REVIEW

Epidermolytic hyperkeratosis: clinical update

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Abstract: Epidermolytic hyperkeratosis (EHK), earlier termed as bullous congenital ichthyosiform erythroderma is a skin disorder characterized as an autosomal dominant and rare disorder which has been observed to affect 1 in over 200,000 infants as a consequence of a significant mutation in the genes responsible for the keratin proteins, mostly keratin 1 and 10. The features present at birth include erythema and blistering. In adults, the hallmarks include hyperkeratosis, erosions, and blisters. The major symptoms including xerosis, pruritus, and painful fissuring lead not only to cosmetic problems but also stress, inferiority complex and other psychological conditions. While clinical inspection followed by confirmatory tests including histopathology and electron microscopic assessment is used for diagnosis, treatment modalities can be further improved for better diagnosis. This article reviews subtypes of ichthyosis, with a focus on EHK, genetics behind the disease, recently reported mutations, the existing diagnostics and treatments for the same and potential of new modalities in diagnosis/treatment.

Keywords: epidermolytic hyperkeratosis, ichthyosis, skin, skin disorder

Introduction

Epidermolytic hyperkeratosis (EHK), earlier termed as bullous congenital ichthyosiformerythroderma (BCIE),[1] is a skin disorder characterized as an autosomal dominant and rare disorder which has been observed to affect 1 in over 200,000 infants as a consequence of a significant mutation in the genes responsible for the keratin proteins.[2,3] This disorder is histopathologically perceived as a heritable keratinization skin disorder which is typically identified by blistering of the skin, clumping of the tonofilament (keratin bundles), and cytolysis in the terminally differentiating epidermal cells.[4–8] Newborns are at a high risk of developing electrolytic diseases which may be fatal, but as the age progresses the blistering and redness reduces and are, over time, replaced by a progressive hyperkeratosis in the stratum corneum; the uppermost layer of skin starts to thicken and shows blistering.[9] For the renewal of the normal human epidermis, keratinocytes are on a constant move from the proliferating basal strata to the terminally well differentiated squames that form the stratum corneum,[10] but in the individuals infected by EHK, this process is hampered due to which the regular epidermal function of being a barrier is ineffective.[11] Insights from cutaneous lesions suggest that the cleavage of the tissue happens intraepidermally with the separation of the mutated suprabasal keratinocytes along with focal hyperkeratosis.[12] The examination of epidermolytic hyperkeratosis skin using electron microscopy has revealed the formation of clumps in the suprabasal epidermal cells of keratin intermediate filaments (KIF)[13,14] along with the presence of keratin 1 and keratin 10.[15,16] Such observations suggested that EHK is linked to keratin 1 and keratin 10. This pair exist as multiple

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heterodimers and form the KIF in the upper epidermal layer, and a mutation in them leads to EHK.[17] The expression of the keratin proteins is specific to epithelial cells depending on the cell type and the state of differentiation.[11]

The keratin protein's general structure is formed by a conserved rod domain along with distinct four alpha-helical structures which are separated by linker sequences that are nonhelical and also by globular and nonhelical sequences which are of varied compositions and size.[18,19] On chromosome 17, the small, acidic type I keratins are encoded (keratins 9 to 19), while on chromosome 12, the more basic and large type II keratins are encoded (keratins 1 to 8).[11,20–23] Each of the two keratin types contributes one protein to form the heterodimer subunit which is a coiled structure that then forms the tonofilaments.[11,24,25] Initially, the basal epidermal cells are observed to be expressing only keratins 5 and 14, but as the cells begin to terminally differentiate and start the migration towards the spinous layer, the expression of keratin proteins 5 and 14 is reduced and instead the expression of keratin 1 and keratin 10 is promoted.[26–29] In the suprabasal spinous and granular cells, clumping of the tonofilaments along with a collapsed keratin filament network surrounds the nuclear region and is the hallmark of EHK.[5,30–32] Such a collapse generally suggests an error in the differentiation specific keratin,[16,33] although the other probable causes for EHK have been identified as deformed filaggrin which is an associated protein for keratin filament,[31] an envelope precursor, involucrin[34] or an abnormality in the metabolism of lysosome.[35] It has been observed that most families that have EHK are predisposed to have linkage near the gene locus of chromosome 12 for type II keratins.[36,37] While several mutations are already known, discovery of new mutations including c.475T>C, p.Ser159Pro), and c.562A>C in the recent years suggest further explorations to understand genetics and heredity of EHK in order to identify newer methods of detection and treatment.

