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Ichthyosis

Clinical Manifestations and Practical Treatment Options

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Contents

Abstract

Ichthyoses constitute a large group of cornification disorders that affect the entire integument. The skin is characterized by visible scaling and in many cases by inflammation, for example, in bullous/keratinopathic ichthyosis or Netherton syndrome. From the viewpoint of classification it is useful to distinguish non-syndromic from syndromic types of ichthyosis. Ichthyosis vulgaris and recessive X-linked ichthyosis are common disorders – often of delayed onset, in contrast to congenital ichthyoses, which belong to the group of rare diseases and present at birth with either the features of collodion membrane or congenital ichthyosiform erythroderma.

The diagnostic steps are based on clinical data, analyses such as the steroid sulfatase activity test, skin biopsies, and genetic results. However, the dramatic increase in knowledge about the pathophysiology of these conditions has not led to a curative therapy so far. The therapeutic management is multidisciplinary and involves ichthyosis patient organizations in many countries. The mainstay of treatment remains with moisturizing creams containing, for example, urea, lactic acid and other humectants and keratolytics, regular bathing, and mechanical scale removal. Patients with lamellar ichthyosis or ichthyosiform erythroderma in particular profit from oral therapy with retinoids or retinoic acid metabolism-blocking agents.

1. Clinical Definition and Classification

Ichthyoses form a clinically and etiologically heterogeneous group of cornification disorders. Clinical hallmarks of the diseases are visible scaling and a thickening of the cornified layer (hyperkeratosis) and very often an accompanying inflammation of the skin presenting as erythroderma.[1-3] The major criterion for classification is the question of possibly associated symptoms such as failure to thrive, severe atopy, neurologic abnormalities, hepatic or skeletal involvement, or hair abnormality. The initial presentation of the disease can be taken as an additional criterion for a diagnostic algorithm. A clinically meaningful view of the classification is given in table I, and distinguishes mainly between syndromic versus non-syndromic ichthyosis.

The First World Conference on Ichthyosis, which took place in Münster, Germany in September 2007, provided an opportunity for many experts to rethink the terminology and classification of these disorders.[5] One proposal concerned the idea that the term 'ARCI,' standing for autosomal recessive congenital ichthyosis, should cover all non-syndromic congenital ichthyoses including lamellar ichthyosis, congenital ichthyosiform erythroderma, and Harlequin ichthyosis. At the Ichthyosis Consensus Conference (ICC) held in Sorèze, France in January 2009, several controversial disease names were redefined and agreed to by an international group of 37 experts: for example, the term *keratinopathic ichthyosis* was proposed as a new umbrella term for all ichthyoses due to keratin mutations, which includes epidermolytic ichthyosis, superficial epidermolytic ichthyosis and ichthyosis Curth-Macklin (see table I).[3,4]

2. Current Knowledge of the Pathophysiology

A better understanding of the pathophysiology of the different ichthyosis types will hopefully have an important impact on the future development of new and specific therapeutic strategies.[6-8] However, ichthyoses belong to the group of rare diseases and share with other orphan diseases problems relating to drug development. Nevertheless, the current knowledge already helps a great deal in establishing an exact diagnosis, which allows adequate genetic counseling in many cases.

2.1 Ichthyosis Vulgaris and Recessive X-Linked Ichthyosis

Ichthyosis vulgaris (Online Mendelian Inheritance in Man [OMIM] number 146700) is characterized by a light gray scaling that often spares the antecubital and popliteal body folds and the face. It is characterized by accentuated creases, so called 'hyperlinear palms and soles' (figure 1). About 1 in 250–1000 children has ichthyosis vulgaris. It is frequently associated with concomitant atopic dermatitis (50–60%) and allergic rhinoconjunctivitis. Further symptoms often reported or seen are hypohidrosis, pruritus, and keratosis pilaris. From a histologic point of view, a diminished or absent granular layer is typical and reflects the defect of the keratohyalin granules.[1,9,10]

Table I. Clinical view of the classification of ichthyosis and examples of disorders

Non-syndromic ichthyosis	Syndromic ichthyosis
Delayed onset	
Ichthyosis vulgaris	Refsum syndrome
Recessive X-linked ichthyosis[a]	Recessive X-linked ichthyosis with contiguous gene syndrome
Congenital	
Autosomal recessive congenital ichthyosis	Netherton syndrome
Harlequin ichthyosis	Sjögren-Larsson syndrome
Lamellar ichthyosis	Neutral lipid storage disease with ichthyosis
Congenital ichthyosiform erythroderma	Trichothiodystrophy
Bathing suit ichthyosis	
Self-healing collodion baby	
Bullous ichthyosis (*Keratinopathic ichthyosis*[b])	
Bullous ichthyosiform erythroderma (Epidermolytic ichthyosis[b])	
Bullous ichthyosis of Siemens (Superficial epidermolytic ichthyosis[b])	
Ichthyosis Curth-Macklin	

a It is possible for neonates to show generalized scaling very shortly after birth, and there might be an increased risk for testicular maldescent/cryptorchidism.

b Novel terms that were endorsed at the Ichthyosis Consensus Conference in Sorèze, France in January 2009.[3,4]

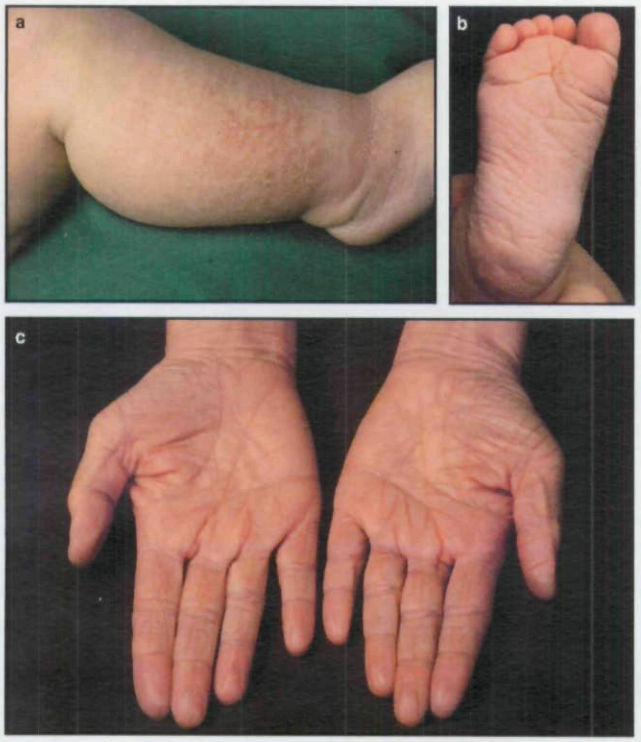

Fig. 1. Manifestations of ichthyosis vulgaris. (**a**) Infant with ichthyosis vulgaris and concomitant eczema. (**b**) In our experience, evidence of increased plantar markings has the same significance as 'palmar hyperlinearity' for the diagnosis of ichthyosis vulgaris, and can be well appreciated in infants. (**c**) 'Hyperlinear palms' in a 40-year-old woman with ichthyosis vulgaris due to compound heterozygous mutations in the filaggrin gene.

