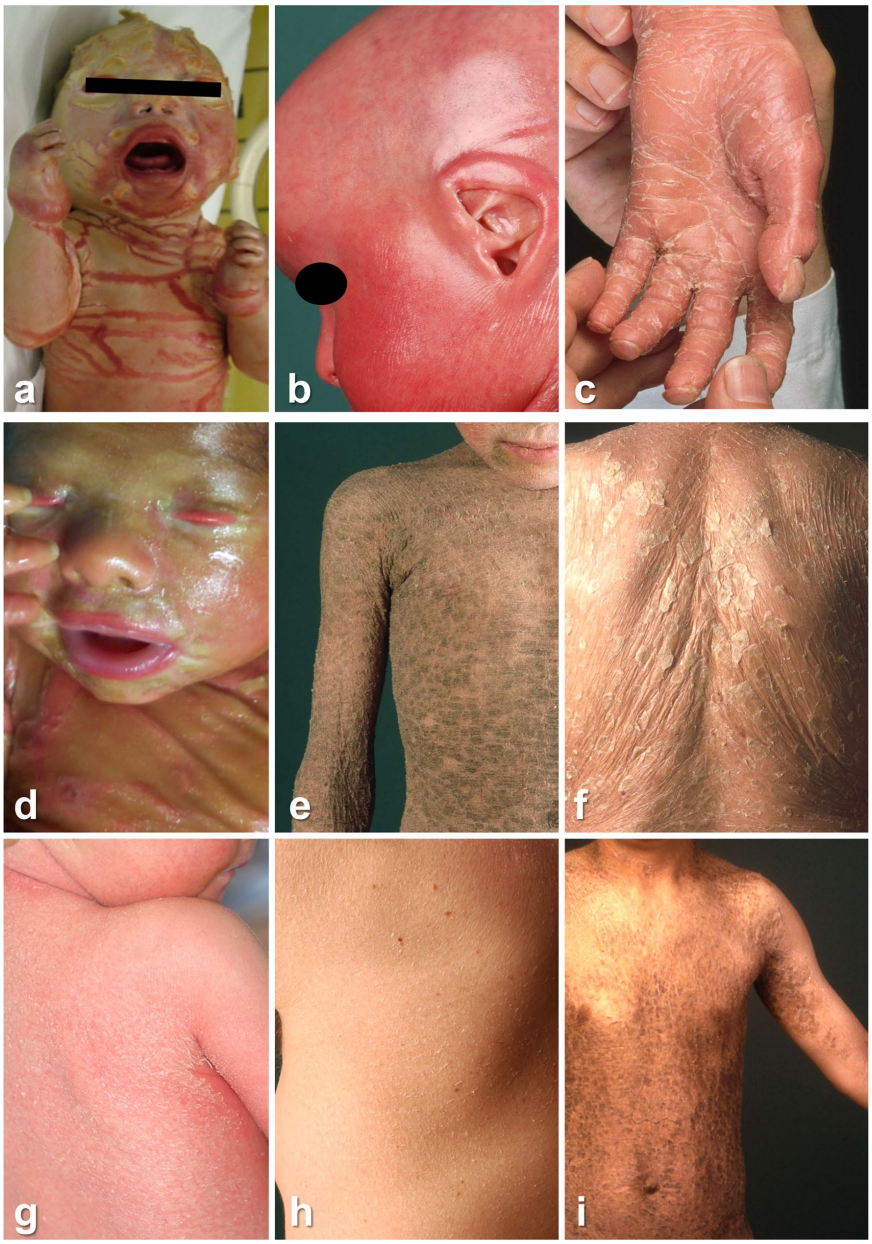

Figure 2 Clinical examples of autosomal recessive congenital ichthyoses. Harlequin ichthyosis (HI) at birth; the scales have a typical armor plate-like appearance and affect the entire body (a). HI evolves into generalized exfoliative erythrodermic ichthyosis (b, c). Collodion membrane with ectropion and eclabium in a patient with lamellar ichthyosis (LI) (d). LI in childhood (e). 79-year-old patient with LI and *TGM1* mutation (f). Congenital ichthyosiform erythroderma (CIE) in early childhood (g). Adult with mild CIE and *ALOXE3* mutation (h). Bathing suit ichthyosis is a variant of LI characterized by localized healing on the extremities (i).