This article reviews subtypes of ichthyosis, with a focus on epidermolytic hyperkeratosis, the genetics behind the disease, recently discovered mutations, the existing diagnostics and treatments for the same and potential of new modalities in diagnosis/treatment.

Subtypes of ichthyosis

Ichthyosis is a set of disorders of cornification which are identified clinically by significant scaling patterns and by hyperkeratosis which is a histopathological characterization. The clinical subtypes of this disorder are usually based on the mode of inheritance and the observed clinical and pathological data.[38] The word "Ichthy" originates from the Greek word for "fish". As the skin becomes thick and appears like fish scales, the disorder has been named as "Ichthyosis". This disorder is either acquired or inherited and around 28 recognized types of ichthyosis and related skin ailments exist.[39] Ichthyosis is usually categorized as; true ichthyosis, epidermolytic hyperkeratosis and ichthyosiform states. Each of these types further is divided into several subtypes. Primarily, the autosomal recessive, autosomal dominant and X-linked recessive types fall under the true ichthyosis type.[40] Some of the major types of inherited ichthyosis that are recognized are: ichthyosis vulgaris, Harlequin ichthyosis, epidermolytic hyperkeratosis, congenital ichthyosiform erythroderma, X-linked ichthyosis, localized ichthyosis and lamellar ichthyosis. Of the various types, ichthyosis vulgaris is the most common type of ichthyosis which occurs in every 1 out of 250 people.[41] The X-linked ichthyosis is specific to only males and its occurrence is approximately around 1 in every 6,000 births.[42] Harlequin ichthyosis is one of the rare but extremely severe kind of inherited ichthyosis wherein an affected child looks like it is wearing a harlequin costume[43] The classical lamellar ichthyosis also called the autosomal recessive congenital ichthyosis is one of the severe forms which effects 1 in every 300,000 births and is associated with recessive genes.[44] Ichthyosiform dermatoses group represent a huge clinical spectrum of disorders with lack of properly defined pathogenetic mechanism responsible for these conditions.[45] Acquired ichthyosis is a condition similar to ichthyosis vulgaris both clinically and histologically and it usually occurs during adulthood in association with other diseases or lymphoma.[46–52]