Recently, a Scottish group from Dundee demonstrated frequent nonsense mutations in the filaggrin gene (*FLG*), resulting in reduced filaggrin expression.[11] For many years it was commonly believed that ichthyosis vulgaris was inherited as an autosomal dominant trait, but today it is more correctly referred to as 'semi-dominant' inheritance. In simple terms, one *FLG* mutation may cause a mild phenotype, but two mutations may lead to a more pronounced expression of the disorder.

However, it can sometimes be difficult to make a clear distinction between ichthyosis vulgaris and recessive X-linked ichthyosis (OMIM_308100) [figure 2c, d]. Indeed, some patients have been found to have both disorders.[12] Generally, about two-thirds of patients with recessive X-linked ichthyosis present with dark brown rhombic scales presenting as 'ichthyoses noire,' while one-third show light gray and, in part, fine scaling reminiscent of ichthyosis vulgaris.[10] It is important to take a good family history (figure 3). The disease manifests exclusively in boys. An affected grandfather on the side of the mother can often be identified, which is typical of X-linked recessive inheritance. The incidence of cryptorchidism may be increased in affected patients (estimated at 5–20%). Birth complications such as delayed cervical dilatation occur in about one-third of the affected boys. Ichthyosis is due to mutations in the steroid sulfatase gene (*STS*), which is frequently deleted, and the condition can be unequivocally diagnosed by steroid sulfatase (arylsulfatase C) testing from edetic acid (EDTA) blood.[13,14]

Less frequently, the *STS* gene deletions can be rather large, as part of a 'contiguous gene syndrome,' which means that neighboring genes are also involved. Hence, these patients with recessive X-linked ichthyosis may have a syndromic type of ichthyosis. A number of patients exhibit both steroid sulfatase deficiency and Kallman syndrome (OMIM_308700) and therefore all patients should be asked whether they have a normal sense of smell.[15]

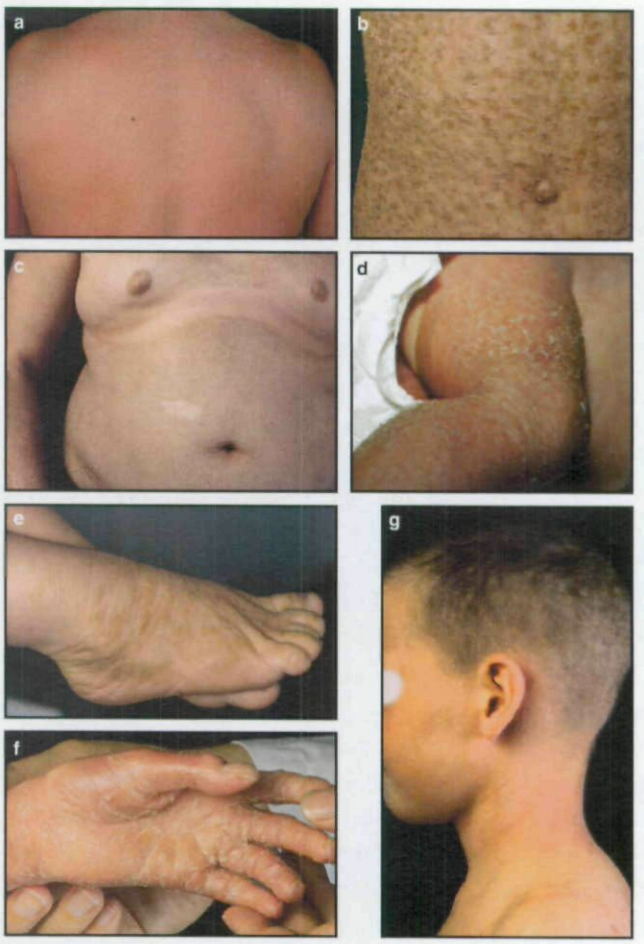

Fig. 2. Different types of ichthyosis. (**a**) Erythematous fine scaling in ichthyosiform erythroderma in a middle-aged man. (**b**) Classical lamellar ichthyosis in a boy. (**c**) Recessive X-linked ichthyosis, with areas of healthy skin. (**d**) Neonate with recessive X-linked ichthyosis showing a transient erythematous scaling after 4 weeks. (**e**) Typical lichenification and spasticity in Sjögren-Larsson syndrome. (**f**) Erythematous lamellar ichthyosis in Harlequin ichthyosis. (**g**) Hypotrichosis and ichthyosis linearis circumflexa in a girl with Netherton syndrome.

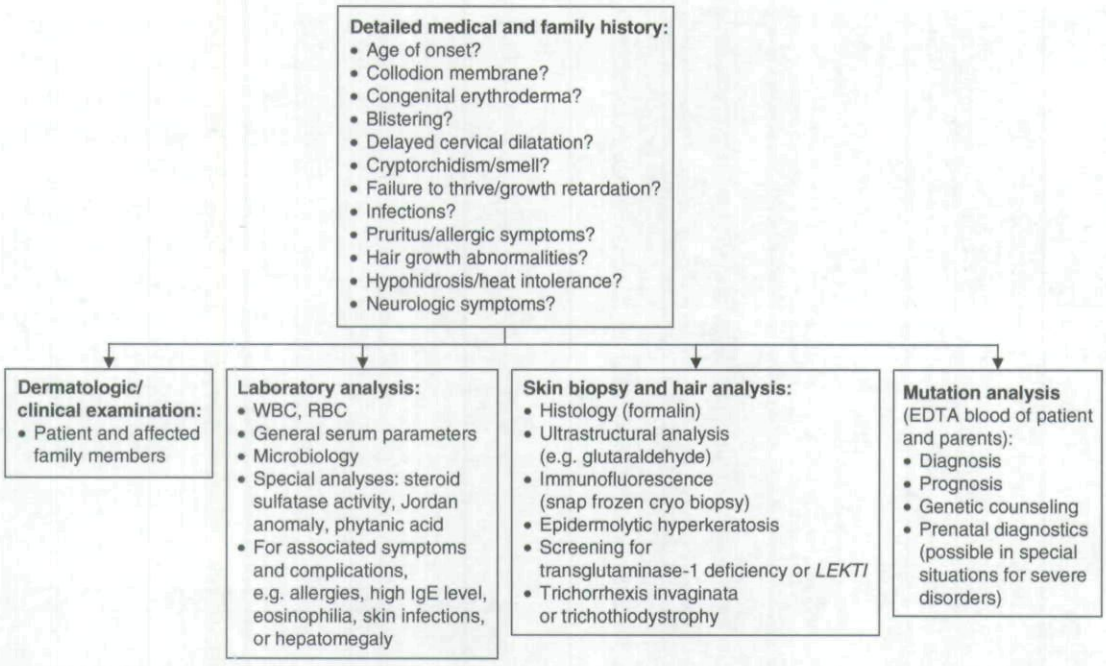

Fig. 3. An overview of the diagnostic procedures for patients with suspected ichthyosis. **EDTA** = edetic acid; **RBC** = red blood cell count; **WBC** = white blood cell count.

