

PROBLEMS OF ICHTHYOSIS : A REVIEW

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Abstract:

Many medical mysteries in the past took on supernatural overtones because of superstitions, folk lore, and scientific ignorance. Though much had been learned medically about the human organism, there were many diseases and disorders thought of as diabolic. One such disease which congenital, dermatological disease represented by thick and scaly skin known as Ichthyosis.

It is one of the rarest diseases. Aberrant keratinization is the main cause of this disease. Extremely dry and scaly skins are the marked symptoms of it, and for such kind of symptoms ABCA12 gene is responsible. Main point is this that the ichthyosis does not show any life shortening effect. Purpose of studying this disease is to aware people about it. What kind of treatment are given, the how people suffering from it face such kind of diseases and which are types of ichthyosis are mentioned in it.

Keywords: Hyperkeratosis, dry and scaly skin, fishy skin, ABCA12 gene

1. Introduction

Ichthyosis^{1,5}

The disease is a group of skin disorders characterized by increased or aberrant keratinisation, resulting in dryness, roughness, and scaliness of the skin. Ichthyosis is a family of genetic skin disorders characterized by dry, scaling skin that may be thickened or very thin. The prefix "ichthy" is taken from the Greek root for the word fish. Each year, more than 16,000 babies are born with some form of ichthyosis. Ichthyosis affects people of all ages, races and gender. The disease usually presents at birth, or within the first year, and continues to affect the patient throughout their lifetime."

2. Types of ichthyosis^{1,5}

Table 1: List of types of ichthyosis along with their signs and symptoms

Sr.No	Type of ichthyosis	Clinical features
1	Harlequin Ichthyosis ^{2,5}	<ul style="list-style-type: none"> Thickening of keratin layer in fetal human skin Skin contains massive, diamond-shaped scales and tends to have a reddish colour. In addition ear, penis and the appendages may be abnormally contracted
2	Xeroderma ^{1,5}	<ul style="list-style-type: none"> Multiple basal cell carcinomas and other skin malignancies frequently occurs at young age

		<ul style="list-style-type: none"> • This involves both sexes and all races
3	Ichthyosis vulgaris ^{1,4,5}	<ul style="list-style-type: none"> • At birth skin may appear normal • Skin gradually becomes dry, rough and scaly, with most signs and symptoms appearing by the age of 5 • Can affect all parts of the body, including the face and scalp. Bends of arms and legs usually spared. • Palms are excessively lined • Associated with atopic dermatitis
4	Lamellar ichthyosis ⁵	<ul style="list-style-type: none"> • Often called collodion baby as at birth the baby is covered by a thickened collodion-like membrane which is then shed • Scaling occurs over the whole body, including creases and bends • May result in drooping lower eyelids (ectropion) • Prenatal testing in subsequent pregnancies is available in some centers • May be associated with mutation in transglutaminase 1 gene
5	X-linked ichthyosis ⁴	<ul style="list-style-type: none"> • Generalized scaling is present at or shortly after birth • Scaling is most prominent over the extremities, neck, trunk, and buttocks • May cause corneal opacities • Associated with steroid sulphatase deficiency in fibroblasts and elevated plasma cholesterol sulphate • Only affects males • May be associated with

2.1 Harlequin ichthyosis^{1,2,5}

Harlequin ichthyosis is a severe genetic disorder that mainly affects the skin. Infants with this condition are born with very hard, thick skin covering most of their bodies. The skin forms large, diamond-shaped plates that are separated by deep cracks (fissures). These skin abnormalities affect the shape of the eyelids, nose, mouth, and ears, and limit movement of the arms and legs. Restricted movement of the chest can lead to breathing difficulties and respiratory failure.

2.1.1. Pathophysiology²

The skin normally forms a protective barrier between the body and its surrounding environment. The skin abnormalities associated with harlequin ichthyosis disrupt this barrier, making it more difficult for affected infants to control water loss, regulate their body temperature, and fight infections. Infants with harlequin ichthyosis often experience an excessive loss of fluids (dehydration) and develop life-threatening infections in the first few weeks of life. It used to be very rare for affected infants to survive the newborn period. However, with intensive medical support and improved treatment, people with this disorder now have a better chance of living into childhood and adolescence.