A rare form of ichthyosis with clinical manifestations at birth is epidermolytic hyperkeratosis (EHK) which is an autosomal dominant disease of unknown etiology which has been recorded to affect approximately every 1 in 30,000 human beings. The disease is characterized primarily with hyperkeratotic scaliness along with severe blistering as a subsequent effect of cytolysis in the suprabasal cells, and also hyperproliferation in the basal cells. As per the histological approach, the epidermis of patients suffering from EHK exhibits a thickened, granular layer and stratum corneum, with irregularly shaped and enlarged cells.[53] On the ulterior structure, only the suprabasal layers are affected, wherein three major aberrancies are observed namely: clumping of tonofilaments, keratohyalin granules and
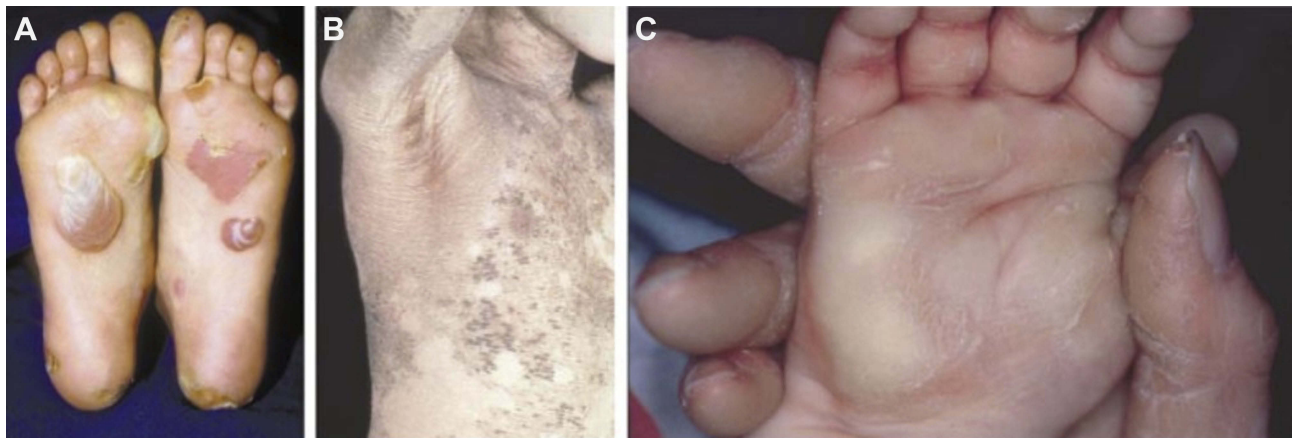
Figure I Clinical features of three keratin diseases. (**A**) Blisters on the soles of a patient with the milder Weber–Cockayne form of epidermolysis bullosa simplex. (**B**) Widespread epidermolytic hyperkeratosis in a bullous congenital ichthyosiform erythroderma patient. (**C**) Site-restricted epidermolytic hyperkerratosis of the palms in a mother and child with epidermolytic palmoplantar keratoderma.
Note: Reproduced from McLean WI. Genetic disorders of palm skin and nail. *J Anat.* 2003;202(1):133–141 with permission from John Wiley and Sons.[54]

nuclei of irregular size and shape, and degeneration of the cell. Figure 1 shows clinical features of three keratin-related conditions associated with EHK.

Pathology of epidermolytic hyperkeratosis

The most important proteins required for the structural development of the epidermis are the keratin proteins.[55] By studying the keratin gene sequences, understanding the switching of the keratin gene expression which occurs as epidermal cells continue to terminally differentiate and analyzing how keratins aggregate into 10 nm filaments has led to the basic understanding of the genetic basis of epidermolytic hyperkeratosis. At the junction between the environmental conditions and the human body, the epidermis plays a protective role.[56] It carries out this role by forming a massive cytoskeletal structure formed by 10 nm keratin filaments. Basal epidermal cells portray a complex network of relatively spread out keratin filaments, formed of the type I keratin K14 and type II keratin K5.[57,58] Once the basal cells cease their division and commence their journey to the surface of the skin, they switch from expressing the K14 and K5 genes to K10 (type I) and K1 (type II).[26,59] Simultaneously, K1/K10 filaments of the suprabasal cells clump together to form tonofibrillar bundles which are thicker than the tonofilament bundles K5/K14 of the basal cells, leading to the enhanced ability of the keratins to survive through the damaging phases when the production of flattened squames occurs, which leaves 85% of the keratinocytes which are terminally differentiated as keratin.

Keratins are part of the superfamily of the intermediate filament (IF) proteins, which can self assemble in vitro into a 10 nm nuclear or cytoskeletal matrix fibers.[60,61] The classical trait of the cytoskeletal IF polypeptides is the 310 amino acid α-helical coil which is centrally located and termed as the rod comprising heptad repetitions of hydrophobic moieties that allow them to wind around another IF protein along a seal which is also hydrophobic. This rod is further divided into four different segments which are known as helix 1A, 1B, 2A and 2B and is also connected by three nonhelical, short linker segments. The rod regions of keratins type I and type II form unstaggered, parallel, heterodimers, of which two then align in antiparallel directions to form structurally stable heterodimers.[61] Over 5,000 heterotetramers then tend to form a network of a complex hierarchy of end to end and lateral associations to form a single 10-nm-IF of length 10^{-20} μm.[62,63]