2.2 Autosomal Recessive Congenital Ichthyosis

As mentioned in section 1, the term ARCI can be employed as a synonym for different terms used in the wide spectrum of lamellar ichthyosis, congenital ichthyosiform erythroderma, or Harlequin ichthyosis. A clear genotype-phenotype correlation remains to be established. Associated clinical symptoms of ARCI types are neonatal dehydration, ectropion, eclabium, skin infections, and often hypohidrosis with severe heat intolerance.

Harlequin ichthyosis (OMIM_242500) is the most severe type of ARCI and has a frequency of probably 1 : 1 000 000. It is due to severe nonsense mutations in the ATP-binding cassette A12 (*ABCA12*) gene.[16,17] The gene encodes a lipid transporter that has important functions in the building up and extrusion of the lamellar bodies (keratinosomes). Today many children with Harlequin ichthyosis survive and later develop a severe type of lamellar ichthyosis characterized by large scales and severe erythroderma (figure 2f). It is of note that special missense mutations in *ABCA12*, most probably allowing a residual function of the protein, can be present in lamellar ichthyosis or congenital ichthyosiform erythroderma (OMIM_601277).[18]

Children with defects of transglutaminase-1 (*TGM1*) [OMIM_242300], which is an important enzyme for the assembly of the cornified envelope, are normally born as collodion babies.[1] The spectrum of transglutaminase-1 deficiency ranges from congenital ichthyosiform erythroderma to severe lamellar ichthyosis,[19] depending on the type of mutations within the gene. Most children later develop generalized, dark brown, lamellar keratosis (figure 2b), while involvement of palms and soles is rather mild. It is of note that *TGM1* mutations are associated with two further clinical variants called self-healing collodion baby and bathing suit ichthyosis.[20,21] In self-healing collodion baby, which may also be associated with *ALOX12B* mutations,[22] a few weeks after birth a dramatic or complete healing occurs. In bathing suit ichthyosis, the healing of the skin is restricted to the face, arms, and legs, while the trunk remains involved.

On chromosome 19, a cytochrome P450 oxidase gene called *CYP4F22* (OMIM_604777) has been identified;[23] on chromosome 17, two lipoxygenase genes lying in very close proximity, *ALOXE3* and *ALOX12B*, have been found to carry mutations (OMIM_242100);[24] and another ARCI gene is *NIPAL4*, also known as *ichthyin*, on chromosome 5 (OMIM_609383).[25] Patients carrying two mutations in these genes are often born with congenital ichthyosiform erythroderma (figure 2a) and develop a rather mild ichthyosis often presenting with pronounced palmar hyperlinearity. It is believed that *CYP4F22*, the lipoxygenase genes, and *NIPAL4* may all play a physiologic role within the so-called hepoxilin pathway, which processes metabolic derivatives (hepoxilins) of arachidonic acid.[23]

2.3 Bullous Ichthyosis (Keratinopathic Ichthyosis)

The prototype of bullous ichthyosis (keratinopathic ichthyosis) is bullous ichthyosiform erythroderma (of Brocq) (OMIM_113800). These forms of ichthyosis are normally inherited as an autosomal dominant trait and often show so-called 'epidermolytic hyperkeratosis,' meaning cytoplasmatic clumping of tonofilaments and small intra-epidermal blistering. The truth is that there are exceptions: first, occasionally keratin 10 (*KRT10*) mutations can also be inherited in an autosomal recessive way; second, not all of the 'bullous' ichthyoses show blistering and epidermolytic hyperkeratosis, for example, ichthyosis Curth-Macklin (OMIM_146590), which is due to special keratin 1 (*KRT1*) mutations and characterized by extensive keratoderma and verrucous hyperkeratosis over joints and flexures.

In bullous ichthyosiform erythroderma (renamed as *epidermolytic ichthyosis* at the ICC in Sorèze),[3,4] neonates show generalized erythroderma with widespread blistering or erosions, but later individuals develop a hyperkeratosis, which persists for the rest of their lives (figure 4a). The disorder is caused by heterozygous mutations of *KRT1* or *KRT10*. More than half of all cases are due to a *de novo* mutation and occur sporadically.[26,27] Patients with *KRT1* mutations, who normally develop palmoplantar keratoderma, can be clinically distinguished from those with *KRT10* mutations, whose palms and soles are normally not affected.

Ichthyosis bullosa of Siemens (superficial epidermolytic ichthyosis)[3,4] (OMIM_146800), which is caused by heterozygous keratin 2 mutations,[28] has a less severe phenotype than bullous ichthyosiform erythroderma and can be distinguished by the lack of erythroderma and by a characteristic 'moulting' phenomenon of the upper epidermal layers. Lichenified hyperkeratosis develops with predilection to flexures, over joints and on dorsa of hands and feet (figure 4b).

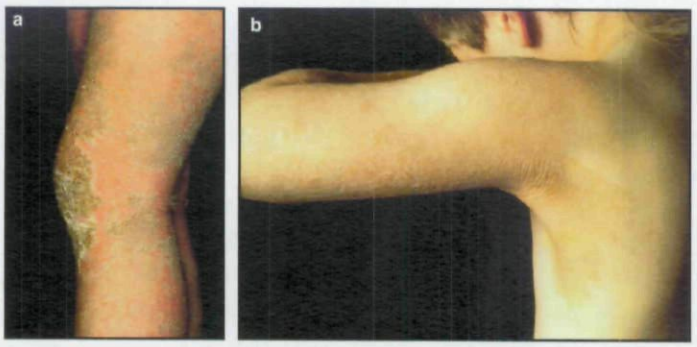

Fig. 4. Manifestations of bullous (keratinopathic) ichthyosis. (**a**) Bullous ichthyosiform erythroderma (epidermolytic ichthyosis) due to a keratin 10 mutation. (**b**) Bullous ichthyosis of Siemens (superficial epidermolytic ichthyosis), with ichthyosis mainly confined to flexural areas.

Generally, it is important to note that patients with epidermolytic epidermal nevi, for example, located along the lines of Blaschko, reflecting a genetic mosaicism, may be carriers of a gonadal keratin mutation, which can result in a generalized full-blown bullous (epidermolytic) ichthyosis in the offspring generation.

2.4 Examples of Ichthyosis Syndromes

There are several rare, mostly metabolic or neurologic disorders that can manifest at birth showing a collodion membrane (e.g. Gaucher disease type II, OMIM_230900) or develop an ichthyosis of delayed onset (e.g. prototype Refsum syndrome, OMIM_266500).