Harlequin-type ichthyosis (also known as "Harlequin baby" Harlequin ichthyosis, ichthyosiscogenita, Ichthyosisfeatalis, keratosis diffusafeatalis, "Harlequin fetus" and "Ichthyosis cogenitagravior" a skin disease, is the most severe form of congenital ichthyosis, characterized by a thickening of the keratin layer in fetal human skin. In sufferers of the disease, the skin contains massive, diamond-shaped scales, and tends to have a reddish color. In addition, ears, penis, and the appendages may be abnormally contracted. The scaly keratin greatly limits the child's movement. Because of resultant cracked skin in locations where normal skin would fold, it is easily pregnable by bacteria and other contaminants, resulting in serious risk of fatal infection.

The harlequin-type designation comes from both the baby's apparent facial expression and the diamond-shape of the scales which are caused by severe hyperkeratosis. The disease can be diagnosed in the uterus by way of fetal skin biopsy or by morphologic analysis of amniotic fluid cells obtained by amniocentesis. In addition, doctors can now usually recognize common features of the disease through ultrasound, and follow up with 3D ultrasound to diagnose the condition. It is associated with a mutation in the gene for the protein ABCA12.

Harlequin ichthyosis is very rare; its exact incidence is unknown.

Mutations in the ABCA12 gene cause harlequin ichthyosis. The ABCA12 gene provides instructions for making a protein that is essential for the normal development of skin cells. This protein plays a major role in the transport of fats (lipids) in the outermost layer of skin (the epidermis). Some mutations in the ABCA12 gene prevent the cell from making any ABCA12 protein. Other mutations lead to the production of an abnormally small version of the protein that cannot transport lipids properly. A loss of functional ABCA12 protein disrupts the normal development of the epidermis, resulting in the hard, thick scales characteristic of harlequin ichthyosis.

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

2.2. Xeroderma Ichthyosis^{1,5}

Xeroderma Pigmentosum, or XP, is an autosomal recessive genetic disorder of DNA repair in which the ability to repair damage caused by ultraviolet (UV) light is deficient. In extreme cases, all exposure to sunlight must be forbidden, no matter how small; as such, individuals with the disease are often colloquially referred to as Children of the Night.

2.2.2. Pathophysiology

The most common defect in Xeroderma Pigmentosum is an autosomal recessive genetic defect in which nucleotide excision repair (NER) enzymes are mutated, leading to a reduction in or elimination of NER. If left unchecked, damage caused by ultraviolet (UV) light can cause mutations in individual cell's DNA. If tumor suppressor genes or proto oncogenes are affected, the result may be cancer. Patients with XP are at a high risk for developing skin cancers, such as basal cell carcinoma, for this reason.

Normally, damage to DNA in epidermal cells occurs during exposure to UV light. The absorption of the high energy light leads to the formation of pyrimidine dimers, namely cyclobutane-pyrimidine dimers and pyrimidine-6-4-pyrimidone photoproducts. In a healthy, normal human being, the damage is first excised by endonucleases. DNA polymerase then repairs the missing sequence, and ligase "seals" the transaction. This process is known as nucleotide excision repair.

2.3. X-linked ichthyosis^{1,3,5}

X-linked ichthyosis (XLI) is a skin condition caused by the hereditary deficiency of the steroid sulfatase (STS) enzyme that affects 1 in 2000 to 1 in 6000 males. Hence also known as steroid sulphatase deficiency. XLI manifests with dry, scaly skin and is due to deletions or mutations in the STS gene. XLI can also occur in the context of larger deletions causing contiguous gene syndromes. Treatment is largely aimed at alleviating the skin symptoms.

2.3.1. Pathophysiology^{4,5}

The STS gene is located on the X chromosome at band Xp22.3. Thus, the syndrome is an X-linked condition, and it affects males and females differently.