EHK is histopathologically characterized by (1) clumping of tonofilaments and aggregation of perinuclear shells of tonofilaments within the suprabasal cells; (2) a basal epidermal layer which is normal but sometimes hyperproliferative; (3) a granular, thickened layer and stratum corneum and (4) degeneration of cells in suprabasal layers, starting in the lower spinous area and aggrandizing while terminal differentiation of the cells occur.[55] Ichthyosis hystrix and palmoplantar keratoderma both have characteristics that imply that they are milder versions of EHK. A basic understanding at the genetic level of EHK roots from the clear similarity between the clumping of the tonofilaments in the suprabasal cells, that occurs in the skin for a person suffering from EHK, with the occurrence

in the basal cells of the skin of a person suffering from Epidermolysis Bullosa Simplex (EBS).[13] EHK clumps associate with only those antibodies which are specific for K10 and K1.[15,16] It was predicted from the initial transgenic mouse based studies that EHK is a genetic disorder for which K1 and K10 are responsible, considering the mirror image parallels among the ultrastructural and morphological traits of EHK and EBS, along with the understanding that as the epidermal cells begin their terminal differentiation, they transcend into the expression of K1 and K10 genes.[64] Pathobiological and biochemical features of human disorder EHK were portrayed by the transgenic mice that were expressing a reduced human K10 gene.[53] In other studies, the linkages of keratin gene clumps on specific chromosomes 12 and 17 of the EHK affected members and palmoplantar keratoderma (PPK) affected members were studied, which further strengthened the idea that these diseases of the suprabasal layers are keratin-based disorders.[10,65–70] Full proof evidence resulted from the direct sequencing of the two genes namely K1 and K10 isolated directly from the DNA of the patient. Point mutations in K1 or K10 genes were observed in three independent studies of separate cases of human EHK initially.[11,37,53] Now, several other significant point substitutions have been reported.[17,71–74]

Inheritance pattern of EHK and new classifications of EHK

As per the results of the First Ichthyosis Consensus Conference in Soreze, 2009, it has been established that ichthyosis falls under the broad category of Mendelian disorders of cornification (MEDOC).[75,76] Inherited ichthyosis is considered as a disease group within the larger group of MEDOC which is characterized by mutations caused in the genes responsible for the skin barrier formation. At present, based on the molecular genetics of the disorder, the inherited ichthyosis is further classified as nonsyndromic ichthyoses and ichthyosis syndromes.[77] Of the nonsyndromic ichthyosis, keratinopathic ichthyosis is a proposed umbrella term under which EHK, annular epidermolytic ichthyosis (AEI), superficial epidermolytic ichthyosis (SEI), etc are covered. The keratinopathic ichthyosis are all characterized by mutations in the KRT1, KRT2 and KRT10 genes of the keratin family. The inheritance pattern of EHK has been studied extensively and it is predominantly understood to be an autosomal dominant inheritance with several cases also being identified as a result of spontaneous mutations. Family history of the disease is studied through pedigree analysis of the specific keratin genes namely KRT1, KRT2 and KRT10. Techniques such as immunohistochemistry, immunocytochemistry, light microscopy, electron microscopy, etc are used to screen the tissue and cellular level expression of the genes and help to determine and diagnose the inheritance pattern.

Mutations and genotype-phenotype correlations

It has been observed that EHK is caused predominantly due to mutations in the KRT1 and KRT10 genes. Several studies report that point mutations in the conserved regions are responsible for the development of this disease. Chipev et al identified a point mutation in the H1 sub-domain of the intermediate keratin 1 filament wherein a leucine to proline mutation occurs.[37] This mutation was observed using electron microscopy and quantitative competition assay and it was concluded that the mutation resulted in seriously affected structure and organization of keratin filaments. Syder et al studied the correlation between disease severity and the extent of mutation for severe EHK incidences.[73] They revealed through their studies that a mutation of arginine to histidine in the amino end of the α-helical rod domain of KRT10 and the tyrosine to cysteine mutation in the carboxy-domain of KRT1 hold significance over the severity of EHK. Virtanen et al . studied an interesting mutation in which a complex insertion/deletion led to the first ever reported case of deletion of an entire exon that is exon 6 of KRT1 which resulted in the removal of 42 amino acids from the 2B helix of the protein resulting in a severe form of EHK.[78] It has been observed that the genotype-phenotype correlations in patients suffering from EHK are very complex. It is a disorder in which the genotype-phenotype relationships are dependent on the mutations in the keratin gene and on the position of the mutation within the gene. The correlation is also understood based on level of mutated allele expression and the functional significance of the amino acid substitution. Clinical studies along with in vivo studies on transgenic mice have been shown to support the theory of mutation in keratin genes resulting in varied phenotype.[79] Research also states that there are mutations in the keratin genes wherein the genetic background is responsible in the modulation of the phenotype. Understanding the molecular mechanisms of these

