ZEBRAS OF MEDICINE
COMPARING HARLEQUIN ICHTHYOSIS AND ICHTYOSIS VULGARIS

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Abstract

Review

BACKGROUND: Ichthyoses are a group of cutaneous disorders that are characterised by cutaneous scaling. Ichthyosis vulgaris is relatively common, and most of these patients have a mild phenotype. Harlequin ichthyosis is a rare disorder, its presentation is impressive, and this disease has a high mortality rate.
OBJECTIVE: This article aims to introduce ichthyoses as a group of cutaneous disorders and to highlight ichthyosis vulgaris with harlequin ichthyosis.
CLINCAL PRESENTATION: Ichthyosis vulgaris is caused by loss-of-function mutations in the *FLG gene*. Children born with ichthyosis vulgaris do not show any signs of disease at birth. It is often sufficient to treat these patients with moisturising ointments and keratolytics.
Harlequin ichthyosis is caused by loss-of-function mutations in the *ABCA12* gene. In contrast to ichtyosis vulgaris, children born with harlequin ichthyosis typically present with extreme hyperkeratosis. The barrier function of the skin is impaired due to scaling, which can result in a high risk of infection and other negative effects. Therefore, the mortality rate in the neonatal period is high, which is why the newborn should be treated in a neonatal intensive care unit. In a later stage in life, ointment needs to applied on the child's skin multiple times a day and frequent baths need to be taken to wash off excess skin.
CONCLUSIONS: There are multiple mutations identified that cause a specific type of ichthyosis. Phenotypes can be widely varying in severity of disease.

KEYWORDS: cutaneous disorders, hyperkeratosis, *FLG gene*

Introduction

To understand cutaneous disorders like ichthyosis, it is first important to know more about the different layers of the skin. The skin has a total of three layers: the epidermis, the dermis and the hypodermis. The epidermis is the outer layer, and it has three functions: producing new epithelial cells (keratinocytes), expressing skin tone through melanocytes and providing a waterproof barrier to the outside world [1]. The epidermis itself is also made of layers, mentioned here from top to bottom: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. New keratinocytes are produced in the stratum basale. While these new cells are produced, old cells are pushed up to the stratum corneum. The upper layer, the stratum corneum consists of 15-30 layers of dead keratinocytes, and these slowly shed to make room for new cells. In a healthy skin, the stratum corneum is replaced entirely in about four weeks. The dermis is the middle layer of the skin and is composed of connective tissue. It contains a lot of structures, such as hair follicles, sweat glands, nerves, blood and lymph vessels. The hypodermis is the last layer of the skin and connects the dermis with the underlying fascia of bones and muscles. The hypodermis consists of loose connective tissue and fat, providing fat storage and insulation [1, 2].

Ichthyoses are a heterogeneous group of cutaneous disorders that are characterised by abnormal epidermal differentiation caused by genetic mutations. If a patient has ichthyosis, the process of renewing keratinocytes and transporting them from the stratum basale to stratum corneum is disturbed. A minor genetic error can cause a skin with an impaired barrier function and/or hyperkeratosis and scaling, as seen in ichthyosis [3]. Examples of these errors are: abnormal lipid composition, absence of lamellar membranes and incomplete differentiation of keratinocytes.

The word ichthyosis is derived from the Greek word *ichthys*, which means fish. It refers to the cutaneous scaling seen in this disease that resembles scales of a fish. This scaling can be localised or generalised [4]. Some of the disorders within this group are rare, others more common. Ichthyosis vulgaris, whereby most patients have a mild phenotype, has an estimated incidence of one in 250 live births [5]. Variants that are rare, such as lamellar and harlequin ichthyosis, have an estimated incidence of one in 200,000 live births. In this article, we will highlight ichthyosis vulgaris with harlequin ichthyosis. Furthermore, we will discuss its presentation, the first care of the newborn, diagnosis and further treatment options.

Clinical presentation

Children born with ichthyosis vulgaris do not show any signs of the disease at birth. During their first year of life, fine white to grey scaling will appear. The scaling is most prominent on the abdomen and extensor surfaces of the extremities, while flexures and face are spared.

Children born with harlequin ichthyosis typically present with extreme hyperkeratosis and already fissured skin, resembling a knight wearing a body armour. Commonly present is eversion of the eyelids (ectropion), eversion of the lips (eclabium) and deformation of the ear. These newborns often have respiratory distress at birth due to restricted chest wall expansion. After seeing a newborn with harlequin ichthyosis, one will remember it for a lifetime. Sometimes children born with severe forms of ichthyosis, whether it is ichthyosis vulgaris or harlequin ichthyosis, manifest at birth with a collodion membrane. This thin transparent membrane covers the newborn's body for his first few weeks of life, resembling plastic foil. The collodion membrane slowly disappears with the application of ointment, and will sometimes be replaced by hyperkeratotic skin with dark scaling. A self-healing collodion baby also exists, whereby the membrane slowly disappears and is replaced by healthy skin [6].

