

Xerosis and Ichthyosis: A Brief Review

ABSTRACT

Xerosis is a common skin condition that becomes more prevalent with age and is a prominent feature in ichthyosis. It primarily resulting from abnormalities in the stratum corneum, influenced by factors like natural moisturizing factors, lipid synthesis, and genetic pathologic variants. The diagnosis of xerosis and ichthyosis is usually made clinically, though specific investigations may aid in the diagnosis of specific ichthyoses. Both conditions can have a considerable negative impact on the quality of life of patients. Management includes moisturization and taking preventive measures to maintain skin health and to prevent xerosis.

KEYWORDS: xerosis, ichthyosis, stratum corneum, natural moisturizing factors

Introduction

Xerosis, commonly known as dry skin, is a highly prevalent condition affecting individuals of all ages, ethnicities, and genders.[1] It can be isolated, associated with other dermatoses such as atopic dermatitis or it may result from non-dermatological conditions such as hypothyroidism.[2] Xerosis is a key feature seen in many types of ichthyoses, a group of disorders of keratinization characterized by persistent dry and rough skin with scaling. Both xerosis and ichthyosis can lead to considerable discomfort and a negative impact on the quality of life of patients. This article explores the epidemiology, pathophysiology, clinical features, and management of xerosis and ichthyosis. It will also explore non-syndromic and syndromic ichthyoses.[3]

Epidemiology

Xerosis is quite common worldwide and affects individuals of all age groups and genders. While few studies have specifically investigated the prevalence of xerosis, a large-scale study in Germany with over 40,000 participants revealed that 29.4% of

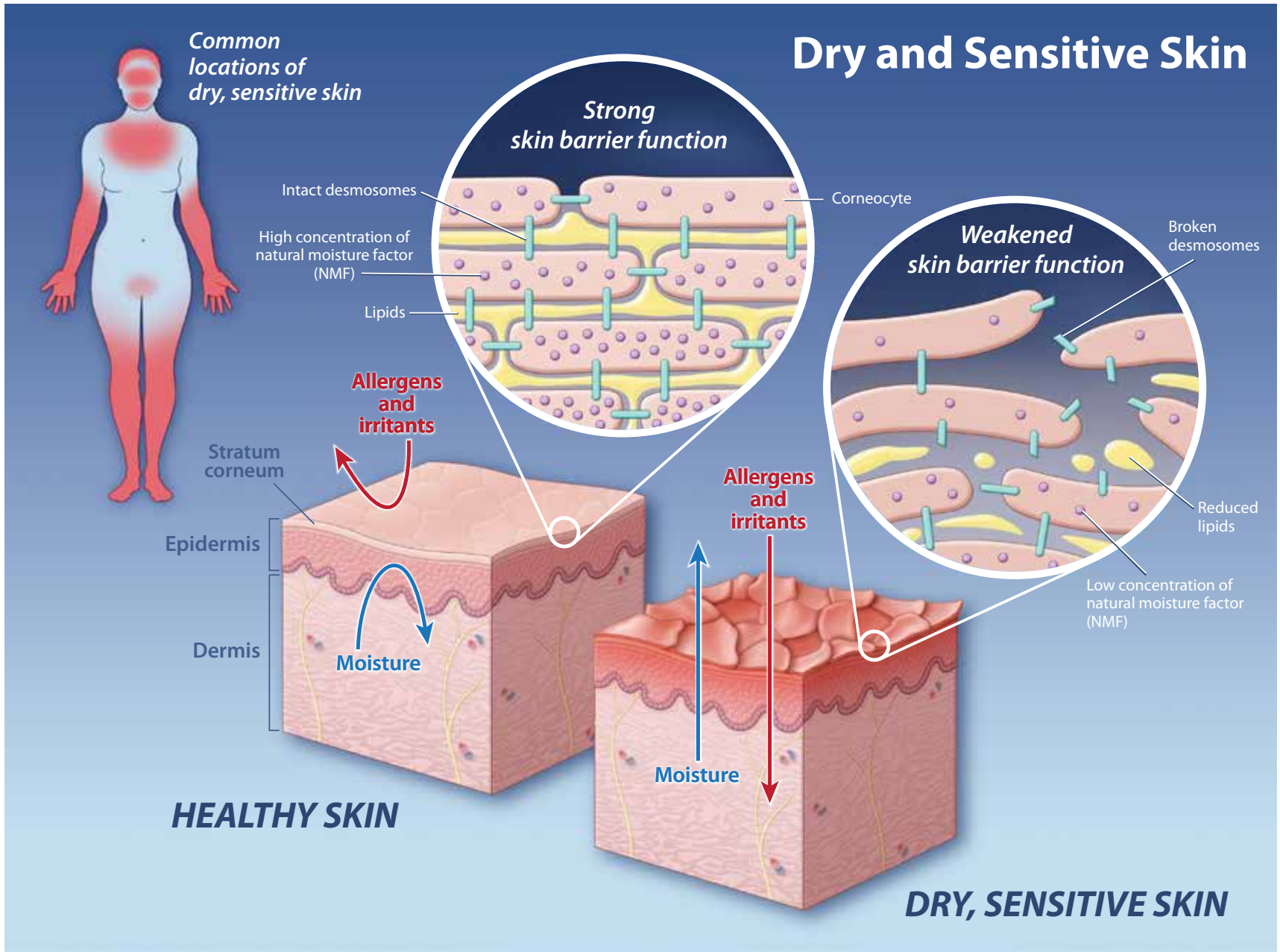
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individuals between the ages of 16 and 70 are affected by xerosis.[1] No gender differences were found. This study also noted that the prevalence of xerosis increased with age. An American study found 60% of individuals over the age of 50 were affected by localized or generalized xerosis.[4]