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mutations can lead the path to gene therapy and gene replacement technologies in order to alleviate these syndromes.

Recent updates in EHK-associated mutations

Chen et al reported a case of heterozygous missense mutation (exon 1 of KRT10) with a T to Ctransition (c.475T>C) leading to proline at amino acid position 159 (p.Ser159Pro). The cases showed severe forms of EHK.[80] A novel mutation in KRT1 (c.562A>C; p.N188H) was reported by Eskin-Schwartz et al. While histology showed cell-cell dissociation in epidermis with foci of acantholysis, epidermolytic changes were not observed. Reduced expression of several desmosomal proteins including desmoglein 1, desmoplakin, plakoglobin, E-cadherin as well as keratin 10 were revealed by immunostaining, suggesting limitations in diagnosis of EHK by histology alone.[81] Some other mutations that could be interesting to explore are KDSR (3-ketodihydrosphingosine reductase),[82] PNPLA1,[83] SDR9C7,[84] and ELOVL1.[85] Terrinoni et al (2018) have shown additional roles of *KRT1* and *KRT10* associated mutations in development of a rare manifestation of epidermolytic ichthyosis—ichthyosis hystrix of Curth-Macklin.[86] While co-occurrence of other diseases is not common, recently, coincidental latent tuberculosis and erythema annulare centrifugum was reported in a 12-year-old female.[87] Such associations need further explorations.

Diagnosis of the disease

The diagnosis of patients with EHK is generally made on clinical grounds; nonetheless, until now just a single clinical scoring framework that incorporates light dim scaling, keratosis pilaris and expanded palmoplantar markings has been proposed for the finding of EHK. In addition to cosmetic problems, EHK patients normally suffer from a progression of medicinal issues that are specifically or indirectly identified with pathophysiological parameters such as cellular collapse, blistering, and impaired barrier function. The compensatory hyperproliferation of these physiological entities leads to hyperkeratosis.

Clinical inspection and dermoscopy

A dermatologist can assess the condition and use a dermoscope for better visualization. Hyperkeratosis can vary from mild to severe and is typically more prominent over joints and in flexural sites. The scale is classically

described as corrugated or cardboard-like. Some patients also experience joint contractures. Hair, nails, and teeth are normal and ectropion is generally absent. Superficial bacterial infections are common and are often associated with a characteristic odor of the skin. Some of the basic symptoms that are in primary focus for the prognosis includes xerosis, pruritus, painful fissuring of the thickened skin, erythema, anhidrosis, ectropion, and decreased range of motion at joints and are mentioned in Table 1.

Biomarker and electron microscopy

Immunohistochemistry (IHC) can be of assistance in the conclusion of EHK and ARCI, if antibodies are accessible against the suspected applicant protein and the patient's mutation(s) causes a deletion of particularly anomalous protein articulation in the epidermis.[88] Electron microscopy patterns in the upper epidermis were one of the diagnostic methods for commenting upon the presence of a condition of EHK or its types in the past.[89] In any case, electron microscopy is expensive, tedious and requires unique neurotic skill not generally accessible. Electron microscopy investigation is nevertheless, extremely valuable in describing the cell organelles in granular cells, and unusual lipid structures in the epidermis utilizing ruthenium tetroxide postobsession, which perfectly images the lipid envelopes and lipid bilayers in the stratum corneum.[90–92]

Histopathological

The histological findings using hematoxylin and eosin cannot be uniquely associated with EHK. Typical findings include marked hyperkeratosis, a thick granular layer, coarse keratohyaline granules, and vacuolar degeneration of the upper epidermis. Occasionally, deeper granular cells become dense, enlarged, and irregularly shaped, and these masses