Clinical symptoms of Refsum disease, also referred to as hereditary motor and sensory neuropathy type 4 (HMSN4), include night blindness, anosmia, progressive deafness, peripheral neuropathy, and cerebellar ataxia. The age of onset varies from early childhood to the age of ~50 years. The ichthyotic skin is reminiscent of ichthyosis vulgaris. The disease is caused by mutations in the phytanoyl-CoA hydroxylase gene (*PHYH*)[29] or, less frequently, in the *PEX7* gene.[30] The impaired function of *PHYH* results in a pathologic plasma and tissue accumulation of phytanic acid. Early diagnosis and treatment with a diet low in phytanic acid can prevent the fatal course of the disease.[31] Another example of non-congenital syndromic ichthyosis is recessive X-linked ichthyosis as part of a contiguous gene syndrome and multiple sulfatase deficiency (OMIM_272200), which is a very rare and severe disorder with a fatal prognosis.

Netherton syndrome (OMIM_256500) features two different phenotypes. On the one hand, it may present as ichthyosis linearis circumflexa, with typical annular and polycyclic lesions, often having double-edged scaling (figure 2g). On the other hand, many patients manifest at birth with a severe congenital ichthyosiform erythroderma, which persists throughout life. In addition, the disease involves the hair, which shows a typical anomaly called trichorrhexis invaginata or bamboo hair.[1] Failure to thrive can be severe and is associated with growth retardation. Moreover, patients are prone to bacterial skin infections, especially by *Staphylococcus aureus*, and some of them show a strong disposition to human papillomavirus-induced skin diseases. Almost all of them have a marked eosinophilia and multiple type I allergies with high total IgE levels (>5000 kU/L).[32] The autosomal recessive disorder is due to mutations in the *SPINK5* gene encoding the serine proteinase inhibitor *LEKTI*, which inhibits trypsin- and chymotrypsin-like enzymes of the epidermis.[33,34]

Sjögren-Larsson syndrome (OMIM_270200) is a recessive neurocutaneous disorder caused by a deficiency of the fatty aldehyde dehydrogenase (FALDH) enzyme.[35] Neonates are often born with ichthyosiform erythroderma and later develop an ichthyosis characterized by a remarkable, cobblestone-like lichenification.[1] During infancy and childhood, patients develop severe body spasticity, leading to contractures and often wheelchair dependency (figure 2e). Non-progressive, mild, or moderate mental retardation is another neurologic feature. Almost all patients have extremely severe pruritus.[36]

Neutral lipid storage disease with ichthyosis (OMIM_275630) is a multisystem triglyceride storage disease with impaired long-chain fatty acid oxidation caused by recessive mutations in the *CGI58* gene.[37] At birth, individuals present with generalized white scaling and a variable degree of erythema. The widespread non-lysosomal tissue deposition of neutral lipids results in a variable expression of associated symptoms. Many children develop a mild to moderate hepatosplenomegaly. Other associated symptoms are cataract, neurosensorial deafness, myopathy, and developmental delay. Numerous lipid-containing vacuoles in circulating leukocytes are diagnostic for the disorder (Jordan anomaly).[38] Prognosis depends on the course of the liver disease.

Patients with trichothiodystrophy syndromes (OMIM_601675) may manifest with collodion membrane or with an ichthyosis-like dry skin.[39]

3. Diagnostic Procedures

The precise diagnosis of ichthyosis is based on the clinical presentation (skin and associated symptoms), detailed medical and family history, skin biopsies, and laboratory findings. The diagnosis should be confirmed by mutation analysis to allow for genetic counseling, which should be offered to the family or affected individual (figure 3). The age of onset and initial presentation distinguish congenital ichthyosis from, for example, frequently occurring types such as ichthyosis vulgaris and recessive X-linked ichthyosis. These can be diagnosed by skin biopsy and steroid sulfatase testing, respectively. Moreover, if available, the screening for frequently occurring filaggrin mutations provides a new diagnostic tool for ichthyosis vulgaris. The general differential diagnoses of ichthyosis of delayed onset include all kinds of acquired ichthyosis-like conditions, which may appear in the context of malignancy, HIV infection, autoimmune, nutritional, or metabolic diseases.[40]

For clinicians in charge of a patient with congenital ichthyosis it is useful to address the following questions:

(i) Is there a history of blistering? Blistering is particularly frequent in ichthyoses that are due to keratin mutations, for example, prototype bullous congenital ichthyosiform erythroderma (epidermolytic ichthyosis).

(ii) Were there clinical manifestations of erythroderma or collodion membrane at birth? In children presenting with marked erythroderma, differential diagnoses are, among others, Netherton syndrome or congenital ichthyosiform erythroderma. In neonates featuring very severe eclabium, extreme ectropion, and contractures, one should consider Harlequin ichthyosis, which can be almost unequivocally diagnosed by electron microscopy.[41]

(iii) Are there associated symptoms? As mentioned in section 2, non-syndromic ichthyoses can be differentiated from ichthyosis syndromes such as Refsum or Sjögren-Larsson syndrome.

General diagnostic guidelines are yet to be established. We recommend a general check-up including laboratory analyses (red blood cell count, white blood cell count, IgE, hepatic enzymes, etc.) and abdominal ultrasound (to exclude hepatomegaly). Electron microscopy provides the clinician with useful and significant criteria to differentiate between ichthyosis vulgaris, ichthyosis due to keratin mutations, Harlequin ichthyosis, and many other entities. For example, in neutral lipid storage disease with ichthyosis, the skin ultrastructure as well as the white blood cell count (Jordan anomaly) reveal important diagnostic findings.[42] In other ARCI types, the ultrastructure analysis may give important clues pointing, for example, to a defect in the hepoxilin pathway,[43] while admittedly in some cases the ultrastructural investigation provides no 'added value.' For bullous (keratinopathic) ichthyoses, ultrastructural as well as histologic examinations of the skin reveal an epidermolytic hyperkeratosis; and there are special variants of keratinopathic ichthyoses that can be diagnosed by an ultrastructural analysis but do not show blistering or epidermolytic hyperkeratosis.[44] The antigen mapping of *LEKTI*, which shows a marked reduction of the protease inhibitor in the epidermis of patients with Netherton syndrome, provides a useful diagnostic tool prior to *SPINK5* mutation analysis.[45,46] The biochemical transglutaminase activity test performed on cryosections represents a useful screening test prior to *TGM1* mutation analysis.[20,47]

Generally, it is strongly recommended to consult a dermatologist, pediatrician, or geneticist who is familiar with congenital ichthyosis (and to take pictures). This contact also helps to plan further diagnostic steps, for example, skin biopsy. Many procedures and the DNA analysis for ichthyosis are normally only performed in specialized centers, sometimes within the context of research projects, which are still necessary for a better understanding of the diagnosis and future therapy of

Table II. Contact details of helpful institutions and patient organizations

Institution	Country	Internet link
Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T.)	USA	www.scalyskin.org
Network for Ichthyoses and Related Keratinization disorders (NIRK)	Germany and others	www.netzwerk-ichthyose.de/
Patient organizations	European network for ichthyosis (common platform of the different European patient organizations)	www.ichthyose.eu/
	Belgium	www.devidts.com/ichthyosis
	Denmark	www.iktyosis.dk
	Finland	www.iholiitto.fi/
	Germany	www.ichthyose.De
	Italy	www.ittiosi.it/
	Spain	www.ictiosis.org
	Sweden	www.iktyos.nu/
	Switzerland	www.ichthyose.ch
	UK	www.ichthyosis.org.uk/
	USA	www.ichthyosis.com

these disorders. Helpful contact details can be downloaded from the Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T.), the Network for Ichthyoses and Related Keratinization disorders (NIRK), or from different ichthyosis patient organizations (table II).