Ichthyosis vulgaris, X-linked ichthyosis, and autosomal recessive congenital ichthyoses (ARCI) comprise the most prevalent forms of non-syndromic inherited ichthyoses.[5] Ichthyosis vulgaris is the most common non-syndromic ichthyosis with an estimated prevalence of 1:80 to 1:250 individuals.[6,7] The onset of this conditions can be later than other inherited ichthyoses and individuals develop characteristic skin changes in early childhood, often in the first few years of life.[8] Ichthyosis vulgaris is transmitted in an autosomal semi-dominant pattern with homozygous individuals exhibiting a more severe phenotype than heterozygous individuals.[5] Non-syndromic X-linked ichthyosis is the second most common type of inherited ichthyosis with an estimated prevalence of 1:2000 individuals. Given its X-linked recessive inheritance pattern, this condition almost exclusively affects males. The typi-



cal onset of symptoms is within the first three months of life.[9] Autosomal recessive congenital ichthyoses (ARCI) typically present at birth and there may be a family history of this condition.[5,9,10] Studies in Germany and Spain suggest that ARCIs have an estimated prevalence of 1:6250 individuals.[11,12]

Syndromic ichthyoses have other organ involvement in addition to hyperkeratosis and scaling of the skin and are much more uncommon. The prevalence of syndromic X-linked recessive ichthyosis is estimated to be 1:100,000, while the prevalence of all other forms of syndromic ichthyoses is estimated to be 1:1,000,000.[13]

Pathophysiology

The xerosis seen in ichthyosis is mainly due to abnormalities in the stratum corneum, the outermost layer of the epidermis.[14] The stratum corneum can be envisioned as a "brick and mortar structure" composed of corneocytes (bricks) and intercellular lipids (mortar).[15] To maintain its mechanical properties and act as an effective barrier, the stratum corneum requires a water content ranging from 15-20%.[14] Xerosis typically manifests when the water level falls below 10%.[16]

Several processes contribute to the maintenance of the stratum corneum and the preservation of the hydration of the skin.[14] This includes the proliferation, differentiation, and cornification of keratinocytes and the synthesis of intercellular lipids, including ceramides, cholesterol, fatty acid).[14] Additionally, the synthesis of natural moisturizing factor (NMF) contributes to the preservation of hydration as it is highly hygroscopic.[17] The NMF of the skin includes urea, lactic acid derivatives and various amino acids.[2] Aquaporin channels are also essential as they distribute moisture evenly between epidermal layers.[18]

Decreased NMF, lipid synthesis and disruptions to keratinocyte synthesis can all lead to a decrease of water retention in the stratum corneum, causing xerosis.[14] There are several factors that lead to this, including environmental triggers (low humidity, cold weather, and exposure to ultraviolet radiation from the sun), exposure to chemical agents (soap, perfumes, detergents), age-related changes, or comorbid conditions (atopic dermatitis, psoriasis, hypothyroidism).[2,19]

