Review paper

HEREDITARY ICHTHYOSIS. PATHOGENESIS AND POSSIBILITIES OF TREATMENT

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ABSTRACT

Introduction. The term *ichthyosis* includes a number of pathogenetically different conditions, clinically displaying a more or less similar appearance. The underlying metabolic or molecular-biologic mechanisms have been elucidated up to now only in some of these conditions.

Known pathogenetic mechanisms. In recessive x-linked ichthyosis (RXLI) the deficiency of the steroid sulfatase has been demonstrated in cultured fibroblasts, leukocytes and keratinocytes. In certain patients with lamellar ichthyosis (LI) a deficient transglutaminase 1 was detected, the defect was located to a 9.3 cM region of chromosome 14q. In ichthyotic scales of non-bullous ichthyosiform erythroderma (NBIE) an increase of n-alkanes was reported. In bullous ichthyosiform erythroderma (BIE) genetic defects in keratins 1 and 10, and in ichthyosis bullosa Siemens (IBS) in keratin 2e were detected.

Systemic treatment. Unfortunately, there is no specific treatment for various entities of ichthyosis. In severe forms of LI, NBIE and BIE retinoids as *etretinatate, etretin* and *isotretinoin* have been applied with varied success, in all instances, however, symptoms recurred after the treatment was stopped. The same is true for corticoids. Certain antimetabolites were also used for suppressing the symptoms.

Topical treatment. This is at present still the most important modality. Various ointment bases including salicylates, urea, corticosteroids as well as other ingredients are commonly applied. During the last years an impaired barrier function in ichthyosis, and in the frequently associated atopic dermatitis, is being stressed. For this reason unsaturated fatty acids and cholesterol are incorporated into ointments.

General Management. As it is known that small children with the severe forms of ichthyosis are sensitive to exposure to lower temperatures, to infections and to inappropriate diet, an adequate general regimen has to be observed.

Conclusion. As intense research is going on and new therapeutic modalities can be expected during the coming years.

KEY WORDS

hereditary ichthyosis, classification, pathogenesis, systemic, topical treatment

INTRODUCTION

The clinical diagnosis *hereditary ichthyosis* includes a number of pathogenetically different conditions displaying a more or less similar appearance. There exists at present no generally accepted clinical classification of ichthyoses. In Europe the scheme presented in Fig. 1 is widely accepted. The underlying pathogenetic mechanisms have been elucidated only in certain variants of ichthyoses and even in these probably still not completely. The problem is complicated by the observation that quite a number of substances and pathogenetic events may provoke ichthyosis-like manifestations in humans as well as in animals. Table 2.

PATHOGENESIS

During the last 20 years many new data concerning ichthyosis have been reported. The most important information of interest to the clinicians is summarized as follows.

In the recessive x-linked ichthyosis (RXLI) the deficiency of the enzyme steroid sulfatase has been demonstrated in cultured fibroblasts, leukocytes and keratinocytes (1). An increased content of cholesterol sulfate in the ichthyotic scales seems to be responsible for the poor shedding. A deficient transglutaminase 1 (TGM 1) was detected in certain patients with lamellar ichthyosis (LI), the genetic defect being located to a 9.3 cM region of chromosome 14q (2). TGM 1 is responsible for cross- linking of proteins in forming the cornified envelope of keratinocytes. This anomaly could be, however, demonstrated only in certain patients and LI turns out to be a genetically heterogeneous condition (3,4). In ichthyotic scales of non-bullous ichthyosiform erythroderma (NBIE, erythrodermia ichthyosiformis congenita) an increased content of n-alkanes was reported (5). In bullous ichthyosiform erythroderma (BIE, epidermolytic hyperkeratosis) vacuolar degeneration and bullae develop after birth in the stratum spinosum. Genetically deficient keratins K1 and K10 are responsible for the clumping of tonofilaments and the following formation of bullae (6,7,8,9). It was shown that point mutations of either K1 or K10 in suprabasal keratinocytes can disrupt the keratin intermediate filaments resulting in blister formation and hyperkeratosis. In patients with ichthyosis bullosa Siemens (IBS) a genetic defect of K2e was reported (10,11). Table 1.