The 23rd pair of chromosomes is typically termed the "sex chromosomes". Females have two X chromosomes and males have one X and one Y chromosome. Therefore, in normal individuals, males carry a single copy of the STS gene and females carry two copies. This gene partially escapes X-inactivation and females normally express higher amounts of the STS enzyme than males.

XLI can occur through new deletions or mutations of the STS gene but is more commonly inherited from a carrier mother. A homozygous deletion or mutation of the STS gene in male results in complete absence of enzyme activity, while a female carrier of a mutation or deletion is heterozygous and still has a normal copy of the STS gene. Female carriers of an STS deletion or mutation still express the STS enzyme, although with decreased enzyme activity. For this reason, XLI most commonly affects males, although individuals with numeric abnormalities of the sex chromosomes (45, X and 47, XXY) who also carry STS deletions or mutations would be exceptions to this rule. In addition, a female could be affected if she were the offspring of an affected male and a carrier female and inherited a deletion or mutation of the STS gene on both X chromosomes.

Since the majority of cases appear to occur through transmission of STS deletion from a carrier mother, enzyme testing or DNA testing should be performed in the mother of any newly diagnosed simplex case (i.e. the first

case in a family). In the case of an extended family with many affected individuals, carrier status can often be assigned based on pedigree analysis.

- Males with XLI will transmit the X chromosome harboring the *STS* deletion or mutation to each of his female offspring, who will therefore be an obligate carrier. However, all male offspring will be unaffected, since they receive their father's Y chromosome.
- Female carriers of an *STS* deletion or mutation have a 50% chance with each pregnancy of transmitting it to an offspring. Thus, each male offspring has a 50% chance of being affected by XLI, while each female offspring has a 50% chance of being a carrier for this condition. Any individual that inherits the mother's normal copy of the *STS* gene will be unaffected and will have an extremely low chance of having a child affected with this condition.

Due to random segregation of the chromosomes during gametogenesis, each pregnancy will be subject to the same probabilities, regardless of the number of previously affected or unaffected offspring. It should be noted that the above recurrence risks are based on the assumption that an affected male or carrier female will have children with an unaffected or non-carrier individual. The risks of having affected offspring would clearly increase in the case of a union between a male with XLI and a carrier female.

2.4. Ichthyosis vulgaris^{1,4,5}

In United States Ichthyosis vulgaris is the most common form and is an autosomal dominant trait with an incidence of 1 case per 300 populations.

2.4.1. Pathophysiology^{4,5}

Ichthyosis vulgaris is characterized by onset in early childhood, usually between age 3 and 12 months, with fine scales and varying degrees of dryness of the skin. Scaling is most prominent over the trunk, abdomen, buttocks, and legs. The flexural areas, such as the antecubital fossa, are spared. An association may be present between ichthyosis vulgaris and atopic diseases because one third to one half of patients show features of atopic disease and a similar proportion have relatives with atopic disease. A reported 11.5% association is noted between atopic dermatitis and primary hereditary ichthyosis. Ichthyosis vulgaris typically produces no significant ocular findings; however, scaling may be present on the eyelid skin, which could lead to punctate epithelial keratitis and recurrent corneal erosion.

- Two loss-of-function mutations in the coding of the filaggrin gene have been identified in both ichthyosis vulgaris and atopic dermatitis. Keratohyalin synthesis is affected because of the filaggrin mutation. Filaggrin is an epidermal protein that normally functions as a barrier molecule against environmental allergens, water loss, and infection.
- In epidermolytic hyperkeratosis, a mild generalized erythroderma is present at birth. Bullae formation may occur, which may become infected and give rise to a foul skin odor. Erythroderma fades in infancy while the characteristic grey, waxy scale progresses. They are particularly prominent in the flexural creases. A mutation in the keratin genes (i.e., *KRT1*, *KRT10*) is the cause of this autosomal dominant disorder.

2.5. Lamellar ichthyosis⁵

Lamellar ichthyosis (LI) is an autosomal recessive disorder that is apparent at birth and is present throughout life. The newborn is born encased in a collodion membrane that sheds within 10-14 days. The shedding of the membrane reveals generalized scaling with variable redness of the skin. The scaling may be fine or plate like,

resembling fish skin. Although the disorder is not life threatening, it is quite disfiguring and causes considerable psychological stress to affected patients.