4. Therapeutic Approaches

Therapy of mild common ichthyoses (ichthyosis vulgaris and recessive X-linked ichthyosis) and severe congenital ichthyoses is, of course, different. As congenital ichthyoses are rare and heterogenous, only a few centers are experienced in their therapeutic management. One problem is that many approaches have not been evaluated by randomized, controlled, clinical trials. From the current literature, reports of eight controlled studies can be found, mostly focusing on retinoids.[48-55] Fortunately, there is one clinical trial of topical urea therapy for ichthyosis, which proves the efficacy and good tolerability of this important method.[52] However, there are some review articles proposing useful guidelines, which are recommended.[56-60] The 'evidence level' of these guidelines is supported by the considerable experience that has accumulated in the expert centers, which are closely linked to patient organizations. These centers have followed up patients for years, and provide insight into the effectiveness and safety of ichthyosis therapy. Our special outpatient clinic for ichthyosis at the Department of Dermatology in Münster, Germany, is part of the NIRK and works in close contact with the German patient organization 'Selbsthilfe Ichthyose e.V.' (table II). As such our therapeutic approach, for example, concerning the new therapy with sodium bicarbonate, has been very much influenced by Wolfgang Küster, who ran an outpatient clinic and inpatient rehabilitation center for ichthyosis patients for many years and unfortunately died in 2006 before clinical trials on his ideas were carried out. His optimistic view on ichthyosis therapy "There is always something you can do!" has been reviewed recently.[57,59]

4.1 Therapy of Ichthyosis Vulgaris and Recessive X-Linked Ichthyosis

Compared with congenital ichthyoses, therapy of ichthyosis vulgaris and recessive X-linked ichthyosis usually presents no major problems, and moisturizing creams containing lactic acid, urea, or glycerol can be used. An overview of useful keratolytic substances and humectants is given in table III. As in infants with congenital ichthyoses, it has to be considered that there is an epidermal barrier defect in ichthyosis vulgaris as well as in hyperkeratotic recessive X-linked ichthyosis,[61] which bears the risk of systemic absorption and toxicity, especially in infants. Some ichthyosis vulgaris patients also experience hypohidrosis and heat intolerance similar to patients with lamellar ichthyosis; they should be advised in a similar way (see section 4.2.2).

It is tempting to speculate that an early, regular, and effective topical therapy will improve the epidermal barrier and prevent the future development of atopic diseases in ichthyosis vulgaris. Clinical data concerning this hypothesis are not yet available.

A non-randomized, half-side, pilot study,[62] an open-label study,[63] and a further case report[64] suggest that, in recessive X-linked ichthyosis, short-term treatment with topical tazarotene 0.05% or 0.1% gel may have good efficacy and a longer

Table III. Overview of important topical agents for ichthyosis[57,59]

Agent	Maximum concentration (%)	Comments
Sodium chloride	10	Frequent adverse effect: irritation/burning
Urea	10	Classical humectant and keratolytic Should be avoided during the first year of life due to possible systemic absorption
Lactic acid	5	Mild alternative to urea Commercial preparations up to 12–14%, if it is optimized by buffering
Salicylic acid	10	Only for stubborn areas (maximum 3 days) Danger of life-threatening poisoning in neonates and small children; in adults, avoid regular use
Topical retinoids		Avoid whole body use
tretinoin	0.025–0.05	Frequent adverse effect: irritation/burning
tazarotene	0.1	Risk of absorption and teratogenicity in women of child-bearing age
Dexpanthenol	5	Additional support of normal epidermal differentiation Good alternative to urea during the first years of life in congenital ichthyosis (including collodion babies and inflammatory types such as Netherton syndrome)
Propylene glycol	15	Moisturizer and keratolytic
Vitamin E acetate	5	Moisturizer
Glycerol	10	Moisturizer

duration of effect compared with normal keratolytics. Elevated systemic tazarotene concentrations have been observed in teenagers using the topical therapy over a period of several months on a body surface area of ~40%.[63] Also, liarozole 5.0% cream (see retinoic acid metabolism-blocking agents in section 4.5.1) has been proven to be very effective in recessive X-linked ichthyosis.[51] In our center, low-dose systemic retinoids are sometimes given for a certain period of time in recessive X-linked ichthyosis patients who are weary of the topical treatment. This is usually possible since men do not have the risk of teratogenicity.

4.2 Therapy of Autosomal Recessive Congenital Ichthyosis

The therapeutic management of congenital ichthyosis is based on a multidisciplinary approach including psychological support and involvement of patient organizations (figure 5 and table II). One of the first challenges for the clinician in charge of a patient/neonate with congenital ichthyosis is to clarify the diagnosis and to honestly explain its meaning to the affected patient or the family. So far, there is no curative therapy available and as such the ichthyoses, except for the self-healing collodion baby, represent life-long conditions, which greatly influence the appearance and physical state of the affected individuals. However, just to explain that the ichthyosis is 'a rare genetic disease for which there is no cure' would be completely inadequate. First, there is a large spectrum of disease expression ranging from very mild to very severe. Second, in many patients the disease improves considerably in the first years of life. Finally, especially in non-syndromic ichthyoses, there are quite a few different therapeutic options that can be initiated to enable an almost 'normal life' for the affected individual. However, it has to be stressed that severely affected patients often need 1–2 hours or more for their daily skin treatment, which shows the extent of burden of the disease.

4.2.1 Neonates

Disorders such as Harlequin ichthyosis, Netherton syndrome, lamellar ichthyosis, and bullous (keratinopathic) ichthyoses, which manifest with severe collodion membrane or ichthyosiform erythroderma, have to be regarded as life-threatening disorders as far as the first weeks or months of life are concerned. The collodion membrane normally cracks within the first days of life and will then be replaced within 4 weeks by a slowly developing scaling, depending on the ichthyosis entity. (Sometimes, e.g. in bathing suit ichthyosis, the collodion membrane vanishes and the skin clears completely at the age of 4–6 weeks, but then scaling returns on the trunk a few weeks or months later.) An important issue for the collodion baby is skin inflammation, which can be marked even in otherwise mild variants of non-syndromic ARCI. The consequences for the epidermal barrier function are considerable: high transepidermal water loss and temperature imbalance. Therefore, collodion babies are usually cared for in intensive care units of neonatal departments to avoid temperature instability, hypernatremic dehydration, cutaneous infections, and septicemia.