Table 1 Common symptoms and pathophysiological parameters for epidermolytic hyperkeratosis

Symptoms	Pathophysiology
(a) Xerosis	Dehydration of stratum corneum
(b) Erythema	Redness of skin or mucous membrane as a result of vasodilation
(c) Fissure	Linear cleft through the epidermis that extends into the dermis
(d) Erosions	Loss of all portion of the epidermis
(e) Anhidrosis	Decreased perspiration
(f) Pruritus	Expression of cutaneous sensations evoking scratch reflex
(g) Keratoderma	Focal or generalized thickening of the skin

appear to be keratohyaline granules. In addition to this, dyskeratosis is also found . in varying concentrations.[93] Patients whose pathologic slides demonstrate continuous involvement of the entire horizontal epidermis with these distinctive findings are more likely to have generalized disease; those with focal involvement revealing skip areas of normal epidermis are more likely to have a mosaic form of epidermolytic ichthyosis.[39]

Genetic testing

Dideoxy sequencing (Sanger sequencing method) was considered to be the inimitable standard for the diagnosis of EHK by which the coding some portion of the suspected EHK causing quality was dissected, exon by exon. In recent times, advances in massive parallel sequencing have been produced and applied for substantial scale hereditary diagnostics, particularly in genetically heterogeneous maladies. However, the next generation sequencing cannot match up with the clinical analysis of the different forms of ichthyosis, but the multigene-panel sequencing that comprises all suspected candidate genes within one analysis is the gold standard diagnostic approach.[94,95]

Fetal screening for EHK

Various approaches are employed for screening an affected fetus, namely: (1) amniocentesis for chromosome analysis, biochemical analysis and for cultured fibroblasts; (2) for fetal skin biopsy and for visual inspection, fetoscopy; (3) maternal serum screening.[96–99] Fetoscopy along with skin biopsy and amniocentesis are the most commonly used diagnostic procedures.[99,100] The epidermal development starts in the initial weeks of life, wherein it comprises of a monolayered sheet of cells and eventually by the end of the second trimester, it develops into a stratified squamous epithelium.[101] For the onset of keratinization, there is a regional variation, that is it occurs by 24 weeks throughout the skin whereas it occurs in about 15 weeks in the hair follicles.[102] Before 24 weeks' gestation, occurrence of precocious hyperkeratosis and keratinization observed via fetal skin biopsy can be diagnosed as epidermolytic hyperkeratosis.[97] Irrespective of these advanced techniques being present, the broad applications of diagnostic screening are being curbed due to several limitations such as limited sensitivity of analysis of a mutation or genetic heterogeneity.[103]

Several modern methods based on optical and spectroscopic techniques such as Raman spectroscopy and optical coherence tomography have shown potential in in vivo identification of diseases such as cancers, including skin cancers and other skin disorders.[104–111] These modalities can be explored for EHK and other skin conditions as well. A recent study by Lima et al has shown classification of nonmelanoma skin cancer from actinic keratosis (AK) and normal skin[112] suggesting potential of the technique in exploring other skin conditions including EHK.

Strategies for treatment of EHK

A systematic review of therapies, clinical trials of drugs and treatment strategies have been discussed in the following section corroborated from different sources.

One of the primary aims in EHK therapy is to evacuate scales and to diminish uncomfortable dryness of the skin (xerosis) without causing excessively irritation. To achieve this, the following viewpoints must be taken into account before endorsing a treatment:

(a) The age and sex of the patient (children have a slender skin and a higher skin surface zone or body: weight proportion, in this manner expanding the hazard for systemic toxicity; pregnant women ought not to be presented to possibly teratogenic compounds).

(b) The type and seriousness of the disease (thick scales require keratolytic agents, xerosis requires just emollients, fissures, crevices and erosions may block the utilization of keratolytics and require antimicrobial treatment).

(c) The degree and location of the skin lesions (entire body application increases the risk for systemic toxicity; face and flexural locales normally require less potent treatment and are more in danger of skin irritation).[113]

Although there is no definitive treatment yet for EHK, several treatment strategies are based on the use of emollients, topical keratolytics, and oral retinoids.