Formation of a collodion membrane is not a specific feature of certain ichthyoses but may be seen with several subtypes, including harlequin ichthyosis, congenital ichthyosiform erythroderma, bathing suit ichthyosis, Conradi-Hünermann-Happle syndrome, trichothiodystrophy and, in some cases, X-linked ichthyosis. While lamellar ichthyosis typically presents with a collodion membrane, isolated IV is never associated therewith.

Collodion baby

A collodion baby (Figure 2d) is born encased in a collodion membrane, which either covers individual parts of the body or the entire skin. In some cases, the skin subsequently heals completely; this is referred to as SICI.

Formation of a collodion membrane is not a specific feature of certain ichthyoses but may be seen with several subtypes, including harlequin ichthyosis, congenital ichthyosiform erythroderma, bathing suit ichthyosis, Conradi-Hünermann-Happle syndrome, trichothiodystrophy and, in some cases, X-linked ichthyosis. While lamellar ichthyosis typically presents with a collodion membrane, isolated IV is never associated therewith.

Newborns with a collodion membrane require monitoring in an intensive care unit. Due to fluid loss, electrolyte abnormalities and the increased risk of infection,

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there is a significant increase in mortality if these babies are left untreated. Collodion babies should initially be placed in an incubator (humidity: about 80–90 %; temperature: about 35°C) to protect them from dehydration and to maintain an optimal body temperature. Ointments with dexpanthenol or glycerin are suitable as emollients. Erosions can be treated with topical antiseptic agents (polyhexanide). Ectropion is common in collodion babies (Figure 2d) and requires an ophthalmology consult [3].

Harlequin ichthyosis

Harlequin ichthyosis is the most severe form of ARCI.

Harlequin ichthyosis (HI) is the most severe form of ARCI (prevalence 1 : 1,000,000). It is caused by mutations in the *ABCA12* gene, which codes for a protein involved in lipid transport. Despite the severity of the disease, some patients may experience considerable clinical improvement over the course of the disease. However, most patients develop very severe scaling and erythroderma (Figure 2b). At birth, the scales may have an armor plate-like appearance and restrict respiration (Figure 2a). Other manifestations include deep fissures, severe ectropion and eclabium. Significant contractures may occur (Figure 2c). The mortality rate in newborns with HI is very high. Some babies already die in utero. Apart from intensive care, treatment with acitretin may be considered [3].

The mortality rate in newborns with HI is very high. Some babies already die in utero. Apart from intensive care, treatment with acitretin may be considered.

Lamellar ichthyosis and congenital ichthyosiform erythroderma

Lamellar ichthyosis manifests itself with coarse dark-brown scaling, whereas patients with CIE present with prominent generalized erythroderma.

Lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE) are characterized by significant variability in their clinical phenotype, ultrastructure and molecular biology. They are commonly caused by mutations in the *transglutaminase 1 (TGM1)* gene. The remaining transglutaminase activity correlates with the severity of the phenotype. In about 10 % of CIE cases, the lipoxygenase genes *ALOXE3* and *ALOX12B* are also affected (Figure 2g, h). Epidermal lipoxygenases are involved in arachidonic acid metabolism. Other causative mutations are found in the *NIPAL4* (*ICHTHYIN*) or *ABCA12* genes (Table 1). There is usually no direct correlation between the phenotype and the causative mutation, as various gene defects may give rise to similar clinical presentations [2]. Lamellar ichthyosis manifests itself with coarse dark-brown scaling (Figure 2e, f), whereas patients with CIE present with prominent generalized erythroderma (Figures 2g, h). Patients with these two types of ichthyosis often have a limited ability to sweat and therefore tend to overheat very quickly, particularly during physical activity. Many patients with ARCI experience severe pruritus. Bathing suit ichthyosis is another rare variant of LI characterized by medium-sized or coarse scaling, primarily affecting the trunk. Cooler skin areas (on the extremities) are spared (Figure 2i). The disorder is caused by temperature-sensitive mutations in the *TGM1* gene [4–6].

Patients with these two types of ichthyosis often have a limited ability to sweat and therefore tend to overheat very quickly, particularly when exercising.

Keratinopathic ichthyosis

The very rare keratinopathic ichthyoses are caused by defects in the genes encoding KRT1 and KRT10 (or KRT2 in superficial epidermolytic ichthyosis [SEI]). These keratins are expressed by suprabasal keratinocytes. The disorders are almost always inherited in an autosomal dominant manner. Infants with this type of ichthyosis may develop generalized erythroderma with blistering ('scalded child' appearance).

