Clinical Characteristics And Etiology of Ichthyosis Vulgaris: A Review

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Abstract
The skin is the most extensive organ of the human body, which fulfills multiple functions in the organism, the most important of which is protection. This can be altered by genetic, environmental or psychological factors, being a part of the body that is exposed to all kinds of situations, and being the letter of presentation of people, has been studied over time a number of diseases that affect the skin both structurally and functionally, as a result has been considered conducting this literature review. Through this article we seek to detail the cutaneous characteristics present in ichthyosis vulgaris, since it is a frequent disease within the classification of ichthyosis with manifestations and etiology that stand out at the time of diagnosing a patient, being a congenital disease and that in turn can appear within the first years of life has relevant characteristics. By means of an intensive and enriching search, a series of articles were obtained, which were filtered and studied in depth to obtain information for the present bibliographic review.
Keywords: skin; ichthyosis vulgaris; disease; congenital.

1. Introduction

Ichthyosis vulgaris is a common inherited skin disorder characterized by dry, scaly, and thickened skin. This disorder affects approximately 1 in every 250 people worldwide, and it is caused by a mutation in the filaggrin gene. The filaggrin gene encodes a protein that is essential for the formation of the skin barrier, which is responsible for retaining moisture in the skin.Patients with ichthyosis vulgaris present with scaling, flaking, and thickening of the skin, particularly on the legs, arms, and abdomen. The condition typically presents in childhood and persists throughout adulthood. In addition to the characteristic skin changes, patients with ichthyosis vulgaris may also experience itching, redness, and inflammation.Recent research has focused on the use of artificial intelligence (AI) to improve the diagnosis and management of ichthyosis vulgaris. One study analyzed data from the Ministry of Public Health in Ecuador from 2013-2017 to extract knowledge about the epidemiology and clinical characteristics of the disease(1,2).

Another study examined the impact of legal research on post-pandemic social issues in Ecuador. Additionally, a study explored the relationship between AI and intellectual property.The right to health is a fundamental human right, and cases of violations of this right have been reported in Ecuador, such as the Albán Cornejo case. Ensuring access to healthcare and proper treatment for patients with ichthyosis vulgaris is essential to upholding this right and improving the quality of life for those affected.In conclusion, ichthyosis vulgaris is a common skin disorder with characteristic clinical features caused by a genetic mutation in the filaggrin gene. Ongoing research into the epidemiology and management of this disease, as well as the use of AI and legal research, is essential for improving patient outcomes and upholding the right to health(3,4,5).

Ichthyosis refers to a group of genodermatoses that corresponds to a pathology of congenital origin or spontaneous appearance during the first years of life, which converges with other types in the alterations of keratinization or cornification. (6)

It presents a hyperkeratosis, desquamation, dry skin which refers to a scale, which is why the name of ICTHYOSIS is given, since it is derived from the Greek "Ichthus" which means fish, as a result of the scaly appearance of the skin. (7).

Approximately in the eleventh century, Avicenza coined the term "black bars", in 1933 Cockayne promotes genetic classification and autosominas and sex-linked forms, in 1965 Wells and Kerr make incapie

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in the forms of inheritance. And in 1978, Kopp evidenced the deficit of steroid sulfatase activity based on etiology, specifically on ILX ichthyosis. (8)

It was discovered in 1985 by Sibert as a defect in the synthesis of a protein of the stratum corneum, filagrima and its predecessor, prophylagrin. Ichthyosis vulgaris arises from a genetic mutation inherited from one or both parents. Because of this, infants who inherit a deficient gene from only one parent have a fainter type of the disease. Children who inherit two deficient genes have a more severe type of ichthyosis vulgaris.(9)

According to the new classification developed in 2009, a change was established at the time of its division, so it will be classified in consideration of clinical characteristics, physiopathological and molecular aspects, so subgroups are established according to the frequency of disease, Mendelian pattern and extracutaneous manifestations.(10)

It was classified into syndromic and non-syndromic forms, which included the most frequent forms such as: ichthyosis vulgaris and X-linked, as well as the infrequent ones such as autosomal recessive ichthyosis and keratinopathic (11)

The skin is the part of the human body that always presents cutaneous manifestations as a result of any congenital or acquired pathology. Ichthyosis vulgaris reflects this statement, being a disease that occurs from a genetic alteration, in this review we will focus on the description of the clinical manifestations of ichthyosis vulgaris.

