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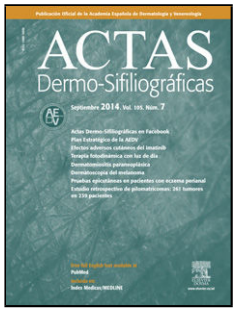

ICTIOSIS: Actualización clínica y molecular. Parte 2: ictiosis sindrómicas. Abordaje diagnóstico y terapéutico de las ictiosis

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Revisión

ICTIOSIS: Actualización clínica y molecular. Parte 2: ictiosis sindrómicas. Abordaje diagnóstico y terapéutico de las ictiosis

[[Translated article]]ICHTHYOSIS: Clinical and molecular update. Part 2: Syndromic ichthyosis. Diagnostic and therapeutic approach of ichthyosis

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Graphical abstract

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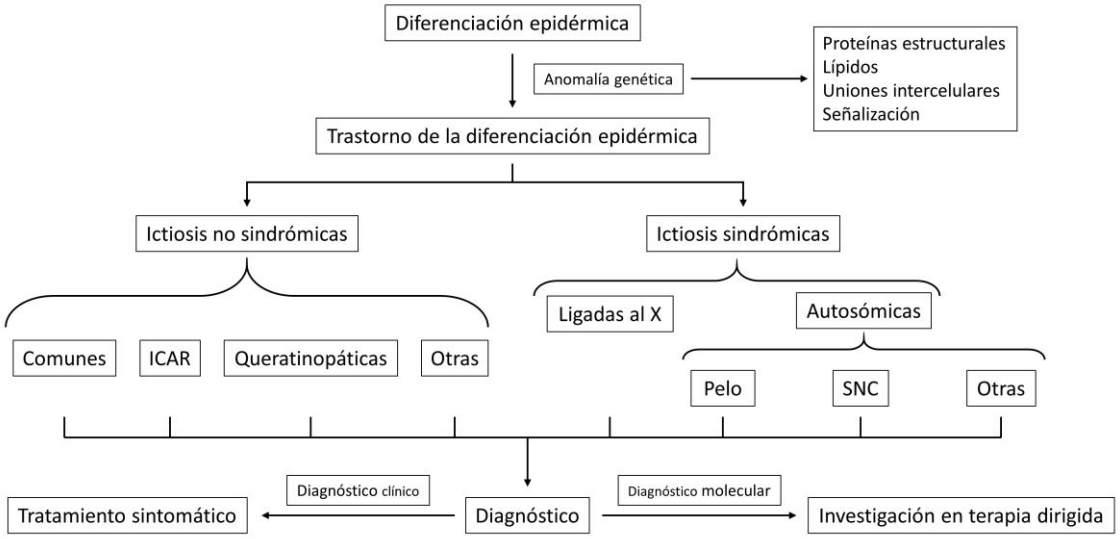

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1.4 Resumen

Las ictiosis sindrómicas son un grupo de enfermedades cuyas alteraciones genéticas tienen repercusión tanto en tejidos epidérmicos como no epidérmicos, por lo que los pacientes presentan clínica cutánea y síntomas en varios órganos o aparatos. La mayoría son excepcionales y en algunas de ellas la descamación ictiosiforme ha sido pobremente caracterizada. Su patrón hereditario es diverso, sus manifestaciones clínicas extracutáneas heterogéneas y la afectación cutánea muy variable, lo cual dificulta una buena subclasificación clínica.

El diagnóstico de las ictiosis reside en una buena anamnesis, una exploración física detallada, y la detección de hallazgos analíticos y/o histológicos asociados. El estudio genético es imprescindible, no sólo para alcanzar el diagnóstico de certeza, sino porque conocer el sustrato molecular concreto en cada paciente es el primer paso para encontrar un régimen terapéutico individualizado. El tratamiento pasa por eliminar las escamas y mantener la piel hidratada mediante el uso de terapia

tópica con exfoliantes y emolientes. Además, en la actualidad, se están desarrollando terapias de reemplazo dirigidas a sustituir las proteínas y los lípidos específicamente alterados en cada entidad, y se están empezando a evaluar estrategias de terapia génica cuya finalidad última es la curación. En la segunda parte de este trabajo hacemos una actualización clínica y genética de las entidades sindrómicas, así como una actualización del diagnóstico y tratamiento de las ictiosis.

1.5 Palabras clave

Ictiosis, desórdenes de la cornificación, genodermatosis, revisión

1.6 Abstract

Syndromic ichthyoses are a group of disorders whose genetic alterations impact both epidermal and non-epidermal tissues. Therefore, patients present symptoms in other organs. Most are extraordinary and, in some, ichthyosiform desquamation has been poorly described. Their patterns of inheritance are diverse; their extracutaneous clinical signs, heterogeneous; and the skin symptoms, highly variable, which hinders a proper clinical classification.

Ichthyosis diagnosis starts with proper anamnesis, detailed physical examination, and detection of associated analytic and/or histologic findings. Genetic testing is indispensable, not only for diagnostic certainty, but also because understanding the molecular substrate for each patient is the first step towards finding an individualized therapeutic regimen. While it will almost invariably involve facilitating desquamation and maintaining skin hydration using topical exfoliants and emollients, recently, replacement therapies aiming at substituting the proteins and lipids specifically altered in each patient are being developed and gene therapy approaches with the ultimate goal of curing the disease are being assessed. In part 2 of this review, we'll be updating the clinical and genetic findings of syndromic entities, ichthyosis diagnosis and treatment

1.7 Keywords

Ichthyosis, disorders of cornification, genodermatosis, review

Syndromic ichthyoses are a group of diseases whose genetic alterations affect both epidermal and non-epidermal tissues, which is why patients present with symptoms in other organs and systems. Most are exceptional and, in some of them, the ichthyosiform desquamation has been poorly characterized, so we will only detail the most relevant forms (Table 1). They are subdivided based on the inheritance pattern and the most relevant extracutaneous signs[1].

i. X-linked syndromic ichthyoses

All causal genes in this group affect cholesterol synthesis.