Lamellar ichthyosis affects all populations. Incidence in males and females is equal. The disease is present at birth and continues throughout life. A rare phenotype of lamellar ichthyosis has been described in South Africa. The term bathing-suit ichthyosis describes the characteristic distribution of the lesions, which involve the trunk, the proximal parts of the upper limbs, the scalp, and the neck, with sparing of the central face and extremities. This form of lamellar ichthyosis is caused by a homozygous missense mutation in TGM1.

2.5.1. Pathophysiology

Patients with lamellar ichthyosis have accelerated epidermal turnover with proliferative hyperkeratosis. This involves a mutation in the gene for transglutaminase 1 (TGM1). There are at least 14 identified different TGM1 mutations. The transglutaminase 1 enzyme is involved in the formation of the cornified cell envelope. The formation of the cornified cell envelope is an essential scaffold upon which normal intercellular lipid layer formation in the stratum corneum occurs. Thus, mutations in the TGM1 secondarily cause defects in the intercellular lipid layers in the stratum corneum, leading to defective barrier function of the stratum corneum and to the ichthyotic phenotype seen in lamellar ichthyosis patients and in transglutaminase 1 knockout mice. To date, 6 genes for lamellar ichthyosis have been localized and 5 of them identified, as follows: TGM1 (14q11), ABCA12 (2q34), 19p12-q12, ALOXE3-ALOX12B (17p13), ichthin (5q33).

2.6 autosomal recessive congenital ichthyosis and congenital ichthyosisform erythroderma (cie) type 1^{6,7,8}

ARCI is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% risk of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if both pathogenic variants have been identified in a family.

4. General treatment for ichthyosis^{8,9}

In the past, the disorder was always fatal, whether due to dehydration, infection (sepsis), restricted breathing due to the plating, or other related causes. The most common cause of death was systemic infection and sufferers rarely survived for more than a few days.

However, there have been improvements in care, most notably retinoid such as the drug Isotretinoin (Isotrex). The oldest known survivor, who was born in 1984 and is in relatively good health, Lifespan limitations have not yet been determined with the new treatments.

4.1. Care Taken While Bathing or showering

- Make sure you soak and have plenty of time to bathe and get ready.
- Try not to take overly hot baths and showers.
- We have found Dove soap to be the best because it is gentler than other soaps and has moisturizers so it won't dry out your skin (even more).
- Use a rough textured bathing glove (can be found at dollar stores) and exfoliate your skin really well. Pay a lot of attention to your feet.
- As much as we hate to touch dry yarn, a yarn wash cloth in the bath works really well on more sensitive areas to exfoliate.

Ask your doctor about Selenium Sulfide, you can only get it by prescription. It's for your scalp and/or skin, It looks and smells a lot like liquid foundation but it is amazing stuff. We should use it for our scalp and have had amazing results.

4.2. Care Taken After Bath or Shower

- Don't rub your skin with the towel just pat dry so your skin is still a little damp.
- Immediately apply a lotion or cream (prefer something with Urea in it or Lubriderm) from head to toe.
- For feet we should prefer Petroleum jelly and then put on a pair of thick socks.
- When it comes to perfumes or cologne it is best to put it on your top layer of clothes so you don't irritate your skin.
- Also a good alternative (mainly for women) is having a pair of cotton leggings and a snug long sleeved shirt works too.

4.3. Medication

Oral retinoid display an impressive antikeratinizing action in ichthyosiform dermatoses. Acitretin (25-50 mg/d) and Isotretinoin (0.5-2 mg/kg/d) have been shown to reduce scaling, discomfort, and disfigurement. However, when these drugs are discontinued, the ichthyotic skin recurs, thereby necessitating long-term use.