The objective of this article is to provide the necessary information on the cutaneous manifestations and etiology of ichthyosis vulgaris, so as to correlate the clinical characteristics, pathophysiology and molecular aspects, which have been the basis for the general classification of ichthyosis.

2. Methods

This bibliographic review was carried out based on the search for reliable and updated information in electronic databases such as Pubmed, Scopus, Web of Science, Scielo, ELSEVIER, Medline, Clinical Key, with search date August 2022 in the Spanish-English language. The term used was "Ichthyosis vulgaris" in addition to "ichthyosis, clinical manifestations, filaggrin", to be able to find articles based on the clinical characteristics of the pathology described. The information of 26 descriptive articles was collected, 6 of them were discarded due to the inclusion and exclusion criteria, respectively we focused on scientific articles that are part of medical journals, publication of clinical cases and in turn bibliographic reviews. Only 20 met the aforementioned criteria to be used in this article.

3. Results

In this literature review, information was compiled from 19 articles, in which the cutaneous characteristics of ichthyosis vulgaris are evidenced.

Ichthyoses are disorders of cornification, their cause can be hereditary or acquired. In 2009 a classification was developed based on clinical, pathophysiological and molecular aspects, where 36 types were found that in turn are divided into subtypes. Hereditary ichthyosis has a syndromic and non-syndromic classification, it is important to mention that the lesions are what determine this classification, since, when there is a genetic defect only in skin it will be called non-syndromic ichtosis, but if lesions in organs or systems are evident, it will be classified as syndromic ichthyosis. (10)

Table 1: Ichthyosis classification 2009

Non-Syndromic Ichthiasis	Ictiosis Sindromicas
Common ichthyosis Ictiosis vulgar X-linked recessive ichthyosis	**X-linked** X-linked recessive ichthyosis IFAP syndrome Conradi-Hunermann-Happle syndrome
ICAR *Major forms* Lamellar ictiosis Congenital ichthyosiform erythroderma Harlequin ichthyosis *Minor forms* Baby collodion Ichthyosis in swimsuit	AUTOSÓMICAS *Hair disorders* Netherton syndrome Tricotiodistrofia IH syndrome IHCE syndrome
ICTIOSIS QUERATINOPÁTICAS *Major forms* Ictiosis epidermolítica superficial *Minor forms* Epidermolytic annular ichthyosis Ictiosis Curth-Macklin Nevus epidermolítico	Neurological disorders Síndrome de SJörgen Larsson Refsum syndrome MEDNIK syndrome
OTHER FORMS Queratodermia loricrina Eritroqueratodermia variabilis Exfoliated skin syndrome	Lethal course Gaucher syndrome type 2 Deficit multiple de Sulfatasas CEDNIK syndrome ARC syndrome
	OTHER ASSOCIATED SIGNS Chanarin-Dorfman syndrome Sindrome KID Prematurity ichthyosis syndrome.

Fountain:(10)

In this review, the pathology of ichthyosis was

developed, using as a central theme the ichthyosis vulgaris subtype, it is a disease of non-syndromic hereditary cause, it has been related to the loss of the function of mutations of the FLG gene.

Ichthyosis vulgaris is a skin pathology considered the most frequent in the classification of ichthyosis, this type of disease has an appearance in the first years of age, is one of the mildest pathologies and can be treated by emollients. These diseases have greater evolution in winter times and predominates in light-colored skin. (13)

The number of cases is not certain, but it is known that this disease is the most common, the range goes from 1 per 2000 births; It forms 65 to 80% of this condition that impacts all types of races and both sexes. It is estimated that there is 1 case for every 550 patients with skin diseases. (6)

Aetiology

Hereditary ichthyosis is given by the alterations of the components of the skin barrier, in this case the corneal layer has the function of preventing the entry of allergens or irritants to the skin, in turn this has essential components that when affected will produce ichthyosis.