- ***Syndromic X-linked ichthyosis***: patients present with a cutaneous phenotype similar to the non-syndromic form, but with variable associated extracutaneous symptoms that may include anosmia, hypogonadotropic hypogonadism—Kallman syndrome—and intellectual disability. It is due to large hemizygous microdeletions affecting both *STS*[2] and contiguous genes, whose absence determines the associated clinical spectrum. Strictly, this type of ichthyosis could be considered non-syndromic since the extracutaneous symptoms are not due to STS deficiency, but by the additional deletion of contiguous genes.
- ***IFAP syndrome*** (*Ichthyosis* follicularis - *alopecia - photophobia):* characterized by generalized cutaneous affectation with erythema, follicular hyperkeratosis, palmoplantar keratoderma, alopecia and photophobia. Additionally, some patients exhibit intellectual disability, corneal opacity, renal dysplasia, cryptorchidism and skeletal malformations (BRESHECK syndrome). It is due to recessive pathogenic variants in *MBTPS2*[3]. Of note, a phenotypically similar entity called hereditary mucoepithelial dysplasia—also called IFAP2—exists and is due to dominant pathogenic variants in *SREBF1*[4], a gene found not in the X chromosome, but in chromosome 17 (Figure 1). Both genes are transcription factors that activate the cholesterol synthesis pathway.
- ***Chondrodysplasia punctata type 2***: this disease is lethal in men and exhibits a peculiar phenotype of ichthyosis along the Blaschko lines due to X chromosome inactivation. Typical symptoms include cataracts, skeletal abnormalities like low height and rhizomelic limb shortening and punctate appearance in long bone epiphysis radiographs. It is due to dominant pathogenic variants in *EBP*[5], which encodes a cholesterol synthesis enzyme.

ii. Autosomal syndromic ichthyosis with prominent hair abnormalities

This group is characterized by patients with characteristic hair abnormalities, a clinical finding that can help with disease diagnosis. However, both the clinical signs and molecular and etiopathogenic causes are very diverse.

- ***Netherton syndrome***: Probably the most common syndromic ichthyosis, and the easiest one to diagnose when hair shaft alterations are identified. Although some cases describe neonatal presentation as a collodion baby, most children are born with erythroderma and a severe alteration of the cutaneous barrier causing recurrent episodes of hypernatremic dehydration and sepsis. Facial erythema is characteristic in these patients, who often exhibit intense and incoercible pruritus. In time, patients may develop a characteristic cutaneous presentation known as *ichthyosis linearis circumflexa*, characterized by arch-shaped or polylobulated lesions with double-edged scaling (Figure 2). Most patients present with *trichorrhexis invaginata* also known as *bamboo hair*, a hair shaft disorder that may affect head hair as well as eyebrows and eyelashes and can be found during exploratory dermoscopy (Figure 3). Consequently, patient hair is short and uneven, since it is fragile and breaks easily along the areas with *trichorrhexis invaginata*. Many patients also suffer from atopic diathesis, with skin eczematiform flares and food allergies, as well as verruciform lesions and a predisposition to human papillomavirus cutaneous infections. Netherton syndrome is caused by recessive pathogenic variants in *SPINK5*[6]. It can be diagnosed by skin biopsy immunohistochemistry, since patients show a lack of LEKTI expression (the protein encoded by this gene, localized in the *stratum corneum*). Its absence prevents kallikrein inactivation, epidermal enzymes responsible for corneocyte degradation needed for physiological desquamation.
- ***SAM syndrome*** (*Severe dermatitis - multiple allergies - metabolic wasting syndrome*): A desmosomal disease whose acronym summarizes its essential clinical characterstics: severe dermatitis with ichthyosiform erythroderma, allergies and metabolic wasting leading to failure to thrive. Since SAM syndrome was described after the last consensus classification, it is not a part of it. However, we believe that its physiopathological origin and clinical signs justify the inclusion of SAM syndrome in the group of syndromic ichthyoses with hair abnormalities. Patients present symptoms since birth, often with repeated life-threatening

systemic infections. Cutaneous symptoms include severe desquamating erythroderma with hypotrichosis and onychodystrophy (Figure 4). Tooth enamel anomalies and transient hyperpigmented lesions whose histology suggest a post-inflammatory origin are not rare findings (Figure 5). SAM syndrome is due to recessive pathogenic variants in *DSG1*[7] or dominant pathogenic variants in *DSP*[8]. This last case may associate cardiomyopathy, since DSP is expressed in heart muscle[9].

- ***Trichothiodystrophy***: characterized by ichthyosis coupled with fragile hair and nails with sulfur deficiency. Ichthyosiform desquamation is usually mild, dark and relatively large, with forehead and trunk affectation (Figure 6). Characteristically, alternating light and dark bands can be observed in the hair shaft under polarized light (tiger-tail banding). It is due to recessive pathogenic variants in *AARS1*[10], *GTF2E2*[11], *MAARS1*[10], *MPLKIP*[12], *RNF113A*[13], or *TARS1*[14], which code proteins involved in protein translation. There is a subtype which also presents photosensitivity, progressive neuropathy and accelerated ageing, caused by recessive pathogenic variants in *ERCC2*[15], *ERCC3*[16], *GTF2H5*[17], which code proteins involved in DNA repair as well as protein translation. Same as the previous cases, this group shows a striking molecular heterogeneity that hinders geno-phenotypic correlation.

iii. Autosomal neurologic ichthyosis with prominent neurologic signs

The most common disease in this grous is ***Sjögren - Larsson syndrome***, characterized by intellectual disability, spasticity and eye abnormalities (crystalline retinopathy), which is highly suggestive for diagnosis. Cutaneous involvement is not very significant and consists of discrete generalized hyperkeratosis which, in some areas, determines parallel linear lesions known as *railway track lesions* which can be reminiscent of lichenification in the flexures. Many patients show severe pruritus. It is due to recessive pathogenic variants in *ALDH3A2*[18], a fatty aldehyde dehydrogenase responsible for synthesis of fatty acids use in ceramide synthesis.

iv. Otras ictiosis sindrómicas

This group includes entities that do not respond to the characteristics of the previous groups.

- ***KID syndrome*** (*keratitis - ichthyosis - deafness*): Characterized by keratitis, hyperkeratosis espinulosa, palmoplantar keratoderma and sensorineural deafness. It is caused by dominant pathogenic variants in *GJB2*[19] or *GJB6*[20], or recessive pathogenic variants in *AP1B1*[21], which

encode gap junction proteins in charge of intercelular comunication and the clathrin-coated vesicle adaptor complex, respectively.

Additionally, postzygotic *GJB2* variants cause keratotic lesions along the Blaschko lines that may be transmitted to the offspring as KID syndrome if it affects the gonads[22]. This mosaic forms have less systemic impact since they spare sight and hearing (Figure 7).

