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OPINION ARTICLE

Ichthyosis keeps surprising us

La ictiosis nos sigue sorprendiendo

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In clinical practice, the pediatric dermatologist from time to time encounters patients who have ichthyosis. Patients with this rare disease need a precise diagnosis, good advice on how to manage their skin condition, and adequate genetic counseling. The old days, when ichthyosis was categorized into only 6 major types are long gone.¹ A recent consensus conference revised the nomenclature and proposed a new classification that distinguishes 36 different types of ichthyosis and 10 related clinical entities (for example, CHILD-syndrome).² Major consensus was achieved on the proposal to categorize ichthyosis into two types: nonsyndromic, in which the phenotypic expression of the underlying genetic defect is only seen in the skin; and syndromic, in which the phenotypic expression of the underlying genetic defect is seen in the skin and other organs. This new classification was a major topic at the recent ichthyosis conference *Jornada de ictiosis* organized by Dr. Ángela Hernández Martín in Madrid.

Ichthyosis vulgaris and atopic dermatitis: An intriguing relationship

In the last six years, we have learned a lot about ichthyosis and both patients and also dermatology as a specialty, have benefited greatly. As recently as 2006, ichthyosis vulgaris was shown to be the result of filaggrin mutations,³ a discovery that quickly led to the insight that the very same

loss-of-function mutations that cause ichthyosis vulgaris also confer a strong predisposition to atopic dermatitis.⁴ These discoveries sparked renewed interest in the function of filaggrin and its role in the epidermal barrier. Animal studies using a genetic mouse model of ichthyosis vulgaris (flaky tail [ft/ft]) mice demonstrate abnormalities in barrier function in association with an absence of filaggrin.⁵

However, some riddles remain. Given the evidence of impaired cohesiveness in the stratum corneum in ichthyosis vulgaris, one would expect that barrier function parameters, such as transepidermal water loss (TEWL), skin hydration, and skin surface pH, would be profoundly affected in these patients. Surprisingly, studies to date reveal a rather moderate effect: for example, an increase in TEWL of less than 30% and only in patients with 2 filaggrin mutations^{6,7}; and a reduction in skin hydration of around 30%.⁷ The same applies to skin surface pH, which has been shown to be only modestly elevated in two studies^{6,8}; in our own series of ichthyosis vulgaris patients having two filaggrin-mutations only a trend toward a slightly increased surface pH was observed. Moreover, no significant effect on epidermal barrier function has as yet been demonstrated in patients with mild ichthyosis vulgaris who have only one filaggrin-mutation.

Interestingly, only around 50% of patients with ichthyosis vulgaris develop atopic dermatitis, and a further 20% develop other atopic diseases, such as allergic rhinitis or bronchial asthma. Thus, a significant proportion of these patients do not develop any atopic disease.⁹ Thus filaggrin mutations predispose patients to atopic diseases but are not sufficient by themselves to cause such conditions. In the future, biochemical studies of epidermal barrier function

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in patients with ichthyosis vulgaris may provide an answer as to how it is possible to prevent the onset of diseases such as atopic dermatitis despite high risk (for example, in patients with 2 filaggrin-mutations). The results of preliminary studies into this question by our group appear to imply that epidermal proteases imbalances may be a factor.

Hypohidrosis – an underestimated clinical problem

The well-known symptoms of autosomal recessive congenital ichthyosis (ARCI) are severe scaling, severe cosmetic disfigurement, skin inflammation, and in some cases significant pruritus. What is often overlooked is the fact that most of these patients can hardly perspire. Many report that the only area of skin on their bodies that can sweat is their nose! In summer, even in cooler European countries such as Germany, this hypohidrosis results in severe thermoregulation and heat intolerance. In my personal experience, some ARCI patients who exhibit only mild scaling have pronounced hypohidrosis. Treatments such as topical urea ointments often have very little effect on this symptom. In contrast, oral retinoids, such as acitretin, can be a very effective remedy resulting in normalization of sweat gland function, as demonstrated by gravimetric measurement of sweat rates before and after treatment.¹⁰ This finding suggests that hypohidrosis in ARCI and other types of ichthyosis may be due to altered sweat gland function rather than to obstruction of sweat gland ducts.