Hydration, lubrication, keratolysis and antimicrobials

The first line of therapy includes the use of wide assortments of emollients and topical keratolytics that aim to expedite desquamation and enhance the appearance of the skin. These include urea, lactic acid, glycolic acid, glycerol, paraffin, propylene glycol, ammonium lactate, salicylic acid, tazarotene, N-acetyl-cysteine and a diversity of fatty creams.[114]

The mechanism of action of common additives in the emollients can be stated as compounds such as NaCl, urea, glycerol particularly act on hydrating the skin. Similarly, petrolatum and other lipids work on the lubrication and accompaniments such as α-hydroxy acids,[21] urea (>5%), propylene glycol, salicylic acid, N-acetylcysteinamide act on keratolysing the epidermal layer. Similarly, retinoids and calcipotriol act as modulators of differentiation antimicrobials.[115] A summary is provided in Table 2. Aqua-glycolic lotion is a commercially available form of α-hydroxy acid. Lactic acid is available in a readymade prescription form of 12% ammonium lactate lotion (Lac-Hydrin) or as compounded by a prescription wherein 5–10% is suitable in a vehicle solvent.

Therapies for mild EHK

The most discerning method for treating ichthyosis vulgaris and X-linked recessive ichthyosis (XRI) would be to make up for absent or surplus components in the horny layer scilicet, inadequate breakdown products of filaggrin and intemperate cholesterol sulfate, respectively. Anyway, some achievement has been accounted for utilizing cholesterol-containing creams to offset the elevated cholesterol sulfate levels in XRI skin.[119] Emollients comprising a physiological blend of ceramides and other skin lipids have been shown to reestablish the skin barrier in different conditions.[120]

Therapies for relentless EHK

By utilizing a combination of at least two keratolytic specialists and lotions in the same lipophilic cream base it is frequently conceivable to accomplish added or even synergistic impacts in lamellar ichthyosis without the need to use chafing concentrations of either agent alone.[121,122]

Table 2 Mechanism of action of common additives in ointments

Mechanism of action	Constituent in cream	References
(a) Hydration (b) Lubrication (c) Keratolysis (d) Modulators of differentiation antimicrobials	NaCl, urea, glycerol Petrolatum and other Lipids α-Hydroxy acids, urea (>5%), propylene glycol, salicylic acid, N-acetylcysteinamide Retinoids, calcipotriol	21,116–118

The therapy for EHK is quite assertive as hyperkeratosis must be decreased to limit the distorting and putrid scales, which harbor numerous microorganisms. An excessively strong keratolytic treatment will aggravate the condition by upsetting the epidermal obstruction further, expanding the danger of excruciating blisters and skin disintegrations inclined to disease. Applications of a few drugs like tazarotene,[123] N-acetylcysteine,[124,125] liarozole and calcipotriol[126-128] have found some success as these medications likely act through decreasing epidermal hyperproliferation and affecting keratinocyte differentiation and hence, corneocyte function.

Effects of topical therapies

Aside from ephemeral stinging, pruritus or skin inflammation while applying the ointments, the early local side effects of topical treatment are generally negligible, and any long-haul lethal impact can ordinarily be limited if the topical cures are utilized effectively. Topical treatment requires significant investment of time and must be administered regularly, as per instructions.

The determination of a reasonable cream base (hydrophilic or lipophilic, nonocclusive or semi-occlusive) is in this manner of significance not only for ideal pharmacological impacts of the dynamic ingredients but also for their pharmacokinetics and transcutaneous penetration.[129]