- ***Neutral lipid storage disease***: Also known as Chanarin - Dorfman disease, it presents with mild congenital ichthyosiform erythroderma, hepatosplenomegaly, myopathy, hypoacusia and cataracts[23]. Histologically, vacuole accumulation is seen in most tissues (Figure 8). It is due to recessive pathogenic variants in *ABHD5*[24], encoding an enzyme that synthesizes linoleic acid used in ceramide synthesis and whose absence leads to intracellular neutral lipid storage.

The main characteristics of the most infrequent syndromic ichthyoses are shown in Table 2.

1.8 Diagnosis

Generalized alteration of the cutaneous barrier in patients with disorders of epidermal differentiation (DED) is present since birth or within the first few months of life, which helps clinical diagnosis. However, the poor phenotype - genotype correlation hinders a more precise diagnosis in many cases. Figure 9 shows a diagnostic algorithm in which adequate anamnesis is of paramount importance.

Blood tests, including red blood cells, hepatic and renal function, blood electrolyte levels, immunoglobulin serum levels and blood smear can help exclude syndromic forms of ichthyosis and their associated anomalies[25]. For example, Netherton syndrome and desmosomal disorders both carry a risk of hypernatremic dehydration in babies[7],[26]. Moreover, serum immunoglobulin levels can be useful to establish differential diagnosis with hereditary immunodeficiencies, which can also present erythema and desquamation. Referring the patient to other specialists based on the clinical findings should be considered[25]. Chanarin - Dorfman presents lipidic droplets in granulocytes and monocytes in blood smear (known as Jordan's anomaly)[27] (Figure 8).

Biopsies for routine histology, immunohistochemistry or, more rarely, electron microscopy may help with differential diagnosis[28]. Absence of LEKTI expression (encoded by *SPINK5*) in immunohistochemistry can confirm a Netherton syndrome diagnosis[29] and is especially useful if genetic analysis is not available[28]. Light microscope analysis of the hair shaft is an accessible and

non-invasive technique that adds useful information in the ichthyoses associated with hair abnormalities, such as *trichorrhexis invaginate* in Netherton syndrome or "tiger-tail banding" under polarized light in trichothiodystrophy[30]. Although clinical diagnosis of ichthyosis is usually easy, phenotype - genotype correlation is often hard to establish. Although genetic testing using next generation sequencing is widely used in developed countries to confirm diagnosis, genetic abnormalities are not found in 15% to 20% of patients with DED phenotype[31–35]. This can be due to undetectable or undescribed pathogenic variants, the latter being the ones that allow a broadening of the group of ichthyosis when associated with distinctive clinical findings.

1.9 Genetic counseling

DED follow patterns of monogenic Mendelian inheritance, which allows for genetic counseling, where information is provided to affected families (patients and relatives) about the molecular mechanisms and odds of transmission to potential offspring. However, perception of the risk of having an affected child changes substantially depending on the disease and a pregnancy may not be considered high-risk by couples if they already have a child with mild symptoms. In contrast, patients with severe forms or a heavy impact on quality of life may ask for genetic counseling to avoid future high-risk pregnancies[36]. Regional, cultural, and socioeconomic idiosyncrasies may also influence access to genetic counseling.

Prenatal diagnosis requires obtaining embryonic tissue. Low levels of unconjugated estriol and copy number alterations in maternal serum—which detects deletions in maternal sexual chromosomes—are closely associated win an increased risk of recessive X-linked ichthyosis in male fetuses and can be used, along with other molecular techniques, for prenatal diagnosis[37,38]. In any case, the method of choice for prenatal diagnosis is the genetic analysis of known pathogenic variants in the family. Pre-implantation diagnosis may be used by at-risk couples to select unaffected embryos prior to *in vitro* fertilization, although many countries do not consider it appropriate for ichthyosis[39].

1.10 Treatment

DED are genetic diseases that currently lack curative treatment. Therapy is currently aimed at alleviating symptoms to improve the patient's quality of life. Therefore, this requires treatments that not only have to be effective but also safe and well tolerated. However, the reality is that there are few studies on the long-term effects of therapies and their efficacy varies greatly across

patients, even among those suffering from the same type of DED. Therefore, the chosen treatment and administration regimen depend on expert recommendations in clinical practice guidelines, information sharing with patient associations, accessibility to treatment and the personal experience of each individual patient[26],[40],[41].

Topical therapy

The basis of all DED therapy is topical treatments, which aim to reduce epidermal thickness and facilitate its desquamation, as well as itching, tightness, and cracking, improving skin appearance. They can act at different levels but the objective is always to normalize the epidermal barrier function[42].

Bathing and exfoliation

Baths aim to soften the scales to facilitate their removal via mechanical exfoliation. Baths should be prolonged and may be supplemented with salts, oils, or bicarbonate to increase hydration and promote exfoliation. Dilute sodium hypochlorite can help control skin infections and decrease odor that can be caused by microbial overgrowth in patients with pronounced hyperkeratosis. Exfoliation can be performed by hand, sponge, file, pumice, or even scissors for larger scales with partial sloughing. This process usually requires between 30 and 60 minutes a day, which is a factor that significantly impacts patient quality of life, as they must prioritize this over other activities such as playing, studying, working, and having leisure time. In DED with scalp involvement it is important to remove scales and crusts to avoid scarring alopecia, which is often unavoidable despite this care.

Emolients

Emolients aim to maintain a correct water balance, hydrating the epidermis and sealing the barrier to prevent water loss. Their formulation has an impact on the degree of hydration, lubrication, and occlusion they provide. However, the occlusive effect may interfere with sweating, aggravating the heat intolerance suffered by many patients. Vaseline and paraffin are inexpensive and effective emolients but they are cosmetically uncomfortable, which can make other formulations based on urea, propylene glycol, or dexpanthenol preferable. Overall, it is usually necessary to apply them at least twice a day[40].

Topical keratolytics

Keratolytics facilitate proteolytic degradation of cytoskeleton and intercellular junctions, which reduces hyperkeratosis and facilitates desquamation. These drugs include urea, salicylic acid, and lactic acid. Adverse effects are usually mild, including itching, burning, and irritation; however, acids can be absorbed and have systemic side effects[43]. This is especially serious in the case of salicylic acid, which can cause salicylism with nausea, vomiting, tachypnea, irritability, coma, and even death. Therefore, it is of paramount importance to limit its application, particularly in children, patients with impaired renal or hepatic function and in cases with a high percentage of affected body surface area[44].