Further pathogenetic mechanisms were mentioned in ichthyoses. Suzuki et al (12) reported that the degradation of desmoglein 1, which is a desmosome component and plays a role in stratum corneum (SC) cell-adhesion, is decreased in ichthyoses. Normally endogeneous trypsin-like and chemotrypsin-like proteases are active in the process of degradation of desmoglein 1 in SC.

BARRIER FUNCTION

Dry skin and scaling are important clinical manifestations in ichthyosis. Dry skin is caused by an increased evaporation through the skin and this can be assayed by measuring the transepidermal water loss (TEWL). The intact SC offers the main protection against an increased TEWL as well as against penetration of foreign substances through the skin and against UV radiation. The mentioned protective activity is known as *barrier function* and

Table 1. Proposed classification of ichthyoses for clinical use

Adapted to viewpoints of Griffith A, Leigh IM, Marks R in Disorders of Keratinization, Rook et al, Textbook of Dermatology, 5th Edition, 1330-41

Proposed classification of ichthyoses for clinical use
1. autosomal dominant ichthyosis (ADI) ichthyosis vulgaris autosomalis dominans
2. recessive x-linked ichthyosis (RXLI) ichthyosis vulgaris recessiva
3. bullous ichthyosiform erythroderma (BIE) epidermolytic hyperkeratosis erythrodermia ichthyosiformis bullosa
4. ichthyosis bullosa Siemens (IBS)
5. non-bullous ichthyosiform erythroderma (NBIE) erythrodermia ichthyosiformis (including erythematous collodion baby)
6. lamellar ichthyosis (LI) ichthyosis lamellaris, (ichthyosis congenita including harlequin fetus,non-erythematous collodion baby)
7. ichthyosis with neurological symptoms
8. ichthyosis with other noncutaneous symptoms

Table 2. Substances and pathogenetic mechanisms inducing ichthyosis-like manifestations in humans and certain experimental animals

Triggering factors	Effect	Subject	Author
linoleic acid defic diet	increase TEWL hyperkeratosis	experimental model mice	Elias, J Invest Derm 1983
diazocholesterol	XLRI-like ichthyosis	hairless mice	Elias, J clin Lab Inv 1983
genetic mechanism defic steroid sulfatase defic transglutaminase defic keratin 1 or 10	 XLRI lamellar ichthyosis bul ichthyo erythro	 humans humans humans	 Shapiro, Lancet 1978 Permantier, Hum Mol Gen 1995 Rothnagel, Science 1992
vitamin A and B defic cutis senilis	dry skin ichthyosis-like symp	humans	Schnyder, Jad-Erganzunswerk VII, 1966
vitamin A hypervitamin	ichthyosis-like symp	humans	Braun-Falco, 4th ed 1996, p 683
chronic liver, kidney dis	dry skin, ichthyosis	humans	Rook, Textbook, 4th ed, p 2322
Infectious diseases: lepra, Tbc, AIDS	dry skin, ichthyosis	humans	Braun-Falco, 4th ed, 1996, p 683
malignancies: mb Hodgkin lymphoma, carcinoma	dry skin, ichthyosis	humans	Rook,Textbook,4th ed, 1986, p 2322
drug eruption: nicotin ac, alopurinol, cimetidin	dry skin, ichthyosis-like	humans	Braun-Falco, 4th ed, 1996, p 863

depends on both, intact corneocytes and the extracellular component of SC, which is characterized by abundat intercellular lamellae (called also bilayers). A proper functionning of the granular layer including the lamellar bodies (LB, kaeratinosomes) is a prerequisite for proper function of the extracellular component which is composed mainly of lipids. The normal extracellular component appears by electron microscopy as repleted by membrane structures called also intercellular lamellae (13).

As it was shown by Elias in experiments on mice the TEWL was essentially increased and a hyperkeratosis of the proliferative type developed, if the animals were fed a diet deficient in essential fatty acids (14). The increased TEWL could be abolished by topical or systemic application of linoleic acid whereas the hyperproliferation was ameliorated by arachidonic acid.

That cholesterol plays an essential role in regulation of proper keratinization as is further substantiated by experiments with diazocholesterol which inhibits cholesterol synthesis and induces in hairless mice a retention-type hyperkeratosis similar to XLRI in humans (15).