Hence, neonates should be regularly examined for fluid balance, electrolytes, and signs of development of skin infections.

Bearing in mind that many individuals with ichthyosis cannot sweat, regular monitoring of the neonate's temperature is important. An incubator with high humidity may be regulated at a lower temperature than normal (e.g. 90–93°F or 32–34°C). A non-medicated cream should be applied thinly 6–8 times a day. In our center, we avoid urea cream in neonates. The use of salicylic acid in neonates or infants is contraindicated.[65] Bathing is useful to remove scaling and residual medication, but should always be followed by relubrication.

Severe ectropion should be managed by an ophthalmologist (avoid desiccation, e.g. through regular application of dexpanthenol eye cream). Ectropion and eclabium often rapidly improve with topical therapy and the humidity of the incubator. Harlequin ichthyosis often shows flexural contractures or armor-like keratoses, which constrict the thorax and impair adequate breathing. In these cases, treatment with oral retinoids may have an additional benefit.[1,66,67] Oral acitretin can be given at a dosage of ~0.5–1.0 mg/kg once per day. When preparing the small amount of the drug, which is unstable in normal daylight, we advise the use of red light, like in a photographic darkroom. The retinoid therapy can usually be withdrawn after a few months. During the neurologic evaluation it is important to check the hearing, which can be impaired by occlusion of the external ear duct. Some babies with congenital ichthyosis, especially in Netherton syndrome or Harlequin ichthyosis, tend to develop a severe failure to thrive, which may necessitate the insertion of a nasogastric tube to facilitate administration of high-caloric nutrition.

Hence, the prognosis during the first year of life depends very much on pediatric intensive care. The overall mortality rate of collodion babies has been estimated at 10–20%.[65,68]

4.2.2 Infants, Children, and Adults

Bathing and Mechanical Scale Removal

In Germany, many clinicians wrongly advise ichthyosis patients to avoid bathing. The basis for this wrong advice is their

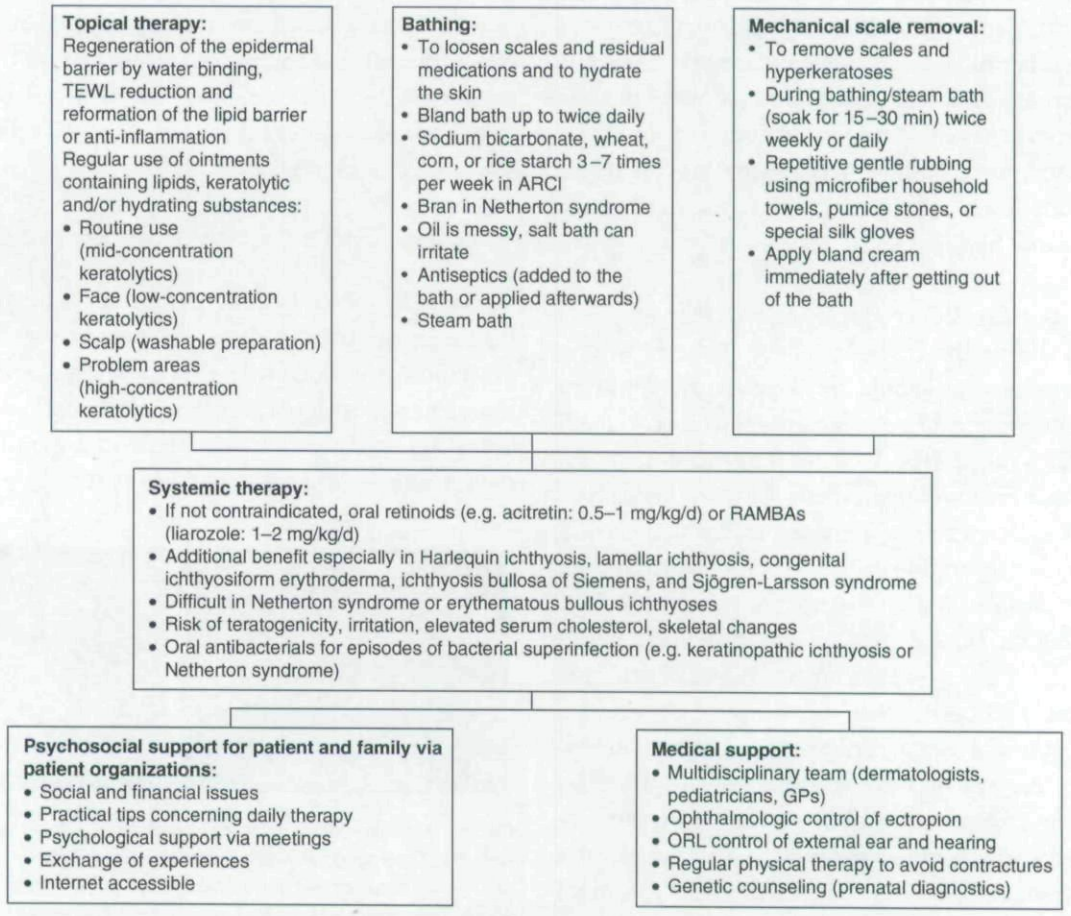

Fig. 5. An overview of the therapeutic management of ichthyosis. The approach is different for commonly occurring ichthyosis types, congenital ichthyosis, and ichthyosis syndromes. Bathing and mechanical scale removal especially refers to lamellar ichthyosis. **ARCI** = autosomal recessive congenital ichthyosis; **GPs** = general practitioners; **ORL** = otorhinolaryngologic; **RAMBAs** = retinoic acid metabolism-blocking agents; **TEWL** = transepidermal water loss.

belief that bathing results in a dehydrating effect on the skin as it is believed to compromise the acid mantle of the stratum corneum. However, patients, at least those with severe congenital ichthyoses, require a cleansing bath each day and should use sponges or microfiber cloths to rub the skin to remove scaling and remnants of creams. The procedure of repetitive gentle rubbing of the skin is relatively painless once the patient has soaked for 15–30 minutes, but the process can be physically exhausting. After mechanical scale removal, additives, for example, bath oil, can be added to the water. A recent development is the use of sodium bicarbonate (pure) as a bath additive.[57,59] Approximately one to two handfuls of sodium bicarbonate in the bath tub is helpful for many patients, especially for mechanical scale removal. Older patients report that sodium bicarbonate as a bath additive sometimes stings or stresses their skin, and most of them use it only two or three times a week. The mechanism probably relates to an increased water influx into the corneocytes of the skin and to a pH change of the skin, which becomes more 'basic.' It is tempting to speculate that the positive effect is also due to the influence on the protease network involved in the desquamation process and trafficking of lamellar bodies.[69] It should be noted that patients with other inflammatory hyperkeratotic disorders, for example, erythrokeratodermia, can experience exacerbations with sodium bicarbonate treatment (personal observation).