Oral retinoids

Retinoids have a keratolytic impact that encourages the slivering of scales from the surface and counteracts unreasonable hyperkeratosis, prompting a more typical density and enhanced functioning of the horny layer.[115] While the range of viability and toxicity of various retinoids are comparative and congruent, they are not indistinguishable. The aromatic retinoids generally have a more prominent impact on volar skin prompting advantage in the treatment of palmoplantar hyperkeratosis.[130–132] One of the side effects of consumption of retinoids is the increased case of skin fragility.[133] When the skin is prone to blistering in the case of EHK, the consumption of retinoids enhances the condition at a more intense level. It has been discovered that retinoid treatment, given topically as tretinoin, tazarotene or adapalene, and foundationally as acitretin, is more viable in patients with mutations in *KRT10* in contrast with those with changes in *KRTl*. Most likely the former patients can more easily endure the unavoidable down-direction of *KRT2* by retinoids.[134] *KRT2* and *KRT1* give off an impression of being commonly replaceable in the heterodimerization of keratin fibers,

clarifying why the presence of the former protein may decrease the negative effect of *KRTl*mutations. On the other hand, a down-direction of *KRT2* is the in all probability explanation to why ichthyosis bullosa of Siemens (IBS), a shallow variation of EHK because of predominant *KRT2* mutations,[135] reacts so well to low doses of retinoids.[136] An equivalent option to engineered retinoid treatment is to control the endogenous level of all-trans retinoic acid (tretinoin) by hindering its cellular catabolism in the skin with retinoic acid metabolism blocking agents (RAMBAs).[137] Despite the fact that the danger of teratogenicity should still be considered amid RAMBA treatment, other retinoidal reactions give off an impression of being insignificant and there is no extended impact of the medication after cessation of treatment.

Isotretinoin (Accutane) treatment

Isotretinoin, a retinoid, is commercially available as Accutane (Roche, Switzerland). Due to known adverse effects, isotretinoin should be prescribed to patients with serious instances of ichthyosis when conventional treatment, including systemic antibiotics are not much effective. Further, among females, isotretinoin is indicated only for non-pregnant cases as it can cause severe birth defects, with abnormalities affecting face, eyes, ears, skull, central nervous system, cardiovascular framework, and thymus and parathyroid organs; teratogenicity is well recognized as a serious potential adverse effect. Fifty percent of pregnancies spontaneously abort, and of the remainder about half of the infants are born with cardiovascular or skeletal deformities.[138] Isotretinoin acts by influencing cell-cycle progression, cellular differentiation, cell survival and apoptosis.[139–141] It results in a significant reduction in sebum production, influences comedogenesis, lowers the effect of ichthyosis, has anti-inflammatory properties,[141] and shows diminishing hyperkeratinization. However, accurate mechanism of action of isotretinoin as well as its influence on metabolics of keratinocytes can be further investigated.[142]

Conclusion

Addressing EHK is extremely important for a patient. Not only are the genetics and physiology of the disease important but also the psychological and social impact on the patient needs to be assessed. Preventive measures for EHK as such do not exist since EHK is a form of a genetic condition but specific medications for EHK such as α-hydroxyl acids or topical antibiotics have been used. α-Hydroxy acids are a group of naturally occurring, simple, hygroscopic acids which aid in the hydration of skin.[143] Several compounds and formulations, including aqua-glycolic lotion, when used twice a day are more effective in reducing the severity of EHK than petrolatum-based creams.[144] EHK is usually accompanied with a secondary infection which mostly is malodorous. To reduce odor as well as for a reduction in the incidences of such infections, topical antibiotics and sodium bicarbonate salts can be used.[143] In order to distinguish EHK from the other subtypes of ichthyosis, prenatal diagnosis can be done for better prognosis. These specialized screening tests are generally labor-intensive, very expensive and the biggest drawback of them all being that they are performed in relatively few specific laboratories.

Molecular biology research and genetic advancements in ichthyosis have significantly improved the conventional nosology as well as prognosis of the different conditions. Gene therapy approaches can also be explored, however, safe and practical gene therapy techniques to either treat or prevent EHK still need to be developed.[103] Future scope and advancements can be broadly categorized as: (1) genetic engineering mediated correction of disorders, (2) improved retinoid therapy to develop better oral medicines, (3) an enhanced understanding of fetal keratinization to aid in precise and an earlier prenatal diagnosis, (4) a developed mechanism for detection of carrier states as well as novel noninvasive methods based on optical and spectroscopic techniques for early detection.

Disclosure

The authors report no conflicts of interest in this work.

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