Ichthyosis vulgaris is caused by a disorder in the filaggrin, the appearance of lesions is evidenced the first years of life as a thin scale on the extremities, sometimes on the trunk, there is hyperkeratosis that varies with choice of plantar palm and the surfaces of the extremities (13)

Pathophysiology of filaggrin

In healthy skin, prophylagrin is processed into filaggrin peptide which bind to keratin filaments, thanks to them keratinization complexes are formed, filaggrin breaks down histidine that works as a skin moisturizer, in patients with ichthyosis vulgaris filaggrin is reduced (heterozygotes) and disappears (homozygotes), consequently, The skin barrier is reduced. It is autosomal dominant, as described in homozygous patients the gene has an early onset and its course is more severe, heterozygous patients have a milder evolution and begins in childhood. (14)

Prophylagrin is compiled by the FLG gene. This gene consists of 3 exons and 2 introns. This starts at exon 2, but it is exon 3 that collects most of the protein. According to the story, filaggrin was identified as a basic protein rich in histidine, to which it is added to keratin filaments, and thus forms macrofibrils.(15)

The stratum corneo is the "barrier" that protects the inner part of the skin from the external environment, this layer of skin is formed continuously thanks to the differentiation of keratinocytes in the different layers of the skin, throughout the differentiation process these cells lose their nucleus and flatten, becoming corneocytes. (16)

The corneocytes are linked to each other through the corneodesmosomes, the union of these cells is known as the structure "bricks and cements" (cornecitos are the bricks and the cement is the hydrophobic extracellular matrix), in turn they are covered cornified envelope, which provides mechanical and chemical resistance, and the most important thing is that this envelope gives the function of barrier and protection between the internal environment of the external environment, thus avoiding the loss of water and electrolytes and the entry of pathogens. (17)

Figure 1: (a) Brick and cement; (b) Corneodemosomes

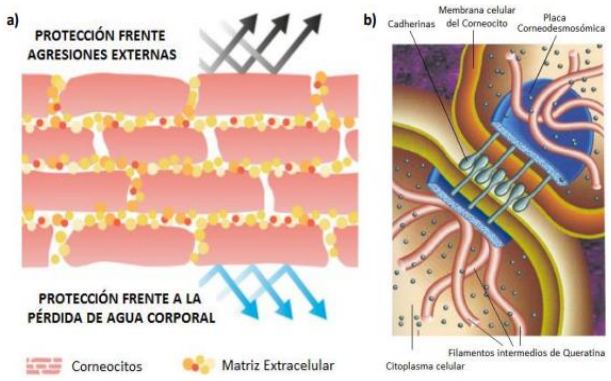


Figure 1: (12)

Consequence of filaggrin deficiency

Deformation will be generated in the structure of the keratin filaments of the cytoskeleton and in the configuration of the cornified envelope, resulting in a disorganized load of lamellar bodies and bilayers. Similarly, there will be a decrease in keratohyalin granules, a marked loss of natural wetting factor and pH alkalization. Different studies have detected that the absence is related to a global loss of the density of corneodesmosomes, intercellular junctions and the structure of the extracellular lipid matrix. Therefore, abnormalities will develop in the cytoskeleton, altering the maturation and exocytosis of laminar bodies and the increase in pH that controlled the enzymatic activity.