Retinoids

Retinoids decrease keratinocyte proliferation and differentiation, controlling the number of cells that can form the *stratum corneum* and reducing hyperkeratosis and inflammation. They are available only in some countries where they are marketed for acne, so they are used off-label. Tazarotene[45] and adapalene[46] have shown efficacy with a low incidence of adverse effects[47].

For patients with more severe symptoms, isolated topical treatment may be time consuming and give suboptimal results, leading to the use of oral retinoids. The most widely used ones are acitretin, alitretinoin, and isotretinoin. Although they are particularly useful in diseases with thick scales such as lamellar ichthyosis, they have proven ineffective in purely erythrodermic forms and poorly tolerated by patients with skin fragility such as epidermolytic ichthyosis. Systemic retinoid-related side effects are usually dose-dependent and include cheilitis, nasal dryness, xerosis, hair loss, conjunctival irritation, and lipid and liver abnormalities. Chronic use may cause skeletal hyperostosis with spurs and calcifications of the spine and tendons. Additionally, they have a prolonged teratogenic potential with washout periods ranging from 1 month (isotretinoin and alitretinoin) up to 3 years (acitretin). Therefore, it is necessary to monitor patients undergoing treatment with oral retinoids, including liver enzymes, lipid profile, X-rays, and pregnancy tests. These considerations, along with age, determine the agent used, and the initial and maintenance doses that should be used[48–50].

Pathogenesis-based therapies

Recently, therapies directed more specifically against the molecular alterations of DED are beginning to appear.

One of these targets is immune dysregulation, since several TDE show polarization towards a Th17/IL-23 phenotype. Consequently, monoclonal antibodies directed against different proteins of this pathway such as IL-17A (secukinumab), IL-12 and IL-23 (ustekinumab) and IL4R/13R (dupilumab) are starting to be used. These antibodies have proven useful in some patients with desmosomal disorders[51],[52] or Netherton syndrome, but their irregular and/or transient efficacy does not allow generalized use[53].

Replacement therapies are directed against the altered proteins and lipids in each DED with the aim of supplying the altered molecules in each disease. Lipid replacement therapy has proven particular useful in CHILD syndrome where treatment with cholesterol and statins markedly improves the phenotype of most patients[54],[55]. Simultaneously, protein replacement therapy is being evaluated to deliver transglutaminase 1 in patients with lamellar ichthyosis[56].

Gene therapy aims to supplement a healthy copy of the affected gene (pharmacological gene therapy) or repair the mutation in the patient's genomic DNA (curative gene therapy). To date, only pharmacological gene therapy strategies have been evaluated in clinical trials targeting *TGM1* in lamellar ichthyosis[57], *SPINK5* in Netherton syndrome[58]. Curative gene therapy is in the early stages of development, due to how difficult it is to modify genomic DNA. Still, there is great interest as it would be the only treatment capable of curing genetic diseases[59].

Special aspects of treatment

Many DED present symptoms associated with skin barrier defects that also need to be controlled. Pruritus is very common and decreases quality of life significantly[60]. Although treatment with monoclonal antibodies targeting inflammatory pathways (dupilumab[61], ustekinumab[62] and secukinumab[52]) seems effective, results are inconsistent and often transient. Hypohidrosis increases the risk of heat stroke, making it necessary to limit physical exercise and stay in cool environments. In eye care, the main objective is to maintain lubrication via prophylactic use of artificial tears[63]. Scaling in the ear canal can cause conductive hypoacusia, increase the risk of infections and cause irreversible damage to the eardrum, requiring regular otorhinolaryngological follow-up[64]. In more severe forms, regular monitoring of metabolic parameters and adequate nutritional supplementation are required[65]. The epidermal barrier defect facilitates the occurrence of bacterial and fungal infections, which may go unnoticed due to the cutaneous phenotype of DED.

The extracutaneous symptoms of DED highlight the critical need for multidisciplinary teams to provide adequate care. Ophthalmologists, otorhinolaryngologists, and nutritionists are especially important. Patients with extracutaneous signs need specialists according to the organs involved, such as neurologists, gastroenterologists, or traumatologists. Therefore, many patients with recessive X-linked ichthyosis present attention deficit and hyperactivity disorders and need neuropsychological attention[66]. Finally, some studies have shown that physical therapy can reduce the severity of symptoms and improve quality of life[67].

Impact on quality of life

DED can have a profound impact on quality of life due to their physical manifestations, the need for constant skin care, and the associated social stigma. The visibility of the disease can lead to psychosocial difficulties and psychological problems, so both physical and emotional needs must be addressed.

Patient associations play a crucial role in improving quality of life by providing information, support, and resources. In Spain, the Spanish Ichthyosis Association (ASIC) (www.ictiosis.org) is dedicated to helping affected individuals and their families, promoting awareness, psychosocial support, and integration of patients into society. ASIC also promotes research and collaborates with health care professionals to improve disease management. This work is represented in Latin America by different associations depending on each country, such as www.ictiosis.cl in Chile, among others.

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JT Hum Mol Genet

V 25

D 2016

P 348-L 357

DOI 10.1093/hmg/ddv481

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JT Hum Mol Genet

V 30

D 2021

P 1711-L 1720

DOI 10.1093/HMG/DDAB123

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JT Am J Hum Genet

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D 2016

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DOI 10.1016/J.AJHG. 2016.02.008

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JT Am J Hum Genet

V 76

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P 510

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JT J Med Genet

V 52

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DOI 10.1136/JMEDGENET-2014-102418

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AT Bi-allelic TARS Mutations Are Associated with Brittle Hair Phenotype

JT Am J Hum Genet

V 105

P 434-L 440

DOI 10.1016/J.AJHG.2019.06.017

D 2019

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JT Hum Mutat

V 9

P 519-L 525

D 1997

DOI 10.1002/(SICI)1098-1004(1997)9:6<519::AID-HUMU4>3.0.CO;2-X

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JT Am J Hum Genet

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JT Nat Genet

V 7

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JT Nat Genet

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JT Am J Hum Genet

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JT J Invest Dermatol

V 122

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DOI 10.1111/J. 0022-202X. 2004.22518.X

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JT Am J Hum Genet

V 105

D 2019

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DOI 10.1016/J.AJHG. 2019.09.021

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JT J Invest Dermatol

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JT J Eur Acad Dermatol Venereol