An alternative to normal bathing in the bath tub is the steam bath. Some patients have bought and installed a steam bath facility in their private homes.

Use of Keratolytic Creams Determined by Age and Skin Area

We avoid urea during the first year of life. Salicylic acid is contraindicated in infants and should only be used on small areas in children or adults, who may use urea and/or lactic acid cream regularly twice daily (table III). It is recommended to use a washable preparation for the scalp, a cream with low keratolytic strength for the face, a cream for routine use on the body, and a special high-strength preparation for problem areas (figure 5). One example of a formula for a urea scalp cream is: urea 7–10 g, lactic acid 1 g, sodium lactate (50%) 4 mL, propylene glycol 10 mL, water 40 mL, cream base (amphiphilic) DAC (Deutscher Arzneimittel-Codex, Eschborn, Germany) to 100 g. Cream base DAC (100 g) has the following composition: glycerol monostearate (60%) 4 g, cetyl alcohol 6 g, middle-chain triglycerides 7.5 g, white vaseline 25.5 g, macrogol-20-glycerol monostearate 7 g, propylene glycol 10 g, purified water 40 g. An example of a urea body cream (water in oil) is: urea 5 g, lactic acid 1 g, sodium lactate (50%) 4 mL, water 35 mL, glycerol (glycerin) 5 mL, Aquaphor® Original Ointment (Beiersdorf, Norwalk, CT, USA) to 100 g.[59]

Severe hypohidrosis is an important problem for many patients with lamellar ichthyosis or ichthyosiform erythroderma. There is a risk of developing heat stroke and convulsions. Therefore, patients should be advised to avoid strenuous activity when the outside temperature is high. Moreover, it may be useful to always have a water spray bottle available in the car, especially in summer. Haenssle et al.[70] recently reported that oral treatment with retinoids not only markedly improved the skin but also normalized the sweat-gland function and thermoregulation by perspiration.

Physical therapy to avoid flexural contractures is important for Harlequin ichthyosis. Many infants with transglutaminase deficiency experience recurrent or persistent occlusion of the external ear duct, which may necessitate regular cleaning by an otorhinolaryngologist in order to ensure sound recognition and vocalisation. We have encountered this problem several times in bathing suit ichthyosis, a condition that illustrates the temperature effect of the disorder (figure 6).

Patients with ectropion have to pay careful attention to eye care, using liquid tears and eye lubricants. Moreover, consequent lubrication of the face, especially the cheeks, has a good effect against ectropion. Skin transplantation from the neck performed by an experienced surgeon can be tried in severe cases, but the operation may have to be repeated after some years (see also Vahlquist et al.[60]).

4.3 Therapy of Bullous Ichthyosis (Keratinopathic Ichthyosis)

Neonates with bullous congenital ichthyosiform erythroderma (epidermolytic ichthyosis) may present as 'enfants brûlé,' exhibiting erythroderma and blistering, and are sometimes misdiagnosed as having epidermolysis bullosa. These neonates are also placed in an incubator (refer to section 4.2.1.). The topical treatment is in principle similar to that of a collodion baby, but

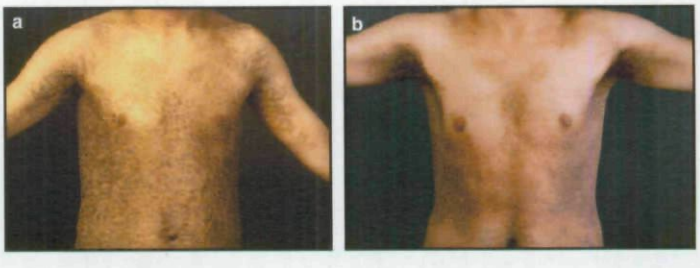

Fig. 6. Illustration of the temperature effect in bathing suit ichthyosis in a boy with the homozygous transglutaminase-1 (*TGM1*) mutation Tyr276Asn. (**a**) The lamellar scaling is confined to the trunk, especially to the warm skin areas. This picture was taken during summer (June) before topical therapy with urea ointments was started. (**b**) The same boy 2 years later, after having used urea ointments regularly. Moreover, he had been advised to wear breathable clothes as far as possible. The picture was taken at the end of winter (March).

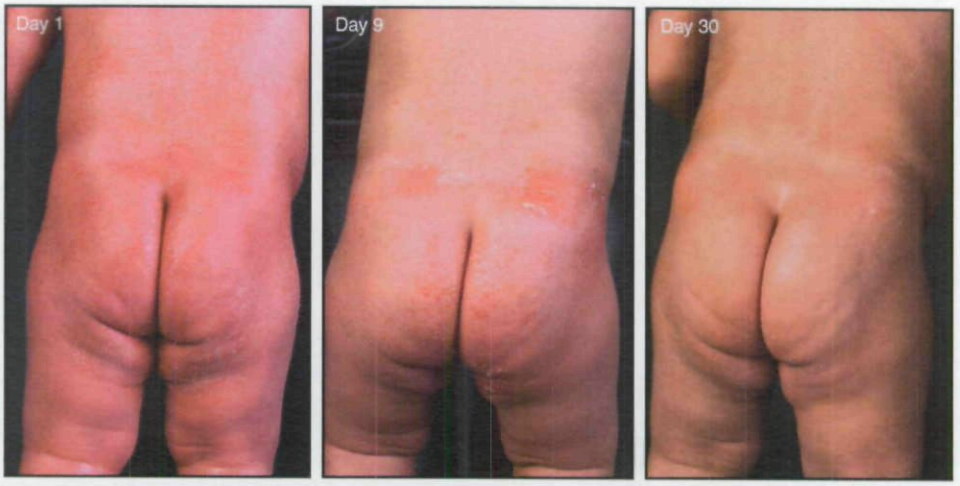

Fig. 7. Treatment of a 2-year-old boy with Netherton syndrome with pimecrolimus cream 1%. There was a good effect and tolerability. The cream was only used for 2 months, because it was difficult to take blood samples regularly to exclude systemic absorption.

regular antibacterial wound management should be initiated in these neonates. Local skin friction has to be avoided. The erythema and blistering normally subsides during the first months or the first year of life, and more or less massive, cobblestone-like or spiky keratoses develop instead (figure 4). Special attention has to be given to the risk of bacterial superinfections, which can cause relapses with erythema and blistering. Early intervention with antiseptics or topical antibacterials may avoid complete inflammation of the integument. Such episodes often require oral therapy with antibacterials. A major social problem for patients with bullous congenital ichthyosiform erythroderma (epidermolytic ichthyosis) is that they tend to have foul-smelling areas of maceration. Therefore, antiseptics such as octenidine 0.1% or polihexanide 0.1% can be added to the bath water or applied directly to the skin after the bath (for use of retinoids in bullous ichthyoses see section 4.5.1).