Inherited ichthyoses are due to loss-of-function pathologic variants in specific genessuch as the filaggrin gene (FLG) in ichthyosis vulgaris and the steroid sulfatase gene (STS) in non-syndromic X-linked ichthyosis.[5,8] Syndromic ichthyoses are also caused by specific pathologic variants such the SPINK5 gene in Netherton syndrome and the ALDH3A2 gene in Sjögren-Larsson syndrome.[13]

Differential diagnosis

- Xerosis cutis
- Non-syndromic ichthyoses:
  - Ichthyosis vulgaris
  - X-linked ichthyosis
  - Autosomal recessive congenital ichthyosis
- Syndromic ichthyoses:
  - Sjögren-Larsson syndrome
  - Netherton syndrome
  - Conradi-Hunerman-Happle syndrome
  - Chanarin-Dorfman syndrome
  - Gaucher disease
  - Keratitis-ichthyosis-deafness syndrome
- Asteatotic dermatitis
- Stasis dermatitis
- Atopic dermatitis
- Nummular dermatitis
- Scabies
- Cutaneous T-cell lymphoma
- Psoriasis
- Irritant contact dermatitis
- Causes of acquired ichthyosis:20
  - Metabolic conditions: hypothyroidism, chronic renal failure, chronic hepatic dysfunction
  - Infectious disease: HIV, HTLV
  - Malignancy: Hodgkin's lymphoma, Non-Hodgkin's lymphoma, leiomyosarcoma
  - Autoimmune/Inflammatory disease: dermatomyositis, systemic lupus erythematosus, sarcoidosis
  - Medications: nicotinic acid, hydroxyurea, cimetidine, cholesterol-lowering agents, EGFR inhibitors

History

A thorough inquiry should cover the general characterization of the condition, including the onset, distribution, disease course in terms of continuity and frequency, as well as the duration of symptoms. Associated symptoms such as pruritus, burning sensation, pain, and the sensation of skin tightness should be carefully assessed.[2]

Understanding triggers exacerbating the patient's xerosis, such as temperature, low humidity, sunlight exposure, and environmental conditions like air conditioning or heating, can provide important insights.[19] Inquiring about exogenous factors like bathing or washing habits, contact with irritants, occupational exposures, and recreational activities can contribute to understanding potential aggravating factors. Identifying palliative factors is equally important.

To rule in or out non-syndromic or syndromic ichthyosis, specific details should be explored. For instance, a personal history of atopy (atopic dermatitis, allergic rhinoconjunctivitis, asthma) may be suggestive of ichthyosis vulgaris or Netherton syndrome.[9,13] A history of a collodion membrane at birth may point towards ARCI, X-linked ichthyosis, or syndromic ichthyoses such as Conradi-Hunermann-Happle syndrome, trichothiodystrophy with ichthyosis, Chanarin-Dorfman syndrome, holocarboxylase synthetase defi-

ciency, Gaucher disease or HELIX syndrome (hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia).[9,21] Intellectual deficits, delayed speech and motor development, or seizures may indicate syndromic ichthyoses like Sjögren-Larsson syndrome or perinatal Gaucher disease.[8,13]

Evaluating the presence of other conditions like diabetes, kidney disease, liver or gallbladder issues, and thyroid disease is important, along with a comprehensive list of current medications as it may point to acquired causes of xerosis.[20] The presence of "B symptoms" (fevers, chills, progressive unintentional weight loss) should also be evaluated as they are suggestive of lymphoma.

Assessment of the overall severity of xerosis should include evaluation of its impact on patients' quality of life. The Dermatology Life Quality Index (DLQI) is a established tool that can be used to assess the impact a variety of dermatological conditions, including xerosis, on the quality of life of patients.[22] Conversely, the Ichthyosis Scoring System (ISS) is a more recently developed tool that aims at measuring the severity of ichthyosis in patients.[23]

Physical Examination

Inspection of objective cutaneous findings should be done to note xerosis, scaling, fissures, and erythema. It is important to note the severity, location, and texture of these skin manifestations. It is crucial to examine the entire body, with special consideration for the palms and soles, where xerosis and scaling tend to be more pronounced, and hair. Calculating the body surface area (BSA) affected may also be pertinent.[2]