V 37

DOI 10.1111/jdv.19235

D 2023

P e1237-L e1241

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JT Am J Hum Genet

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DOI 10.1086/324121

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AT Proposal for a 6-step approach for differential diagnosis of neonatal erythroderma

JT J Eur Acad Dermatol Venereol

DOI 10.1111/JDV. 18043

D 2022

V 36

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AT Management of congenital ichthyoses: European guidelines of care, part two

JT Br J Dermatol

V 180

D 2019

P 484-L 495

DOI 10.1111/BJD. 16882

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JT Liver Int

V 41

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DOI 10.1111/LIV. 14794

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AT Ichthyoses—A Clinical and Pathological Spectrum from Heterogeneous Cornification Disorders to Inflammation

JT Dermatopathology (Basel)

V 8

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JT Br J Dermatol

V 151

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JT J Clin Pathol

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JT Br J Dermatol

V 182

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JT Pediatr Dermatol

DOI 10.1111/PDE.14944

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JT JAMA Dermatol

V 158

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JT Exp Dermatol

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DOI 10.1111/EXD. 14345

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JT Acta Derm Venereol

V 96

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JT Actas Dermosifiliogr

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JT Zhonghua Fu Chan Ke Za Zhi

V 57

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DOI 10.3760/CMA.J.CN112141-20220125-00043

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JT Front Genet

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JT J Hum Reprod Sci

V 14

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JT Br J Dermatol

V 180

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DOI 10.1111/BJD. 17203

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JT Br J Dermatol

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JT J Pediatr

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JT J Am Acad Dermatol

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JT Br J Dermatol

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Figura 1 Displasia mucoepitelial hereditaria por variante patogénica en *SREBF1*. Eritema gingival típico de la enfermedad. gr1.

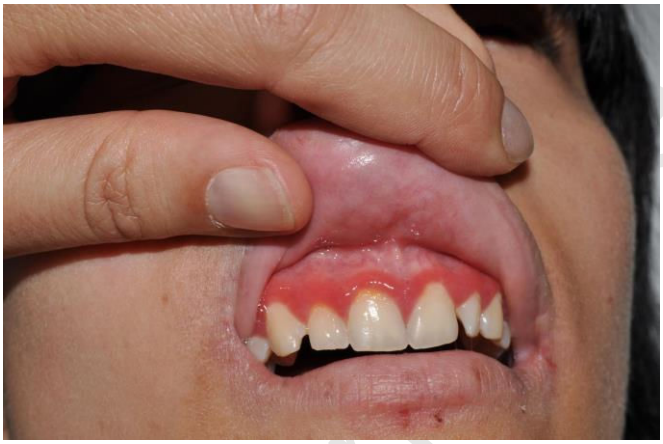

Figura 2 Síndrome de Netherton. Lesiones arciformes polilobuladas con doble borde descamativo características de la ictiosis lineal circunfleja en el paciente con variante patogénica en el gen *SPINK5*. gr2.

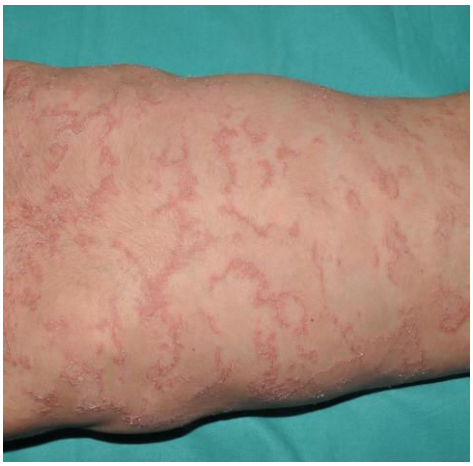

Figura 3 Síndrome de Netherton. Imagen dermatoscópica del pelo de las cejas en la que se aprecian las alteraciones del pelo típicas de la enfermedad (tricorrexis *invaginata*). gr3.

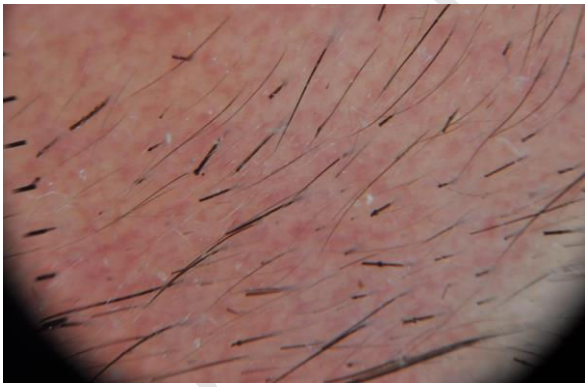

Figura 4 Síndrome SAM (S*evere dermatitis, mutiple* A*llergies and* M*etabolic wasting*; dermatitis grave, alergias múltiples y desgaste metabólico). Eritrodermia ictiosiforme grave e hipotricosis de cuero cabelludo en un paciente con una variante patogénica en *DSG1*. Obsérvese cómo el rascado secundario al intenso picor deja sangre en las uñas. gr4.

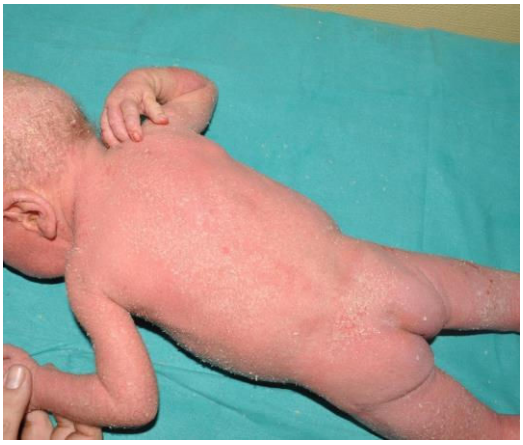

Figura 5 Síndrome SAM (S*evere dermatitis, mutiple* A*llergies and* M*etabolic wasting*; dermatitis grave, alergias múltiples y desgaste metabólico). Eritrodermia ictiosiforme, onicodistrofia e hiperpigmentación postinflamatoria focal en el dorso de la mano y el 4.º dedo en un paciente con una variante patogénica en *DSP*. gr5.