(subtypes: superficial epidermolytic ichthyosis; epidermolytic ichthyosis, formerly known as: *bullous congenital ichthyosiform erythroderma [Brocq]*)

The very rare keratinopathic ichthyoses are caused by defects in the genes encoding KRT1 and KRT10 (or KRT2 in superficial epidermolytic ichthyosis [SEI]). (Figure 3d, e). These keratins are expressed by suprabasal keratinocytes. The disorders are almost always inherited in an autosomal dominant manner. Infants with this type of ichthyosis may develop generalized erythroderma with blistering ('scalded child'

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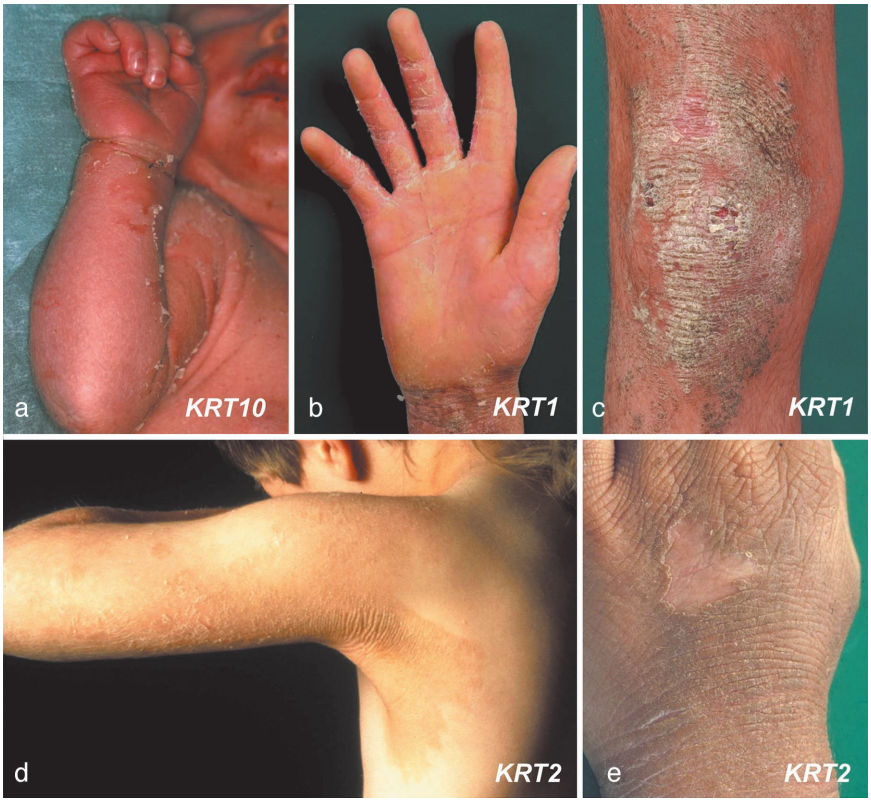

Figure 3 Clinical examples of keratinopathic ichthyoses. Patients with epidermolytic ichthyosis (EI) caused by *KRT10* mutation: superficial blistering at birth; the palms are not affected (a). Patient with EI caused by *KRT1* mutation (b, c) and palmoplantar keratoderma (b). In infancy, EI often presents with hyperkeratosis, primarily affecting the joints and areas exposed to mechanical trauma (c). Superficial EI (SEI) caused by *KRT2* mutation, confined to certain areas of the arm and axillary region (d). 'Moulting' phenomenon in SEI (e).

appearance) (Figure 3a). Over time, blistering becomes less frequent, and the phenotype is subsequently dominated by corrugated hyperkeratosis affecting the nape of the neck, the flexor aspects but also the extensor surfaces of the extremities (Figure 3c). Patients with *KRT1* mutations may also develop palmoplantar keratoderma (Figure 3b).

Similar to epidermolysis bullosa, essential aspects of patient management include the treatment of blisters and avoidance of mechanical trauma. Overly aggressive keratolytic measures and fatty ointments should be avoided. Non-adhesive wound dressings and thorough antiseptic measures are recommended. Although acitretin may be indicated in cases of SEI or KRT10-associated epidermolytic ichthyosis, it should be noted that this may induce increased blistering (particularly in patients with *KRT1* mutations) [3].