When there is a reduction in filaggrin metabolites, the level of natural hydration factor is reduced, the pH will rise in the superficial part of the skin and especially the loss of water, which will provide the characteristics of a xerotic skin. (18)

The sequence of the gene was obtained in the year of 1992, despite this it is not until 2006 that for the first time the mutations that caused the loss of the function of the gene are identified, two types of mutations R501X and 2282del4 were identified, which were found and described in 15 patients with iosis vulgaris. (17)

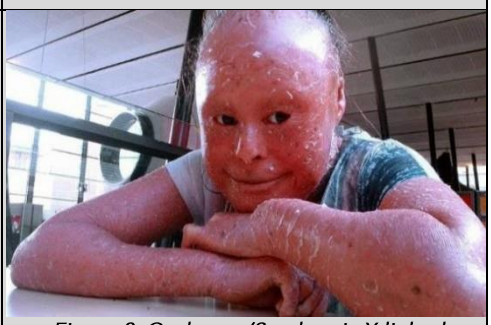
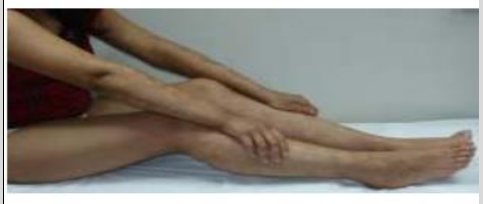
Filaggrin abnormality in ichthyosis vulgaris

The result due to mutations that cause loss of function of the FLG gene, causes a decrease in the number, size or total loss of keratohyalin granules. These mutations lead to partial or total deficiency of filaggrin, as mentioned above, there is an imbalance in the mechanical barrier and as a consequence a loss of water, immunological alteration of the skin and xerosis. (19)

Xerosis, desquamation, keratosis pilaris and

hyperlinearity, dead cells that are shed from the stratum corneo tend to accumulate creating the clinical condition as very dry and scaly skin is known. (20)

Table 2: Differential diagnosis with other nonsyndromic types of ichthyosis

Ictiosis Vulgar	• Beginning in childhood • Autosomal dominant • Xerosis • Desquamation • Whitish • In erythema • Associated with palmoplantar hyperlinearity • It is limited in popliteal and antecubital fossae.	 *Figure 2: Colombian Association of Dermatology and Dermatological Surgery*
X-linked recessive ichthyosis	• At birth • Erythroderma • Mutations in the STS gene (steroid sulfatase) • Desquamation • Large dark scales • It limits the part of the face, palms, soles, and flexion folds • Adults: abdomen, legs, dorsos of feet and popliteal hollows	 *Figure 3: Orphanet (Syndromic X-linked ichthyosis), last updated March 2012.*
Lamellar ictiosis	Baby collodion Autosomal recessive Mutation of the gene encoding transglutaminase-1 Generalized, dark, large scales MosaiGco pattern Alteration in sweat glands Queratodermia palmoplantar Nails with onychogrysis Subungual hyperkeratosis	 *Figure 4: (5)*
Congenital ichthyosiform erythroderma	Autosomal recessive Baby collodion Fine white scales Base erythema Associated with mild ectropion Does not respect bending folds Diffuse flaking	 *Figure 5: (5)*
Harlequin ichthyosis	• At birth • Autosomal recessive inheritance • Severe collodion baby • Red fissures hard plates extending to the dermis • Clinical picture similar to that of the laminar type	 *Figure 6: (2)*

The function of the skin barrier to be altered will cause the development of repair mechanism to compensate for losses, which will produce epidermal hyperplasia that results in hyperkeratosis. (18)

Clinical manifestations

Ichthyosis vulgaris decreases the skin's natural shedding process, thus causing excessive storage of the protein in the top layer of the skin. The most common in patients vary in rise of dry and scaly skin, sharp and painful fissures in the skin. In general, these symptoms manifest themselves more precipitously in cold and dry environments, and may improve or disappear in hot and humid

environments. Moisture is involved in the processing of filaggrin, which helps to understand why the folds of certain parts of the body are respected and the cause of environmental factors.
(6)
It begins in childhood, approximately postnatal, approximately manifests between 3 months and 5 years of age, is characterized by xerosis, whitish scales, keratosis pilaris, palmar hyperlinearity (typical finding), does not present erythema, but respects certain body areas, such as flexor surfaces, neck, popliteal fossas and folds, it is worth mentioning that xerosis presents fine desquamation which affects extremities, scalp, trunk and centrofacial region. In addition, there are fissures in hands, heels or fingers. (16)
Palmar hyperlinearity and keratosis pilaris, are not only present in ichthyosis vulgaris, but also in patients who are carriers of mutations in the FLG gene, which was corroborated according to a study in which it was determined that 71% of children with hyperlinearity are carriers of the mutation. About 35-70% of patients with ichthyosis vulgaris may develop atopic disease. (16)