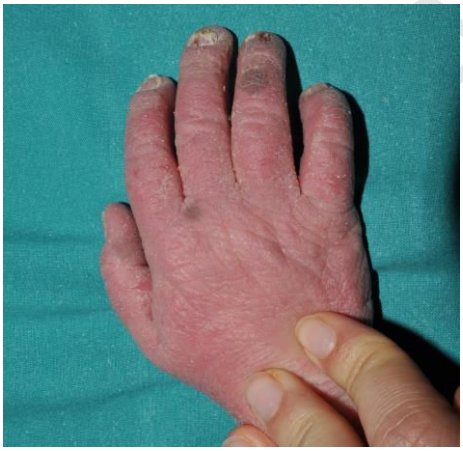

Figura 6 Tricotiodistrofia. Descamación marrón de aspecto laminar en el tronco de una paciente con variante patogénica en *MPLKIP*. gr6.

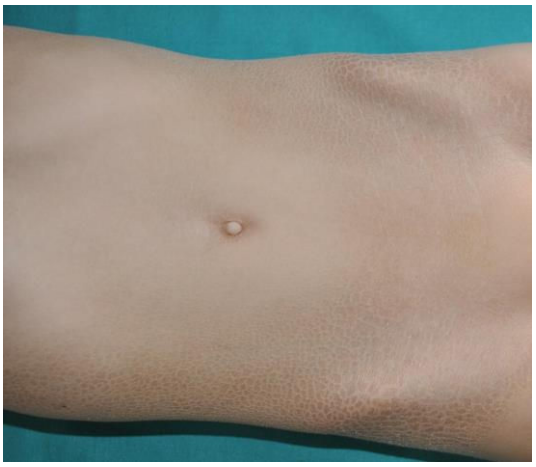

Figura 7 Síndrome KID (*keratitis, ichthyosis and deafness*: queratitis, ictiosis y sordera) en un paciente con una forma mosaico de la enfermedad por variantes de aparición poscigótica en *GJB2*. Se observa afectación lineal de distribución blaschkoide y el importante engrosamiento plantar. gr7.

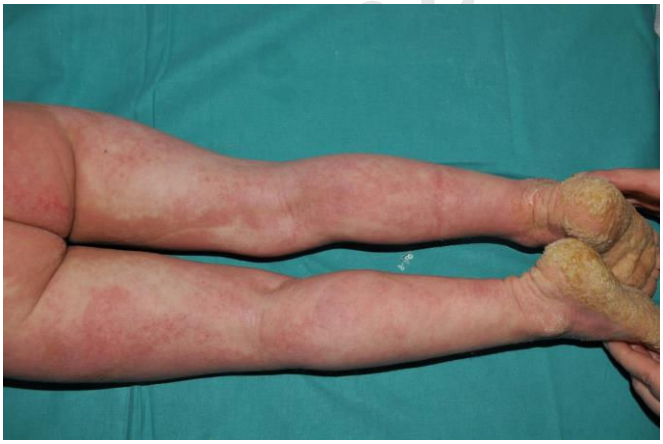

Figura 8 Síndrome de Chanarin Dorfman. Extensión de sangre periférica de un paciente con una variante patogénica en *ABHD5* donde se observan gotas lipídicas en el citoplasma de los granulocitos (anomalía de Jordan). gr8.

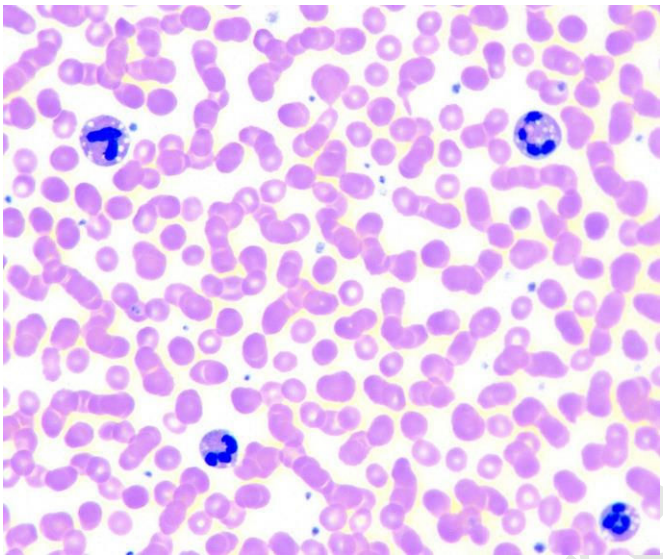

Figura 9 Algoritmo diagnóstico de las ictiosis congénitas. Fuente: modificado de Gutiérrez-Cerrajero C, Sprecher E, Paller AS, Akiyama M, Mazereeuw-Hautier J, Hernández-Martín A, et al. Ichthyosis. Nat Rev Dis Primers. 2023;9:2. doi: 10.1038/s41572-022-00412-3. gr9