Syndromic ichthyoses

Herein, we will present Comèl-Netherton syndrome (or Netherton syndrome) and Sjögren-Larsson syndrome as examples of syndromic ichthyoses (Figure 4b). Further syndromic ichthyoses can be found in Table 1 and Figure 4.

While ichthyoses are usually limited to the skin, there are syndromic forms that may affect other organs and that require interdisciplinary cooperation.

While ichthyoses are usually limited to the skin, there are syndromic forms that may affect other organs and that require interdisciplinary cooperation.

Netherton syndrome

Netherton syndrome (Figure 4d) is a syndromic ichthyosis caused by mutations in the *SPINK5* gene, which encodes LEKTI, a complex serine proteinase inhibitor. There is an anti-LEKTI antibody that can be diagnostically used for immunohistochemical staining.

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Brittle hair is a key diagnostic sign in patients with NTS. Trichoscopic examination (without plucking any hairs!) shows the typical presentation of trichorrhexis invaginata. This hair anomaly is detected only after infancy.

Patients characteristically present with erythroderma as a sign of the inflammatory component of the disease. There is frequently severe pruritus and a significant tendency for type I hypersensitivities [9]. Growth retardation and failure to thrive may occur, and affected individuals have an increased susceptibility to infections. Besides erythroderma, patients also exhibit significant hypotrichosis (or even alopecia), which may be ameliorated by adequate skin care of the scalp and which tends to improve during adolescence. Brittle hair is a key diagnostic sign in patients with NTS. Trichoscopic examination (without plucking any hairs!) shows the typical presentation of trichorrhexis invaginata. This hair anomaly is detected only after infancy. Hair analysis also plays a decisive role in the diagnosis of trichothiodystrophy (TTD) (Figure 4a), characterized by sulfur-deficient hair and tiger tail banding when viewed under polarizing microscopy.

Antipruritic measures and sufficient hydration of the skin are the mainstay of treatment for NTS (e.g., with dexpanthenol 5 % as additive). Keratolytic agents should only be used with caution. Topical corticosteroid therapy (class 2–3) may be used for antiinflammatory purposes, but only for short periods of time. When using topical agents in NTS patients, it is important to keep in mind that skin absorption is increased. Topical calcineurin inhibitors are not recommended, given the patients' susceptibility to HPV infection. Other aspects to be observed in routine practice include superinfections and the increased risk of developing squamous cell carcinoma. Some individuals may benefit from immunoglobulin treatment during childhood. Affected patients should not be treated with systemic acitretin, as this is known to aggravate the skin inflammation associated with NTS [3].

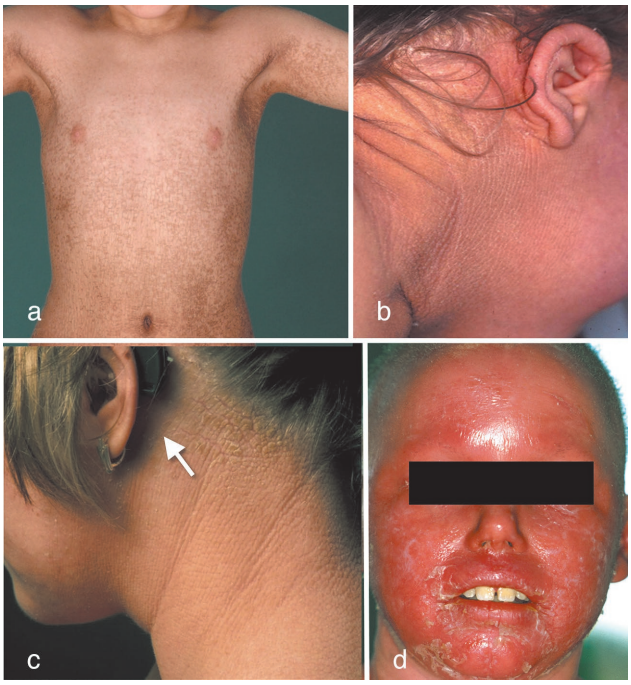

Figure 4 Clinical examples of syndromic ichthyoses. Ichthyosis in a patient with trichothiodystrophy (a). Sjögren-Larsson syndrome (b). Keratitis-ichthyosis-deafness (KID) syndrome (c). Netherton syndrome (d) (courtesy of Dan Ben Amitai, MD).