Further experiments have shown that in aged human skin there is a decreased number of extracellular lamellar bylayers (16). In aged humans as well as in aged mice under normal conditions the barrier functions more or less normally, however if it was perturbed after either aceton extraction or tape stripping, it recovered more slowly in aged than in young subjects (16). The process of restoring the barrier function could be speeded up by topical application of an equimolar mixture of cholesterol, ceramide, linoleic and palmitinic acid or cholesterol alone. In untreated LI the extracellular lamellar bilayers were decreased and lipid vacuoles were observed in keratinocytes (17).

Table 3. Laboratory investigations in various types of ichthyosis

diagnosis	heredity	genetic defect	epidermo poiesis	scales	histology
ADI	autos dom	filagrin decreased	normal		hyperkeratosis str gran reduced
RXLI	x-linked rec	steroid sulf decreased	normal	cholesterol sulfate increased	hyperkeratosis
NBIE	autos rec	heterogeneous	increased	n-alkanes increased	hyperkeratosis parakeratosis acanthosis
LI	autos rec	transglut 1 chrom 14q	no essential increase	increased sterols, free fatty acids	compact hyperkeratosis hypergranulosis
BIE	autos dom	K1 or K10	increased		vacuolar deg str spinosum
IBS	autos dom	K2e			suprabasal epidermolysis

Legend: ADI - autosomal dominant ichthyosis vulgaris, RXLI - recessive x-linked ichthyosis vulgaris, NBIE - non-bullous ichthyosiform erythroderma, LI - lamellar ichthyosis, BIE - bullous ichthyosiform erythroderma, IBS - ichthyosis bullosa Siemens

SYSTEMIC TREATMENT

As etiologic treatment at present is not possible, various rather different drugs are being used, especially in moderately severe and severe cases. Due to their side-effects these are applied either on a temporary basis or, in severe cases, patients may remain on a maintaining dose for years. One has to be extremely careful in treating children.

Corticosteroids seem to be indicated in severe forms of NBIE, less frequently in other severe forms of ichthyoses. The dosis is usually being prescribed at an individual basis (18).

Retinoids. Etretinate in a dose of 0.5 to 1.0 mg per kg body weight (b.w.) is efficiently reducing the hyperkeratosis but usually has less effect on erythroderma. The first reports, dealing mostly with single cases, were rather encouraging (19,20). Atherton and Wells treated with etretinate 9 patients with NBIE and 11 patients with BIE, the latter responding better to the treatment. The average dose used was 1.5 mg/kg b.w. in NBIE and 1.2 b.w. in BIE (21). In a further clinical study 7 patients with LI were treated first with etretinate and later on with acitretin, producing a marked improvement. The dynamics of dosage adjustment provided two response patterns: some patients required 35 mg daily or more, while others responded well to 10-25 mg daily (22). From these as well as from further reports it may be deducted that LI answers to treatment with retinods and specially to acitretin. Lacour et al. (23) confirm that acitretin was a safe drug in 46 children, they observed only minor abnormalities in liver function tests and triglicerides, which did not necessitate a change in therapy. They suggest a starting dose of 0.5 mg/kg body weight.

Essential fatty acids (EFA) given orally were efficient in removing ichthyosis-like hyperkeratosis in an experimental model in mice. According to several reports treatment with EFA was successful in patients with atopic dermatitis where an increase of linoleic acid and a decrease of its metabolite the gama-linoleic acid was observed in plasma (24). Therapeutic attempts in patients with hereditary ichthyosis seem to be not that much encouraging.

Cyclosporine A. Some observations were made in ichthyosis patients who were treated with cyclosporin A after kidney transplantation. Ho et al included ichthyoses into the group with minimal response to cyclosporine (25).

LOCAL TREATMENT

In view of many side effects of different systemic treatment modalities, the topical treatment is still of primary importance, even in the most severe cases. The main objectives of topical treatment are to reduce the dryness, TEWL, soreness, eventually also redness, as well as to remove the scales and in such a way to restore the normal hydratation of the skin. Unfortunately the success is usually only a partial one. The commonly used vehicles (basis ointments or creams), the most important therapeutical components and further ingredients such as emulsifiers, stabilizers, preservatives and accelerants are shortly discussed.