Liarozole (150 mg bid), an imidazole derivative, inhibits the cytochrome P450-dependent 4-hydroxylation of retinoic acid, resulting in increased tissue levels of retinoic acid and a reduction in epidermal proliferation and scaling. It is a broad-spectrum antifungal agent; inhibits cytochrome P450 metabolic pathways, increasing levels of cytochrome P450 metabolized drugs. The US FDA has not approved this medication for use. Patients with epidermolytic hyperkeratosis may develop chronic bacterial infections of the skin necessitating long-term antibiotic therapy. N-acetylcysteine 10% emulsion, a nontoxic and hypoallergenic amino acid derivative, can be safely and efficaciously used in the topical treatment of neonatal ichthyosis.

A. Retinoid-like Agents

These agents decrease cohesiveness of abnormal hyperproliferative keratinocytes and may reduce potential for malignant degeneration. They modulate keratinocyte differentiation and have been shown to reduce risk of skin cancer formation in renal transplant patients.

- **Isotretinoin (Amnesteem, Claravis, Sotret)**

The synthetic 13-cis isomer of the naturally occurring tretinoin (Trans-retinoic acid). Both agents are structurally related to vitamin A.

- **Acitretin (Soriatane)**

Metabolite of etretinate and related to retinoic acid and retinol (vitamin A). Mechanism of action unknown but thought to exert therapeutic effect by modulating keratinocyte differentiation, keratinocyte hyperproliferation, and tissue infiltration by inflammatory cells.

B. Antibiotics:

Patients with epidermolytic hyperkeratosis may develop chronic bacterial infections of the skin necessitating long-term antibiotic therapy.

- **Erythromycin (EES, Ery-Tab, Erythrocin)**

This is for patients with epidermolytic hyperkeratosis who develop bacterial infections of the skin.

C. Keratolytic agents:

These agents are used to prevent cicatricialelectropion in lamellar ichthyosis; a humidified atmosphere combined with the use of topical moisturizing agents is beneficial. Petrolatum ointment and 10% urea cream applied to the eyelid skin several times daily helps to prevent skin contracture. Salicylic acid 2% and retinoic acid 0.1% ointments are also effective, but local irritation may limit their frequency of use.

- **Urea (Ureacin, Carmol, Keralac)**

Promotes hydration and removal of excess keratin in conditions of hyperkeratosis

D. Ophthalmic Lubricants:

In chronic ocular surface disorders associated with ichthyosis, no preserved artificial tears (carboxymethylcellulose sodium 0.5-1.0%) and ointment (white petrolatum 56.8%, mineral oil 41.5%) are preferred to prevent complications from dryness and exposure. Preservative-free lubricants may be used as often as needed while decreasing the incidence of preservative-related allergies. In cases where poor corneal epithelial adhesion is present, bandage contact lenses and temporary collagen shields may decrease symptoms and promote surface healing.

- **Carboxymethylcellulose 0.5 to 1% (Optive, Refresh Plus)**

Lubricates and relieves dry eyes and eye irritation associated with deficient tear production.

E. Mucoytic Agents:

Agents in this category may prove effective in the topical treatment of neonatal ichthyosis.

- **N-acetylcysteine (Acetadote)**

N-acetylcysteine is a glutathione precursor. It may provide effective photoprotection by increasing the availability of glutathione, a potent antioxidant. A nontoxic 10% emulsion and hypoallergenic amino acid derivative can be safely and efficaciously used in the topical treatment of neonatal ichthyosis.

5. Conclusion:

Ichthyosis is rarest skin disorder, mostly due to genetic modification in the body. Various types of ichthyosis causes due to various conditions and their treating terms are also different. But the main highlight of this disease is that it is not the contagious disorder and it do not affect on life span of patient.

The terms and conditions for taking care of ichthyosis causing person are quite difficult to maintain. Any particular or specific medicines do not cure this disease, moisturizing the skin; applying lotions on skin are the primary circumstances to treat it. Along with it surgical, medicinal care should be done proper diet should be follow. Completely it is not get cure but the can be managed at certain levels.

Knowledge regarding this condition and treating care of it is possible by reviewing this disease. People get aware about it and at some level they will try to take care of their skin is the main purpose of studying ichthyosis.

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