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Sjögren-Larsson syndrome

Sjögren-Larsson syndrome (SLS) is a neurocutaneous disorder.

Sjögren-Larsson syndrome (SLS) is a neurocutaneous disorder. Clinically, it is characterized by generalized ichthyosis with yellowish-velvety hyperkeratosis predominantly affecting the flexor surfaces (Figure 4b), mild erythroderma, neurological abnormalities (including symmetric spasticity, particularly of the lower extremities), mental retardation and speech defects. Ocular symptoms are also common [4]. SLS is caused by a defect in the gene that encodes the enzyme fatty aldehyde dehydrogenase. SLS patients frequently have very severe pruritus. In such cases, treatment with 5-lipoxygenase/leukotriene inhibitors may be considered. Low-dose acitretin therapy may also be indicated. Other (currently not evidence-based) treatment approaches include a low-fat diet to prevent lipid deposits in the brain.

SLS patients frequently have very severe pruritus. In such cases, treatment with 5-lipoxygenase/leukotriene inhibitors may be considered.

Diagnosis

Important components in the diagnostic workup of ichthyoses include a detailed history and careful inspection of the skin. For narrowing down the differential diagnosis, it is first essential to ascertain the time of disease onset and the family history. Compared with rare disease variants, common ichthyoses usually tend to manifest themselves later in the first year of life. Mapping a family tree may offer clues as to whether the disorder is indeed a genodermatosis, and if so, if the inheritance pattern is recessive, dominant or X-linked. Relevant aspects regarding the cutaneous manifestations include the site of the lesions and the type of scaling (polygonal, fine scales, coarse scales). The palms and soles may also offer important differential diagnostic clues, as they may show signs such as hyperlinearity and hyperkeratosis. In addition, it is essential to know whether blistering has occurred and whether there is adnexal involvement (e.g., hypotrichosis). Finally, physicians should always inquire about extracutaneous manifestations.

A family tree and a detailed history may aid in narrowing down the differential diagnosis. It is important to look for extracutaneous manifestations.

If hereditary ichthyosis is suspected following a thorough history and clinical examination, it is recommended to contact a reference center before ordering any laboratory tests. As new diagnostic procedures are constantly emerging, early consultation may avoid taking unnecessary blood or skin samples. Contacts can be found in the guidelines for "Diagnosis and Treatment of Ichthyoses [3]. Diagnostic lab tests for ichthyosis include histological evaluation, immunohistochemical studies, hair analysis and ultrastructural studies (electron microscopy). Enzyme activity analyses are also useful (Table 1), including measurement of steroid sulfatase activity, which is decreased in XLI, and measurement of TG1 in patients with TG1 deficiency.

Molecular genetic tests should be used to confirm the diagnosis. Panel testing (next-generation sequencing) allows for the identification of various mutations. This is especially useful when dealing with rare forms of ichthyosis. Prior to this step, however, clinical findings and other diagnostic procedures should be used to narrow down the diagnosis. It is essential that patients be informed about the benefit of molecular genetic testing. Genetic analyses are crucial when a pregnancy is planned (particularly in severe cases) or in order to assess disease course and prognosis of a given ichthyosis. Genetic testing is also useful with respect to potential future therapies (e.g., gene therapy). Once a mutation has been detected, patients should be offered genetic counseling.

Diagnosis of ichthyosis is usually based on clinical examination and can be confirmed by molecular genetic testing. Immunohistochemical, biochemical and electron microscopy studies may aid in the diagnosis.

Interdisciplinary cooperation of dermatologists, neonatologists, ophthalmologists, ENT specialists, internal medicine specialists, pediatricians, gynecologists and possibly urologists is required to assess the extent of involvement of other organs. This applies to syndromic ichthyoses in particular.

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Treatment

Intensive topical therapy is currently the mainstay of ichthyosis treatment. In many cases, this approach relieves symptoms and helps prevent sequelae such as contractures and joint stiffness. Physical therapy and ergotherapy can be very useful supplementary measures.

Various topical agents are used for the treatment of ichthyoses (Table 2), and affected patients require an enormous amount of creams and ointments. Frequency of use depends on the form of ichthyosis and on the patient. Apart from treating symptoms such as pruritus and preventing contractures or superinfections, cosmetic aspects also play an important role. The frequency with which a given patient applies emollients to the skin is an individual decision that is guided by how burdened he/she feels psychologically and by his/her symptoms.