Vehicles. Up to two decades ago or so, the vehicles were relatively simple materials, such as various animal greases, soft paraffin (vaseline, petrolatum), lanolin and others. Dermatological preparations for topical use were developped empirically, active ingredients were mixed with the vehicle according to physicians' prescription, the mutual influence of the vehicle and the active ingredient were not studied in details.

At present a topical preparation has to fulfill a number of criteria: the vehicle should be easy to apply and remove, non-toxic, non-irritant, non-allergogenic, chemically stable, homogeneous. bacteriostatic, resistent to moulds, cosmetically acceptable and pharmacologically inert. For these reason, in treating ichthyoses mostly emulsions oil in water (O/W) and water in oil (W/O) or semisolid water-free and water-containing ointments produced by pharmaceutical companies are being used. The importance of vehicle is now well recognized not only for its physical properties but also as a delivery system for the many new active topical drugs. The vehicle is chosen as carefully as the incorporated drug (18,26). The so-called magisterial preparations (extemporaneous dermatological formulations) are being restricted to selected situations, ichthyoses will probabely remain such a field of activities.

Active ingredients. Following are a few substances which have been reccommended for topical treatment of ichthyoses:

- salicylic acid 2-6% and urea 10% in O/W creams or ointments for removing the scales;
- cholesterol 10% is both active in restoring the barrier function (16) and is also an emulsifier (26). Various alpha hydroxy acids (AHAs) e.g. glycolic, lactic, pyruvic and tartaric acid or ethylpyruvate dissolved in water or ethanol, incorporated in W/O or O/W ointments or creams in 2-5% concentration, were advocated (27) in treatment of lamellar ichthyosis. Individuals with sensitive skin may not tolerate products formulated with AHAs. For this reason a neutral amid derivative, methoxypropylgluconamide was developped (28).

Tretinoin 0.25% in a gel or 0.5% in a cream was also mentioned as being efficient (18).

Topically applied calcipotriol was reported to be beneficial in congenital ichthyoses, especially in LI (29). In a further study 27 patients with ichthyosis vulgaris, RXLI and congenital ichthyoses were treated with calcipotriol ointment (50 ug/g) in amounts up to 100 g weekly, twice daily. The authors concluded such short-term treatment (a few weeks) was moderately efficacious and safe in adult patients (30).

Preservatives are needed to prevent secondary infections with bacteria, fungi, molds and viruses. Various esters of the parahydroxybenzoic acid (parabens) are widely used, occasionally they may provoke sensitization. Further such substances are chlorocresol, phenoxyethanol, sorbic acid as well as others.

Emulsifiers are large molecules with both strongly polar (water soluble, hydrophilic) and non-polar (oil soluble, lipophilic) groups; they dissolve partly in water and partly in oil. Two types are differentiated:

1. producing W/O systems e.g. polyvalent metallic soaps, propylene glycol fatty acid esters and others.
2. producing O/W systems like alkylsulphates, synthetic phosphoric acid esters and others.

Stabilizers prevent reactions between the vehicle and the active ingredient as well as other chemical reactions so that do not change in a given period of time.

Accelerators increase the permeability of the skin. Propylene glycol or dimethyl sulphoxide (DMSO) can be mentioned as examples.

VEHICLES RECCOMMENDED

The vehicles which are mostly used in Slovenia are Lekobaza*and Linola** but also Diprobase*** and Belobaza****. In the Table 2 the active ingredients and their concentrations are given as suggested by the producers.

CONCLUSIONS

As it was mentioned ichthyoses are a rather heterogeneous group. A number of pathogenetic mechanisms have been elucidated, an etiologic treatment is however still not possible. Systemic medicaments e.g. corticosteroids and retinoids are quite efficient, but usually produce considerable side effects, for this reason a continuous, long lasting application can not be recommended. Adequate local treatment chosen according to patient's condition is still of great benefit.

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Lekobaza- LEK, Ljubljana; Linola**- A. Wolff, Bielefeld; Diprobase***- Schering-Plough, Kenilworth; Belobaza****- BELUPO, Koprivnica*

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