In cases of inherited ichthyosis, specific signs may be present, such as dark brown or gray scales, asymptomatic corneal opacities, or cryptorchidism in non-syndromic X-linked ichthyosis.[5,11] Keratosis pilaris and palmoplantar hyperlinearity are features suggestive of ichthyosis vulgaris, while ectropion, eclabium, and scarring alopecia are particularly common in lamellar ichthyosis, an ARCI.[3,5,11] Similarly, syndromic ichthyoses may present with specific suggestive signs. For instance, brittle hair may be seen on physical exam for Netherton syndrome or trichothiodystrophy with ichthyosis.[8,13] Neurological signs like spasticity and muscle weakness in the arms and legs may be suggestive of Sjögren-Larsson syndrome.[5,13] Palmoplantar keratoderma is also a feature of certain syndromic ichthyoses, namely keratitis-ichthyosis-deafness syndrome.[8,11,13] A comprehensive physical examination encompassing these aspects aids in the accurate assessment and diagnosis of xerosis and its potential underlying etiologies.

Investigations

The diagnosis of xerosis is clinical based on history and physical examination.[2] Similarly, the diagnosis of hereditary ichthyoses can often be made based on the history, clinical manifestations, associated abnormalities, and family history.[9] Typically, skin biopsies show variable pattern of hyperkeratosis and inflammation, which may be suggestive, but not diagnostic of specific ichthyoses.[9,10] Genetic testing may be considered to confirm the suspected diagnosis of various ichthyoses and for genetic counselling.

Specific investigations may aid in the diagnosis of suspected syndromic ichthyoses. For instance, in Chanarin-Dorfman syndrome, a peripheral blood smear can reveal characteristic lipid vacuoles in granulocytes.[13] In Netherton syndrome, trichoscopy may reveal trichorrhexis invaginata, or bamboo hair, which is pathognomonic for this condition.[5,8,13,24] Conversely, in trichothiodystrophy with ichthyosis, while findings on trichoscopy may be non-specific, polarized light microscopy may show tiger-tail banding of the hair shaft.[13,24] In Conradi-Hunermann-Happle syndrome, plain radiographs of the upper and lower extremities typically reveal stippling of the epiphyses and there is an increased concentration of 8(9)-cholestenol and 8-dehydrocholesterol in plasma, scales from skin lesions, or cultured lymphoblasts or fibroblasts.[13,25]

For suspected cases of acquired ichthyosis, thyroid function, kidney function, and liver function may be assessed biochemically. If there is a suspicion of an infectious process or malignancy, additional investigations may be conducted.[20]

Management

The general approach to managing xerosis involves applying topical moisturizers to the skin with the goal of occluding the surface and reducing transepidermal water loss (TEWL) while augmenting the lipid content of the stratum corneum. In addition to this, preventative measures such as limiting contact with water and wearing soft, loose-fitting clothing, can help minimize triggers or exacerbating factors of xerosis.[2,14]

There are several essential components of moisturizers. Lipids can play a crucial role in using adequate hydration of the skin. Non-physiological lipids such as petrolatum or mineral oils act as occlusives by forming a layer on the skin's surface, thereby preventing water evaporation and reducing TEWL.[14,26] Physiological lipids such as cholesterol, ceramides, and fatty acids penetrate the stratum corneum and improve skin barrier function and membrane fluidity.[14] Additionally, ceramides have a role in signal transduction for keratocyte proliferation.[2]

Humectants such as glycerol and urea also provide moisture

SUMMARY OF KEY POINTS

Xerosis is a common condition worldwide and it is a prominent feature of both syndromic and non-syndromic ichthyoses.

Both xerosis and ichthyosis can have a considerable negative impact on the quality of life of patients.

The diagnosis of xerosis and inherited ichthyoses is based on history, clinical manifestations, associated abnormalities, and family history, but several specific investigations may aid in the diagnosis of syndromic ichthyoses.