Topical preparations with glycerin 5–10 %, dexpanthenol 5 % and polyethylene glycol (batch 400) are suitable to improve hydration. These additives are especially recommended in cases with mild scaling as well as inflammatory, erythematous or exfoliative ichthyoses. Glycerin can be compounded with any oil-in-water and amphiphilic base, preferably at concentrations of 5–10 %. The following NRF (New German Formulary) formulations already contain glycerin 4.25 % and can be used as a base for extemporaneous preparations: non-ionic hydrophilic cream SR (NRF S.26) and lipophilic cream base (NRF 11.204) [3]. However, if tolerated well, patients may certainly be treated with commercially available drug products.

For keratolysis in patients with coarse or very adherent scales, topical products containing urea are especially suitable. However, patients with very mild scaling may experience a burning sensation when using urea at a concentration ≥ 5 %. Glycerin-containing topical preparations may be used for facial skin care. Occlusive overnight treatment is useful for severe scalp scaling. Salicylic acid should generally be avoided, as there is an increased risk of absorption and thus metabolic acidosis; possible exceptions include the treatment of very localized areas in adult patients. Severe scaling in and around the ears may result in occlusion of the external auditory canal. An ENT specialist should be consulted if there are signs of hearing impairment.

Antiseptic treatment is particularly important in patients with blisters as well as individuals with NTS. Supportive measures for patients with blisters include compresses soaked in black tea or potassium permanganate baths. Erosions can be dabbed with polyhexanide solution. Dexpanthenol is a suitable ingredient in topical preparations for NTS or to treat erosions.

Some ichthyosis patients show a decreased ability to sweat, especially during physical activity. Cooling sprays may be used to counter this phenomenon [3].

Balneotherapy is an essential component of ichthyosis treatment. While the frequently uttered (false) claim that frequent bathing will promote skin dehydration may be unsettling for patients and their families, there is no need for worry. Balneotherapy is very useful in efficiently loosening and removing both scales and skin care residues across large areas. After the bath, lipid-replenishing emollients must be generously applied to prevent dehydration. Whey or molasses are suitable bath additives, while oils should be avoided due to a significant risk of slipping in the bathtub. Salts may also be used (note: these may lead to burning sensations). Keratolytic bath additives are also frequently used in balneotherapy, including baking soda (sodium bicarbonate [3–6 grams per liter bathing water]), wheat starch or corn starch. Washcloths and pumices may aid in mechanical keratolysis [3].

Acitretin is approved for systemic treatment of ichthyoses. However, it is important to note that rigorous topical treatment will still be necessary in most cases

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Table 2 Topical agents for the treatment of ichthyosis [1–3].

Agent	Concentration/dosage	Mechanism of action	Indication(s)	Contraindication(s)	Additional information
Glycerin	5 %–10 %	Promotes corneocyte shedding; accelerates desmosome degradation; hydrating and smoothing effects	IV; mild forms of XLI and ARCI; facial skin care; inflammatory, erythematous or exfoliative ichthyoses	Intolerance	Non-ionic hydrophilic cream SR (NRF S.26) and lipophilic cream base (NRF 11.204) are possible bases for extemporaneous formulations [2]
Dexpanthenol	5 %	Promotes cell proliferation	Mild scaling; inflammatory, erythematous or exfoliative ichthyoses; collodion baby; nose or eye ointments with dexpanthenol; eyelid treatment in patients with ectropion	Intolerance	
Urea pura	5–10 %	Reduces epidermal proliferation; regenerates the skin barrier; anti-microbial, keratolytic, and smoothing effects; promotes penetration of other ingredients into the skin	Very adherent, coarse scaling (e.g., in XLI, LI);- For the scalp: – Therapeutic shampoos (5%) – Occlusive dressing with urea 10 % in DAC cream	Before 2nd year of life; inflammatory, erythematous or exfoliative ichthyoses (burning sensations may occur; in such cases, use dexpanthenol or glycerin); concentrations > 3 % on the face	Urea 5 % + glycerin 5 %: good efficacy while simultaneously decreasing the irritant potential
Lactic acid	5 % in amphiphilic cream base	Keratolytic and hydrating effects	Very adherent scales	Inflammatory, erythematous or exfoliative ichthyoses; concentrations > 5 % (irritant potential; dysesthesia may occur) [3]; Use in newborns or in cases of extremely impaired skin barrier (risk of lactate acidosis) [3]	

Continued

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Table 2 Continued.