First care for the newborn

Newborns affected by severe forms of ichthyosis are exposed to various risks. They need supportive care to prevent infection, dehydration and starvation. The barrier function of the skin is impaired due to scaling and

impaired barrier function of the skin, which can result in transepidermal water loss and increased heat loss. Therefore, the newborn should be treated in a neonatal intensive care unit and his vital signs should be closely monitored. An incubator with increased humidity around 50-70% is ideal, as the newborn will dehydrate quickly. Furthermore, a calorie-dense diet should be offered because of the high metabolic rate of these newborns. Currently the mortality rate in the neonatal period for harlequin ichthyosis is around 50%, but improved neonatal intensive care and oral retinoids may increase survival [7]. The use of oral retinoids will be explained later in this article.

Diagnosis

Diagnosis of ichthyosis is a combination of clinical findings and histopathologic findings. The physician first examines the skin phenotype and pays attention to the following details: scale pattern, skin colour, presence of a collodion membrane, erythroderma, erosions or blistering, photosensitivity and hair abnormalities. Parents are asked about the time of onset, development over time and the family history regarding ichthyosis. A skin biopsy can provide additional information to find the diagnosis. Genetic testing is more specific, as multiple genetic mutations have been identified that cause syndromes associated with ichthyosis, such as the Kallmann syndrome and Netheron syndrome.

Ichthyosis vulgaris is caused by loss-of-function mutations in the *FLG* gene and is autosomal semi-dominantly inherited [8]. Patients with one mutated allele have a mild phenotype, patients with two mutated alleles have a more severe phenotype. Still, the phenotype varies considerably. Histologically, ichthyosis vulgaris is characterised by a reduction of keratohyalin granules or an absence of the stratum granulosum in electron microscopy.

Harlequin ichthyosis is caused by loss-of-function mutations in the *ABCA12* gene [9]. *ABCA12* encodes for an ATP-binding cassette transporter, which is a lipid transporter in keratinocytes. These mutations result in a loss of the skin lipid barrier. Histologically, harlequin ichthyosis is characterised by extreme hyperkeratosis, follicular plugging and the absence of lamellar bodies and lipid bilayers in electron microscopy [10].

Further treatment

Patients with ichthyosis vulgaris often experience seasonal variation in severity. The condition of the skin improves in warm and sunny weather with a high degree of humidity and worsens in dry and cold weather. Moisturising ointments and keratolytics are often sufficient as treatment. Patients with ichthyosis vulgaris have an increased risk for atopy, especially atopic eczema because of the impaired skin barrier and should be checked for asthma and allergies

Patients with harlequin ichthyosis that survive the neonatal period need lifelong treatment. Ichthyosis is a chronic skin disorder that takes a lot of time to manage, especially for the parents or caretakers. Ointment needs to applied on the child's skin multiple times a day and frequent baths need to be taken to wash of excess skin. Monitoring vitamin D levels is also important, as children with harlequin Ichthyosis tend to get limited sun exposure [11]. Intermittent use of oral retinoids such as acitretin is often prescribed. Oral retinoids are frequently used in keratinisation disorders of the skin, such as psoriasis or ichthyosis. Retinoids normalise epidermal cell proliferation, differentiation and cornification [12]. They also accelerate shedding of hyperkeratotic skin [13]. Futhermore, they help to reduce ectropion of the eyelids without needing surgical procedures [12, 14]. However, there are some serious side effects associated with the use of retinoids, which includes teratogenicity, dryness and irritation of mucous membranes, thinning of the skin, hair loss, photosensitivity, hepatotoxicity, hyperlipidaemia and skeletal abnormalities [13].

Furthermore, psychological aspects of this disease should not be forgotten; support from other patients and a psychologist could be helpful. However, there is very little scientific research available about the quality of life of patients with ichthyosis. A specific quality of life questionnaire has been developed for families of patients with ichthyosis, but no other studies have been published using this questionnaire [15]. *Readers who are interested in stories from a patient's perspective, can visit the website of the Foundation for Ichthyosis and Related Skin Types at http://www.firstskinfoundation.org.*

Conclusion

Ichthyoses are a heterogeneous group of cutaneous disorders. There are multiple mutations identified that cause a specific type of ichthyosis. Phenotypes can be widely varying in severity of disease. Newborns with harlequin ichthyosis need to be admitted to a neonatal intensive care unit, but unfortunately the mortality rate is around 50%, whereas patients with ichthyosis vulgaris are born healthy and only show symptoms later in life.

Acknowledgements

RAMS would like to thank dr. H.D. De Koning, MD PhD, Mauritskliniek Nijmegen, the Netherlands for proofreading and providing feedback on this article.

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