Managing xerosis includes applying topical moisturizers with key components like lipids and humectants while proactive preventive measures are vital for preventing triggers of the condition.

to the skin. These substances are highly hygroscopic, and thereby attract and retain water in the stratum corneum.[19,26] Urea has also been shown to help maintain the barrier function and improve the elasticity of the skin when these deficiencies are not due to lipid loss.[27] Glycerol plays a vital role as it is the sole agent capable of preventing or rectifying alterations in aquaporin-3, which is an epidermal transporter responsible for distributing moisture evenly between epidermal layers. This helps enhance skin hydration and elasticity.[28]

Antipruritic agents such as pramoxine or menthol can be helpful in conditions where xerosis is combined with a degree of eczema such as asteatotic dermatitis.[2,29] In such cases, antipruritic agents act by breaking the itch-scratch cycle which prevents the further exacerbation of xerosis.[2,14] Pramoxine is a topical anesthetic and it can have an anti-pruritic effect as the sensations of pain, itch, and temperature are all transmitted through C-type fibers of the peripheral nervous system.[29,30] Similarly, menthol and its derivatives such as menthoxypropanediol can have a transient cooling effect that decreases pruritus through the same sensory conduction pathway.[2,31,32]

Dexpanthenol is a precursor to vitamin B5 and helps increase fibroblast proliferation and lipid synthesis.[14] In clinical trials, this has been found to restore the skin barrier and reduce TEWL.[33] Given it is well tolerated, it is a common ingredient in moisturizers.[2]

The choice of vehicle for a topical moisturizer, whether a lotion, cream or ointment, is important as it influences factors such as skin hydration, moisture retention, cosmetic acceptability, and patient preferences.[34] Climate and seasonal factors can influence the choice of vehicle. In dry or cold climates, ointments may be preferred to provide a stronger barrier against moisture loss. The affected body

area may also affect the choice of vehicle. The skin in facial and abdominal areas are more rich in lipids compared to the upper and lower extremities.[14] Creams may be preferred for the face and abdominal areas or during the summer. Conversely, ointments may be preferred for the extremities or during the winter.

Alongside moisturization, the effective management of xerosis includes proactive preventative measures to minimize triggers and exacerbating factors. These measures include limiting contact with water and advising patients to opt for shorter showers or baths with lukewarm water to prevent excessive moisture loss. The use of mild, non-alkaline soaps, lipid-replenishing synthetic detergents, and bath oils can contribute to a gentler cleansing regimen that safeguards the skin's natural lipid barrier and acidic pH. Encouraging the selection of soft, loose-fitting cotton clothing helps reduce friction and potential irritation. Protection from dry, hot climates and intense sun exposure is vital, as environmental conditions play a significant role in xerosis. Indoor humidity can be improved through the use of humidifiers, helping to maintain skin hydration. By adopting these preventive measures, patients can take proactive steps towards maintaining skin health and preventing the onset or worsening of xerosis.[2,14,19]

Conclusion

Xerosis, or dry skin, is a common condition worldwide, with a prevalence that increases with age. It is a prominent feature of patients with ichthyosis. Xerosis is primarily attributed to abnormalities in the stratum corneum which relies on the structure of corneocytes and intercellular lipids for its mechanical properties, water content, and barrier function. Decreased levels of natural moisturizing factors, disrupted lipid and keratinocyte syn-

CLINICAL PEARLS

Understanding and addressing triggers such as temperature, low humidity, sunlight exposure, and environmental conditions like air conditioning or heating can be essential in managing xerosis effectively.

Evaluating the overall severity of xerosis and ichthyosis may include the use of established tools like the Dermatology Life Quality Index (DLQI) and the newer Ichthyosis Scoring System (ISS) to assess their impact on patients' quality of life.

Identifying signs such as brittle hair, neurological abnormalities, and palmoplantar keratoderma can be suggestive of syndromic ichthyoses. These indicators are valuable for recognizing these rare conditions and guiding further examination or evaluation.

thesis, and pathological variants in specific genes are key factors leading to xerosis in both inherited and syndromic forms of ichthyosis. The diagnosis of xerosis and inherited ichthyosis is based on history, clinical manifestations, associated abnormalities, and family history. Several specific investigations may aid in the diagnosis of syndromic ichthyoses. The management of xerosis involves using topical moisturizers containing components like occlusive agents, humectants, and emollients in an appropriate vehicle. In addition, proactive preventive measures play a crucial role in maintaining skin health and preventing xerosis.