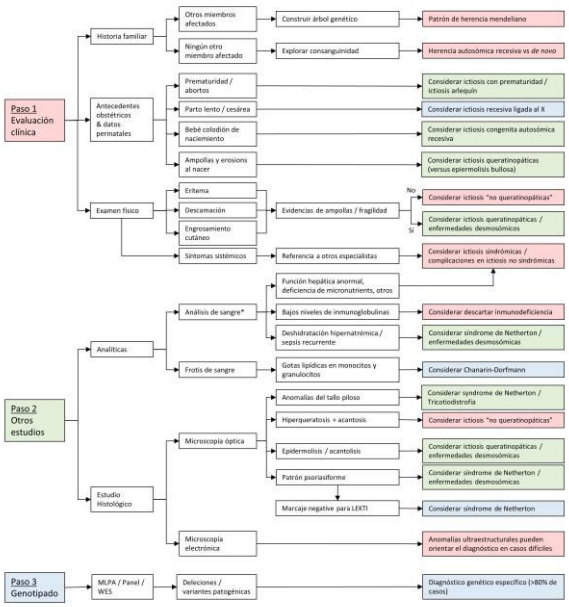

Tabla 1 Clasificación de las ictiosis sindrómicas

Ictiosis sindrómicas
Ictiosis sindrómicas ligadas al cromosoma X (ORPHA: 281210)
Ictiosis recesiva ligada al cromosoma X sindrómica (ORPHA:281090)
Síndrome IFAP (ORPHA: 2273)
Condrodisplasia punctata tipo 2 (CDPX2, ORPHA: 35173)
Síndrome MEND (ORPHA: 401973)
Síndrome CHILD (ORPHA: 139)
Ictiosis sindrómicas autosómicas con anomalías prominentes del pelo (ORPHA: 281222)
Síndrome de Netherton (ORPHA: 634)
Síndrome SAM (ORPHA: 369992)
Síndrome IHS (ORPHA: 91132)
Síndrome ILVASC (ORPHA: 59303)
Tricotiodistrofia (ORPHA: 33364)
Ictiosis sindrómicas autosómicas con signos neurológicas prominentes (ORPHA: 281238 y ORPHA: 281241)
Síndrome de Sjögren - Larsson (ORPHA: 816)
Enfermedad de Refsum (ORPHA: 773)
Síndrome CEDNIK (ORPHA: 66631)
Síndrome MEDNIK (ORPHA: 171851)
Queratodermia ictiótica - paraplejia espástica - hipomielinización - facies dismórfica (ORPHA: -)
Síndrome de ictiosis congénita - discapacidad intelectual - cuadriplejia espástica (ORPHA: 352333)
Síndrome ARC o ARKID (ORPHA: 2697)
Enfermedad de Gaucher fetal (ORPHA: 85212)
Deficiencia múltiple de sulfatasas (ORPHA: 585)
Síndrome de Neu - Laxova (ORPHA: 2671)
Ictiosis similar a arlequín con trombocitopenia (ORPHA: -)

Trastornos congénitos de la glicosilación (ORPHA:137)
Otras ictiosis sindrómicas (ORPHA: 281244)
Síndrome KID (ORPHA: 477)
Enfermedad por depósito de lípidos neutros (ORPHA: 98907)
Síndrome de ictiosis - prematuridad (ORPHA: 88621)
Síndrome de HELIX (ORPHA: 528105)
Síndrome de ictiosis - estatura baja - braquidactilia - microesferofaquia (ORPHA: 363992)
Queratodermia palmoplantar y perianal / ictiosis similar

IFAP: *ichthyosis follicularis, alopecia, and photophobia* (ictiosis folicular, alopecia y fotofobia), MEND*: male* EBP *disorder with neurological defects* (desorden *EBP* masculino con defectos neurológicos), CHILD: *congenital hemidysplasia with ichthyosiform erythroderma and limb defects* (hemidisplasia congénita con eritrodermia ictiosiforme y defectos en las extremidades), SAM: *severe dermatitis, multiple allergies, and metabolic wasting* (dermatitis grave, alergias múltiples y desgaste metabólico), ILVASC: *ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis* (ictiosis, vacuolas en los leucocitos, alopecia y colangitis esclerosante), CEDNIK: *cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma* (disgénesis cerebral, neuropatía, ictiosis y queratodermia), MEDNIK: *intellectual disability, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratoderma* (discapacidad intelectual, enteropatía, sordera, neuropatía periférica, ictiosis y queratodermia), ARC: *arthrogryposis, renal dysfunction, and cholestasis* (artrogriposis, disfunción renal y colestasis), ARKID: *autosomal recessive keratoderma, ichthyosis, and deafness* (queratodermia, ictiosis y sordera autosómica recesiva), KID: *keratitis, ichthyosis, and deafness* (queratitis, ictiosis y sordera), HELIX: *hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia* (hipohidrosis, desequilibrio electrolítico, disfunción lacrimal, ictiosis y xerostomía)

Tabla 2 Formas infrecuentes de las ictiosis sindrómicas

Enfermedad	Genes causales	Características principales
[0,1-3]*Síndromes con ictiosis ligada al X (ORPHA: 281210)*		
Trastorno EBP masculino con defectos neurológicos (MEND, ORPHA: 401973)	*EBP*[1] (XR, MIM: 300960)	Caracterizado por ictiosis, síntomas neurológicos (retraso en el desarrollo y convulsiones) y dismorfia craniofacial, con posible afectación de otros órganos[1].

▒Hemidisplasia congénita con nevo ictiosiforme y defectos en las extremidades (CHILD, ORPHA: 139)	*NSDHL*[2] (XD, MIM: 308050)	Caracterizada por un nevo principalmente ipsilateral (afectando estrictamente a la mitad del cuerpo a lo largo del plano sagital) con hipoplasia de las estructuras esqueléticas (baja estatura o ausencia de extremidades) y, en algunos pacientes, del cerebro y los órganos (pulmones, corazón y riñones)[2].
[0,1-3]**Síndromes ictióticos autosómicos (con)**		
[0,1-3]*Anomalías prominentes del pelo (ORPHA: 281222)*		
▒Síndrome de ictiosis - hipotricosis (IHS, ORPHA: 91132)	*ST14*[3] (AR, MIM: 602400)	También conocido como síndrome de ictiosis - atrofodermia - hipotricosis - hipohidrosis. Se caracteriza por ictiosis congénita difusa, indentaciones foliculares sin pelo (atrofodermia folicular), hipotricosis e hipohidrosis[3].
▒Síndrome de ictiosis - leucocitos vacuolados - alopecia - colangitis esclerosante (ILVASC, ORPHA: 59303)	*CLDN1*[4] (AR, MIM: 607626)	También conocido como síndrome de ictiosis neonatal - colangitis esclerosantes. Se asocia a ictiosis, hipotricosis del cuero cabelludo, alopecia cicatrizal, anomalías dentales e inflamación de los conductos biliares[4].
[0,1-3]*Signos neurológicos prominentes (ORPHA: 281238 and ORPHA: 281241)*		
▒Enfermedad de Refsum (ORPHA: 773)	*PEX7*[5] (AR, MIM: 308100)*, PHYH*[6],[7] (AR, MIM: 266500)	También conocida como neuropatía motor y sensorial hereditaria tipo 4, heredopatía atáctica polineuritiforme o deficiencia de fitanico - CoA hidroxilasa. Se caracteriza por pérdida progresiva de función retinal (retinitis pigmentosa), neuropatía periférica, falta de olfato (anosmia), falta de coordinación motora (ataxia cerebelosa) e ictiosis. La elevación (>200µmol/l) de los niveles de ácido fitánico en suero es patognómica[5].
▒Síndrome de disgenesia cerebral - neuropatía - ictiosis - queratodermia palmoplantar (CEDNIK, ORPHA: 66631)	*SNAP29*[8] (AR, MIM: 609528)	Suele causar muerte prematura por neumonía por aspiración[8].