Agent	Concentration/dosage	Mechanism of action	Indication(s)	Contraindication(s)	Additional information
Polyethylenglykol Charge 400 (Macrogol 400)	20–30 % in amphiphilic base [3]	Hydrating effects	Can be used in various forms of ichthyosis	Use during the 1st or 2nd year of life (percutaneous absorption with subsequent changes in blood osmolarity is being discussed)	
Retinoids (tazarotene, vitamin A acid and tretinoin)	0,05–0,1 %; sometimes combined with urea	Promote cell differentiation	Localized hyperkeratosis on the hands, feet, lower legs or over the joints (Note: irritant potential)	Pregnancy; women of childbearing age without effective contraception (teratogenic potential) [3]	
Salicylic acid	5 % Please pay attention to contraindications!	Keratolytic and proteolytic effects	Localized topical use in adults	Warning: Whole-body treatment in ichthyosis patients is contraindicated (absorption and depot effects possible) [3]; Use in children is contraindicated (toxic effects and metabolic acidosis possible; risk of Reye syndrome)	

Abbr.: ARCI, autosomal recessive congenital ichthyosis; IV, ichthyosis vulgaris; LI, lamellar ichthyosis; XLI, X-linked ichthyosis.
Note: In case of very adherent keratoses (e.g., in XLI and some ARCI patients), occlusive dressings may be useful.
Alpha-hydroxycarboxylic acids: high irritant potential. Some case reports of patients with lamellar ichthyosis suggest good tolerability and efficacy in this form of ichthyosis, but further investigations are needed.
Topical corticosteroids: In case of inflammatory ichthyoses such as Netherton syndrome, very short-term topical corticosteroid (class 2–3) treatment may be indicated. However, topical corticosteroids are generally not recommended for treatment of ichthyoses [1, 3].
References: [4, 14, 15].

despite acitretin therapy and that routine laboratory monitoring is required (note: increase in blood lipids). Patients must be informed that effective contraception is essential, given the teratogenic effects associated with retinoic acid derivatives (up to three years after treatment discontinuation in women). Special caution is required in individuals with epidermolytic ichthyosis with *KRT1* mutation as well as NTS patients. In these cases, acitretin may result in increased blistering or exacerbation of dermatitis. In harlequin ichthyosis, on the other hand, acitretin treatment may be considered even for newborns, at a dose of 0.5 mg/kg (maximum: 1 mg/kg). Further information concerning dosages can be found in the guideline [3, 4].

Oral vitamin D substitution should also be considered, as ichthyosis patients tend to develop vitamin D deficiency due to the severe scaling and subsequently decreased exposure to sunlight. Regular monitoring of vitamin D levels and, if necessary, adequate replacement are therefore very important [1].

There is hope that, in the future, biologics may be added to the treatment options available for ichthyosis, especially for anti-inflammatory treatment. There are currently only a handful of case reports on the use of biologics in patients with ichthyosis; in one of them, omalizumab was given to a patient with NTS [10]. Other cases involved on-label dupilumab treatment in ichthyosis patients with co-existing atopic dermatitis, and the use of TNF-alpha blockers for the treatment of inflammatory ichthyoses with psoriasiform lesions. While some of these cases have not yet been published, it has been shown that patients with ichthyosis have an IL-17 dominant immune profile [11].

There have also been reports of enzyme replacement therapy. Although topical replacement of transglutaminase 1 using liposomes has as yet been reported only from animal models, this approach may become available in the future [5, 6].

Another emerging approach is gene therapy, which has as yet only been used in other genodermatoses such as epidermolysis bullosa. Recently, the gene *LAMB3*, which encodes laminin-332, was replaced in a 7-year-old boy with epidermolysis bullosa. For this purpose, an intact version of the gene was inserted into a retrovirus. The virus was subsequently used to infect the patient's keratinocytes where it reproduced. The proliferation of keratinocytes that contained the intact version of the gene occurred in cell culture in the laboratory. The cells thus harvested were used to grow sheets of epidermis that were subsequently transplanted onto the patient [12]. Other therapeutic approaches for epidermolysis bullosa include the CRISPR/CAS9 method, which can specifically eliminate mutated alleles [13].