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Xerosis Key Points for the Practitioner

History (key points to cover)

- Onset, distribution, disease course, and symptom duration, including assessing associated symptoms like pruritus and pain
- Environmental triggers such as temperature, humidity, and sunlight exposure
- Exogenous factors like bathing habits, contact with irritants, and occupational exposures
- Specific details to help in distinguishing non-syndromic and syndromic ichthyosis, including a history of atopy, collodion membrane at birth, and intellectual or motor deficits
- Conditions that can cause secondary ichthyosis such as diabetes, kidney disease, and thyroid issues, as well as a list of medications
- To assess severity and impact on quality of life, tools like the Dermatology Life Quality Index (DLQI) and the Ichthyosis Scoring System (ISS) can be used

Physical Examination (key things to note)

- Examine the entire body and note the morphology, location, severity and texture of cutaneous findings, with a special focus on palms and soles
- Assess the hair for any abnormalities such as brittle hair or scarring alopecia
- Calculating the affected body surface area (BSA) may be relevant
- Assess signs that may be present in inherited ichthyoses such as keratosis pilaris, palmoplantar hyperlinearity, corneal opacities, or neurological symptoms.

Selected DDx (key entities to consider and differentiating features)

- Xerosis
- Non-syndromic ichthyosis:
  - Ichthyosis vulgaris: associated with keratosis pilaris, palmar hyperlinearity, and atopy
  - X-linked ichthyosis: Affects males, collodion membrane at birth, corneal opacities, cryptorchidism
  - Autosomal recessive congenital ichthyosis: collodion membrane at birth, ectropion and eclabium
- Syndromic ichthyoses:
  - Sjögren-Larsson syndrome: delayed speech and motor development and neurological symptoms such as spasticity or seizures
  - Netherton syndrome: trichorrhexis invaginata and associated with atopy
  - Conradi-Hunermann-Happle syndrome: collodion membrane at birth, stippling of the epiphyses on x-ray and high levels of sterols in the blood
  - Chanarin-Dorfman syndrome: collodion membrane at birth, peripheral blood smear with lipid vacuoles in granulocytes

Xerosis and Ichthyosis Information for the Patient and Family

What are xerosis and ichthyosis?

Xerosis, which is a medical term for dry skin, is a common problem that can affect anyone, regardless of their age or gender. It can make your skin feel rough and uncomfortable. Sometimes, it happens all by itself, but it can also be linked to other skin issues like eczema or even conditions like an underactive thyroid. Inherited forms of dry skin, or ichthyosis, can cause your skin to be very dry, rough, scaly, and can be associated with other features unrelated to the skin. Unlike xerosis, which can happen at any age, ichthyosis often shows up right after birth or in the first few months of life.

What causes xerosis and ichthyosis?

Xerosis occurs when the outermost layer of our skin, known as the stratum corneum, doesn't have enough water. Several factors contribute to maintaining this moisture balance in the skin, such as the production of skin cells, making a fatty layer in the skin, and natural moisturizing factors. Environmental factors, like low humidity, exposure to harsh chemicals, and certain health conditions, can disrupt this balance, leading to xerosis. Ichthyosis, in contrast, is a rarer condition that is usually due to changes in specific genes responsible for skin development.

How can these conditions be treated?

1. **Hydration:** Treating xerosis involves using moisturizers, which act as a shield for your skin. It helps by sealing in moisture and preventing water loss. There are different types of moisturizers, including those with lipids that create a protective layer on your skin, reducing water evaporation.
2. **Attracting Moisture:** Some moisturizers contain ingredients like glycerol and urea. These are like moisture magnets. They attract water and keep it in your skin. This is especially useful if you have severely dry skin.
3. **Relief from Itching:** If dry skin makes you itchy, there are moisturizers available that contain substances like menthol. These help soothe the itching, so you're less likely to scratch, which can make your skin worse.
4. **Enhancing Skin Health:** Certain moisturizers contain dexpanthenol, which acts like a skin vitamin. It promotes the production of essential components in your skin, helping it stay healthy and less prone to dryness.
5. **Choosing the Right Moisturizer:** The type of moisturizer you need depends on where you plan to apply it and the time of year. In dry, cold climates, thicker creams or ointments are beneficial because they create a strong barrier that locks in moisture. For your face, especially in the summer, lighter lotions work well. It's all about personal preference and what suits your needs.
6. **Preventing Dryness:** In addition to using moisturizers, you can take proactive measures to prevent dry skin. This includes taking shorter showers with lukewarm water, using gentle non-soap cleaners like synthetic detergents, and opting for soft clothing that reduces friction. Protecting your skin from dry, hot weather and excessive sun exposure is vital because environmental factors play a significant role in dry skin. Using humidifiers in indoor spaces can also help maintain the moisture levels in your skin.