4.4 Therapy of Netherton Syndrome

Many children with Netherton syndrome need intensive medical care immediately after birth due to a severe failure to thrive and significant transepidermal water loss (refer to section 4.2.1). Because of the marked development of atopies it is necessary to avoid type I allergies, in particular, food allergies against fish and nuts. Improvement of the skin barrier by the frequent application of creams containing antibacterials, for example, triclosan 2%, can help protect against frequent superinfections, which themselves may aggravate the disease. Many patients with Netherton syndrome experience hypotrichosis (figure 2g), which often tends to improve after puberty. Girls may especially profit from wearing a wig. One aspect is that many patients need anti-inflammatory treatment. If topical corticosteroids are required for a short time, we only recommend those with a high therapeutic index. In our experience (with three patients), it was not possible to completely avoid relapses of skin inflammation/scaling erythema by the use of long-term treatment with calcineurin inhibitors, but topical pimecrolimus 1% or tacrolimus 0.1% were useful alternatives to help avoid the use of corticosteroids and their associated adverse effects (figure 7).[71] However, there should be regular blood monitoring to check for the possibility of systemic absorption when these drugs are used for a longer period of time.[72]

Bran as a bath additive may have a good effect on pruritus, which frequently represents a major clinical problem in Netherton syndrome. Older patients with Netherton syndrome should be checked for human papillomavirus-induced skin cancers.

4.5 Special Aspects of Clinical Management

There are some aspects that especially apply for severe types of ichthyoses.

4.5.1 Retinoids and Retinoic Acid Metabolism-Blocking Agents

Like other cornification disorders, the ichthyoses can be treated systemically with derivatives of vitamin A (figure 5). Retinoids such as etretinate or acitretin have been found to be efficacious, especially in lamellar ichthyosis and congenital ichthyosiform erythroderma.[73] Isotretinoin may be preferred in female patients considering the shorter duration of the teratogenic risk after discontinuation of the drug.[60] Systemic retinoids induce a decrease in hyperkeratosis (which of course recurs after discontinuation of the drug), but one adverse effect is skin fragility. Therefore, retinoids should be carefully used in bullous (keratinopathic) ichthyoses and started at low doses.

There is a risk of exacerbation, especially in bullous (epidermolytic) ichthyosis due to keratin 1 mutations. Bullous ichthyosis of Siemens (superficial epidermolytic ichthyosis) responds well to low retinoid doses.[74] The same applies to Sjögren-Larsson syndrome. In contrast, retinoids are relatively contraindicated in Netherton syndrome.[60]

The pharmacologic activity of external retinoids is limited by the rapid rate of metabolism via cytochrome P450 enzymes and the direct retinoic adverse effects, especially teratogenicity. An alternative is the new class of retinoic acid metabolism-blocking agents. One of them, namely liarozole, has been granted orphan drug status for the treatment of congenital ichthyosis by the European Medicines Agency (EMEA) and the US FDA. Liarozole inhibits the function of several mammalian cytochrome P450 isoenzymes, including one involved in the catabolism of endogenous all-trans-retinoic acid. As a consequence, the body's own retinoic acid levels in plasma and predominantly skin are increased. This mechanism of action may offer a better pharmacokinetic profile and possibly a more favorable tolerability profile compared with synthetic retinoids.[48] Other enzymes blocked by liarozole are involved in the conversion of androgens to estrogens, but this effect does not seem to be clinically relevant, as has been proposed by a dose-ranging study of oral liarozole in psoriasis.[75] A recent phase II/III, randomized, double-blind, controlled study indicated that liarozole at a daily dose of 150 mg is equally effective as treatment with acitretin and indeed showed a trend towards a more favorable tolerability profile of the retinoic acid metabolism-blocking agent.[48] Our patient with lamellar ichthyosis treated with liarozole 150 mg/day also showed a significant reduction in lamellar scaling and good tolerability of the drug (figure 8). Unfortunately, the regular use of this drug in patients has not been approved by the EMEA as yet.

4.5.2 Genetic Counseling and Prenatal Diagnostics

After diagnosis of ichthyosis, patients or other family members, for example, parents, should be offered appropriate genetic counseling to explain the nature of the disorder, its mode of inheritance, and the probability of future disease manifestations in the family. For individuals or couples at risk of having children with Harlequin ichthyosis,[76] Sjögren-Larrson syndrome,[36] very severe forms of Netherton syndrome,[77] or severe forms of congenital bullous (keratinopathic) ichthyoses,[78] prenatal testing performed by chorionic villus sampling (at 10–12 weeks of gestation) and pre-implantation genetic diagnosis has become a novel translational benefit of basic research.[79] However, the ethical situation is different for many other types of ichthyosis, for example, moderate lamellar ichthyosis, which cannot be completely cured but can be treated rather effectively.

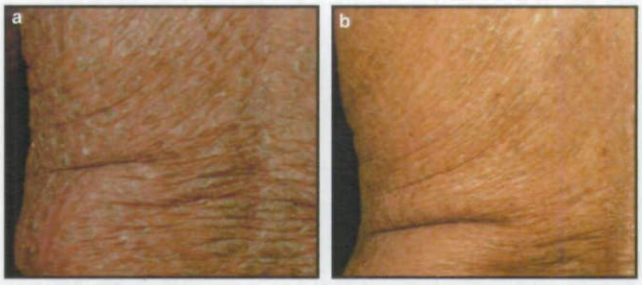

Fig. 8. Example of a 60-year-old man with lamellar ichthyosis due to transglutaminase deficiency, who participated in a multinational, double-blind, placebo-controlled trial with oral liarozole. (**a**) Rough lamellar scaling of the entire integument before start of medication. (**b**) The scaling was significantly reduced after 3 months. The patient was in the active treatment group receiving liarozole 150 mg/day. Because the drug is not yet available in Europe, the patient received acitretin after the study. (Since then he has contacted the center several times asking whether liarozole has been approved.)

5. Conclusions

The exact diagnosis of ichthyosis disorders is based on clinical presentation, medical and family history, skin biopsy, and laboratory findings. Currently, therapy of ichthyoses is not specific but rather is symptom relieving. Moisturizers, keratolytics or topical retinoids, bathing, and mechanical scale removal are the mainstay of topical therapy. Systemic therapy is limited to retinoids and hopefully liarozole in the near future. Superinfections of the skin are frequently seen in Netherton syndrome and bullous (epidermolytic) ichthyoses and should be anticipated and treated early. Many special signs and symptoms have to be considered in ichthyoses, for example, the epidermal barrier defect in collodion babies, failure to thrive in some disorders, and, especially in ARCI, the failure to sweat, ectropion, and ear occlusions leading to impaired hearing. Affected individuals should be counseled on the outlook and genetic nature of their disorder, and should be informed of patient organizations or foundations like F.I.R.S.T.

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