At present, treatment for ichthyosis is primarily symptomatic and uses topical agents. In most cases, the disease can be rendered tolerable through a combination of intensive topical therapy, balneotherapy and physical therapy. However, treatment is frequently very time-consuming and expensive. In the future, gene therapy or targeted molecular therapies might improve the situation of patients with severe forms of ichthyosis and potentially life-threatening complications.

Some of the figures and legends were published in Oji et al. 2010 (JAAD).

Treatment for ichthyosis is primarily symptomatic and includes rigorous application of emollients and balneotherapy. Many patients thus treated experience significant symptom relief. Some patients benefit from systemic acitretin therapy. Novel treatment approaches include biologics, enzyme replacement and gene therapy.

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[CME-Questions/Lernerfolgskontrolle]

1. Welche Ichthyoseformen werden differenzialdiagnostisch klinisch leicht verwechselt?

a) Ichthyosis vulgaris und X-chromosomale Ichthyose
b) Ichthyosis vulgaris und lamelläre Ichthyose
c) Ichthyosis vulgaris, Harlekin-Ichthyose und Bathing-Suit-Ichthyose
d) X-chromosomale Ichthyose und keratinopathische Ichthyosen
e) Syndromale Form der X-chromosomalen Ichthyose und Netherton-Syndrom

2. Welche Substanzen eignen sich nicht als Zusatz in Externa für die tägliche Anwendung bei Ichthyosis vulgaris?

a) Urea pura
b) Glycerin
c) Dexpanthenol
d) Salicylsäure
e) Polidocanol

3. Für welche Form der Ichthyose ist eine Systemtherapie mit Acitretin nicht gut geeignet?

a) Lamelläre Ichthyose
b) X-chromosomale Ichthyose
c) Epidermolytische Ichthyose (KRT10-Mutation)
d) Bathing-Suit-Ichthyose
e) Netherton-Syndrom

4. Welche Ichthyoseform kann bei der Geburt nicht das Bild eines Kollodiumbabys zeigen?

a) Ichthyosis vulgaris
b) Conradi-Hünermann-Happle-Syndrom
c) Kongenitale ichthyosiforme Erythrodermie
d) Lamelläre Ichthyose
e) Bathing-Suit-Ichthyose

5. Welche Form der Ichthyose geht typischerweise mit einer Haarschaftanomalie einher?

a) Netherton-Syndrom
b) Ichthyosis vulgaris
c) X-chromosomale Ichthyose
d) Keratinopathische Ichthyose
e) Lamelläre Ichthyose

6. Welches Gen ist am ehesten betroffen, wenn eine epidermolytische Ichthyose und zusätzlich eine palmoplantare Hyperkeratose auftritt?

a) *FLG*
b) *STS*
c) *KRT1*
d) *KRT10*
e) *SPINK5*

7. Welche Frage ist der Anamnese von Patienten mit einer Ichthyose nicht sinnvoll?

a) Familienanamnese (Stammbaum)
b) Aussehen bei der Geburt
c) Frage nach Dysurie
d) Frage nach Schwitzfähigkeit
e) Frage nach Riechvermögen

8. Welches der folgenden Proteine kann bei lamellärer Ichthyose in seiner Aktivität gestört sein?

a) Filaggrin
b) Steroidsulfatase
c) Transglutaminase 1
d) LEKTI
e) Corneodesmosin

9. Welches diagnostische Verfahren ist bei der Diagnostik der Ichthyosen wenig hilfreich?

a) Filaggrinfärbungen bei Ichthyosis vulgaris
b) Histologie bei keratinopathischer Ichthyose
c) Steroidsulfatase-Messungen bei X-chromosomaler Ichthyose
d) Molekulargenetische Diagnostik bei autosomal-rezessiven kongenitalen Ichthyosen
e) Indirekte Immunfluoreszenz bei Trichothiodystrophie

10. Bei welcher Form der Ichthyosen wird von den Müttern öfters von Verzögerungen des Geburtsvorganges berichtet?

a) Netherton-Syndrom
b) Ichthyosis vulgaris
c) X-chromosomale Ichthyose
d) Keratinopathische Ichthyose
e) Lamelläre Ichthyose

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 11. Mai 2020.
Die richtige Lösung zum Thema „Neuartige Therapien auf der Grundlage der Pathophysiologie der atopischen Dermatitis“ in Heft 11 (November 2019) ist: (1c, 2d, 3c, 4e, 5e, 6c, 7a, 8e, 9a, 10b).

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