Fountain:(5)
Being one of the mildest diseases of all types of ichthyosis, the treatment is clearly based on minimizing the skin manifestations of the patient, the main thing is to try to reduce desquamation, moisturize the skin and increase the function of the skin barrier, it can be treated with emollients, moisturizers or keratolytic agents. (20)
In addition, a psychological treatment must be established at the same time as the pharmacological treatment, being an external and visible organ that is affected, it will be altered in the psychological state of both the patient and the family. Being a genetic disease, adequate support and information must be provided to parents, so that they can contribute to the treatment of the patient, psychological care will help guide the family in better care and adaptation, and in relation to the patient what is sought is to face the disease and possible future situations and the acceptance of living with it without feeling discriminated against or separated by their condition. (21)

4. Discussion

The bibliographic review was based on a series of articles containing information on the clinical manifestations and etiology of ichthyosis vulgaris(22).. This pathology, being the most frequent and mild, has unique characteristics that give the opportunity to make a differential and correct diagnosis when treating a patient with this pathology(23).
Ichthyosis is a very broad disease according to its classification, by the form of presentation and morphology, being a disorder that affects the cornification of the skin, the main sign is xerosis, since this occurs as a result of alterations in the FLG gene, having the ability to affect both the skin and systemic level depending on its evolution
In ichthyosis vulgaris one of the greatest characteristics of impact is its etiology, since it shares the problem in the alteration of the skin barrier, being skin pathologies are very sensitive to changes either congenital or environmental factors(24). Among the most frequent manifestations in this pathology we have xerosis, hyperlinearity plants, keratosis pilaris, desquamation, the presence of whitish scales and above all highlights the respect of certain areas of the body, as is the case of folds, this characteristic occurs because it does not affect the areas that still have the natural moisture factor(25).
Therefore, a series of clinical and molecular characteristics have been proposed in each type of ichthyosis. However, despite all the clinical manifestations it presents, it has been classified as a milder and more frequent ichthyosis of all the others, due to its good prognosis and treatment(26).

5. Conclusions

According to the information collected, the different types of ichthyosis vary according to the severity and clinical characteristics, so it is necessary to rely on the clinical manifestations, time of onset and anamnesis on family history to establish if it is acquired or hereditary, the disease has specific times in which the symptoms will develop, It is affected by different environmental factors as in the case of winter seasons.
Ichthyosis vulgaris, has been one of the mildest and most frequent diseases in the category of ichthyosis, so it presents unique manifestations that help differentiate it from other types of ichthyosis, although it is necessary to emphasize that each type and subtype has a chronology and clinical manifestations that identify them.
In the physical examination, unparalleled signs can be observed in relation to other pathologies, such as the shape and color of the scales, palmar hyperlinearity, keratosis pilaris and the year of life that the pathology begins. It is the autosomal dominant type, within the non-syndromic hereditary classification since it affects only the skin, the mutation produces the loss of the function of the FLG gene, consequently, the protective function of the skin is decreased, leaving it vulnerable and predisposed to the development of the disease.
The predisposing factor for this disease is the mutation of the gene, which has a wide impact on diseases other than ichthyosis, all the pathophysiology has focused on the alteration of the skin barrier, which by not providing adequate protection allows the development of various pathologies. Even so, the severity of ichthyosis vulgaris is very mild, so the different clinical manifestations can be treated with hydration of the area and the use of emollients.

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