Síndrome de discapacidad intelectual - enteropatía - sordera - neuropatía periférica - ictiosis - queratodermia (MEDNIK, ORPHA: 171851)	*AP1S1*[9] (AR, MIM: 609313), *AP1B1*[10] (AR, MIM: 242150)	Causado por variantes patogénicas recesivas en *AP1S1*. Un síndrome fenotípicamente similar, llamado síndrome autosómico recesivo de queratitis - ictiosis - sordera (KIDAR, ORPHA: -), está causado por variantes patogénicas recesivas en *AP1B1*.
Queratodermia ictiótica - paraplejía espástica - hipomielinización - facies dismórfica (ORPHA: -)	*ELOVL1*[11] (AD, MIM: 618527)	Caracterizada por queratodermia ictiótica, paraplejía espástica, hipomielinización y facies dismórfica.
Síndrome de ictiosis congénita - discapacidad intelectual - cuadriplejía espástica (ORPHA: 352333)	*ELOVL4*[12] (AR, MIM: 614457)	También conocido como neuroictiosis asociada al gen ELOVL4, esta enfermedad también presenta convulsiones
Síndrome de artrogriposis - disfunción renal - colestasis (ARC, ORPHA: 2697)	*VIPAS39*[13] (AR, MIM: 613404), *VPS33B*[14] (AR, MIM: 208085)	Caracterizado por artrogriposis neurogénica, disfunción de los túbulos renales, defectos en la producción de bilis (colestasis) ictiosis y muerte en el primer año de vida[14]. Esta enfermedad es alélica con queratodermia - ictiosis - sordera - autosómica recesiva (ARKID, ORPHA: -), también causada por mutaciones patogénica recesivas en *VPS33B*[15].
Enfermedad de Gaucher fetal (FGD, ORPHA: 85212)	*GBA1*[16] (AR, MIM: 608013)	También llamada enfermedad de Gaucher tipo II o perinatal letal. Se caracteriza por movilidad fetal reducida, contractura de las articulaciones (artrogriposis), dismorfia facial, con trombocitopenia ocasional, ictiosis y muerte en útero o poco después del nacimiento[16]. Estos neonatos y niños experimentan deterioro neurológico progresivo.
Deficiencia múltiple de sulfatasas (MSD, ORPHA: 585)	*SUMF1*[17] (AR, MIM: 272200)	También conocida como sulfatidosis juvenil tipo Austin. Se caracteriza por ictiosis similar a IRLX, retraso en el desarrollo y las anomalías neurológicas y esqueléticas de las enfermedades de almacenamiento y muerte prematura debida a complicaciones respiratorias[18].

▒Síndrome de Neu-Laxova (NLS, ORPHA: 2671)	*PHGDH*[19] (AR, MIM: 256520), *PSAT1*[20] (AR, MIM: 616038), *PSPH*[21] (AR, MIM: -)	Caracterizado por membrana colodión, malformaciones severas, microcefalia y retraso en el crecimiento intrauterino que lleva a muerte *in utero* o poco después del nacimiento[21].
[0,1-3]*Trastornos de la glicosilación*		
▒Deficiencia de UDP - glucosa ceramida glicosiltransferasa (ORPHA: -)	*UGCG*[22] (AR, MIM: -)	Se manifiestan como bebé colodión con contracturas congénitas de las articulaciones[22]. Esta condición descrita recientemente ha sido mayoritariamente letal en los primeros meses de vida, pero se espera que tuviera efectos neurológicos graves[22].
▒Trastorno congénito de la glicosilación tipo 1F (CDG-1F, ORPHA: 79323)	*MPDU1*[23] (AR, MIM: 609180)	Caracterizado por tono muscular excesivo (hipertonía), retraso psicomotor e ictiosis[23].
▒Trastorno congénito de la glicosilación tipo 1M (CDG-1M, ORPHA: 91131)	*DOLK*[24] (AR, MIM: 610768)	También conocido como deficiencia de dolicol quinasa o hipotonía con ictiosis debido a deficiencia de fosfatasa de dolicol. Se caracteriza por reducción del tono muscular (hipotonía), inflamación, cardiomiopatía frecuente e ictiosis[24].
▒Trastorno congénito de la glicosilación tipo 1Q (CDG-1Q, ORPHA: 324737)	*SRD5A3*[25] (AR, MIM: 612379)	Presenta colobomas oculares, malformaciones cerebrales con discapacidad intelectual, hiperplasia de la glándula pituitaria e ictiosis[25].
▒Síndrome de coloboma - enfermedad cardíaca congénita - dermatosis ictiosiforme - discapacidad intelectual - anomalías de las orejas (CHIME, ORPHA: 3474)	*PIGL*[26] (AR, MIM: 280000)	Presenta coloboma, enfermedad cardíaca congénita, dermatosis ictiosiforme, discapacidad intelectual y anomalías de las orejas[26].
[0,1-3]*Otros signos asociados (ORPHA: 281244)*		
▒Síndrome de ictiosis - prematuridad (IPS, ORPHA: 88621)	*SLC27A4*[27] (AR, MIM: 608649)	Caracterizado por nacimiento prematuro, asfixia neonatal y placas ictióticas adoquinadas con extensa descamación que recuerda a la vernix[27] y suele mejorar drásticamente durante el periodo neonatal

		hasta dar lugar a piel casi normal. Los niños nacen con prematuridad cubiertos con una gruesa película parecida al vérmex especialmente expresiva en el macizo facial
Síndrome de hipohidrosis - desequilibrio electrolítico - disfunción lacrimal - ictiosis - xerostomía (HELIX, ORPHA: 528105)	*CLDN10*[28] (AR, MIM: 617671)	Caracterizado por hipohidrosis, pérdida renal de iones Na^+ y Cl^- causando desequilibrio electrolítico, ojo y boca secos (xeroftalmia y xerostomía) e ictiosis[28].
Síndrome de ictiosis - estatura baja - braquidactilia - microesferofaquia (ORPHA: 363992)	*CERS3*[29] + *ADAMTS17*[29] (HD, MIM: -)	También conocido como síndrome de microdeleción del 15q26.3. Se caracteriza por estatura baja, dedos cortos (braquidactilia), anomalías del cristalino (microesferofaquia) y miopía, características del síndrome de Weill - Marchesani (asociado a *ADAMTS17*), así como ictiosis con fenotipo EIC (asociado a *CERS3*)[29].
Queratodermia palmoplantar y perianal / ictiosis similar a arlequín con trombocitopenia (ORPHA: -)	*KDSR*[30] (MIM: -)	Los pacientes presentan trombocitopenia con, o bien hiperqueratosis en palmas, suelas y piel anogenital, o bien síntomas cutáneos similares a la ictiosis arlequín

AD: autosómico dominante, AR: autosómico recesivo, HD: deleción homocigota, XD: dominante ligado al X, XR: recesivo ligado al X