Novel clinical entities

Another surprising facet of this disease is that novel clinical entities continue to emerge. Thus, inflammatory type B peeling skin syndrome has been considered to be a clinical variant of the Netherton syndrome featuring erythroderma and extensive skin peeling.¹¹ However, true peeling skin syndrome does exist and was recently shown to be due to loss-of-function mutations in the gene for corneodesmosin.¹² It shares a number of clinical features with Netherton syndrome – including erythroderma, extensive skin peeling, pruritus, and atopy in the form of food allergies and highly elevated total IgE levels – but lacks the hair abnormality (trichorrhexis invaginata) so typical of that syndrome.

Exfoliative ichthyosis¹³ is another disease characterized by erythroderma at birth and slight hyperkeratosis accompanied by exfoliation in later life. The clinical hallmark of this condition is the water sensitive palmoplantar keratoderma that distinguishes it from type B peeling skin syndrome. This type of keratoderma is markedly exacerbated by exposure to moisture, with patients' hands and feet resembling the fingers of washing women who have manually washed clothes for several hours. Surprisingly, loss-of-function mutations in the gene encoding cystatin A have been identified in this disease. Like LEKTI, cystatin A is a component of the cornified envelope and a protease inhibitor that can inhibit dust mite allergens, such as the dust mite-derived cysteine proteases Der p1 and Der f1.¹⁴ Although cystatin A is involved in processes such as sensitization against house dust mite, it may have other biological roles in the lower epidermis. Interestingly, in

water sensitive plantar keratoderma, electron microscopy reveals prominent intercellular edema of the suprabasal and basal cell layers and aggregation of tonofilaments, implying that skin peeling originates at the basal/suprabasal level.¹⁵

Bathing and bath additives rediscovered

Several years ago, patients with ichthyosis were strongly discouraged from bathing by many dermatologists, who felt that it would negatively affect skin surface pH for all skin diseases. Today we know that ichthyosis patients should take a cleansing bath daily and rub their skin with special gloves to mechanically remove some of their scales. In many, although not all patients, this mechanical scale removal is greatly facilitated by adding two handfuls of sodium bicarbonate (baking powder) to the bath water. This therapy, developed by our late colleague and friend Wolfgang Küster,¹⁶ has also been used successfully in the United States.¹⁷ The mechanisms underlying the usefulness of sodium bicarbonate as a bath additive in this setting have not yet been well studied; however the addition of sodium bicarbonate to bath water raises the pH (from 5.5 to 7.9 in the example cited).¹⁷ We now know that normal desquamation requires the enzymatic dissolution of corneodesmosomes by KLK5 and KLK7 and that these serine proteases have alkaline pH optima.¹⁸

Topical retinoids rediscovered

In the past, pharmaceutical companies have neglected ichthyosis and focused on common dermatologic conditions, such as acne, rosacea, and psoriasis. However, there is now a renewed interest in ichthyosis and scaly skin, and 2 topical retinoids are currently in clinical trials. One of these is tazarotene, which has produced quite promising results in a Phase II trial. The other is still in phase II. Moreover, a large multicenter clinical trial has been undertaken with the drug liarozol in the management of ARCI. Although the clinicians involved in this study observed a significant beneficial effect on scaling, the primary endpoint chosen (investigator global assessment) was not achieved, a good example of the difficulties involved in choosing appropriate endpoints and in study design (for example, the need for large control group when studying rare diseases). However, there is hope that the overall encouraging experience with liarozol will stimulate the pharmaceutical companies to continue to explore this option. The future, of course, lies with targeted therapies. Using a skin humanized mouse model, a Spanish–German collaboration has assembled the first experimental evidence showing that topical enzyme replacement therapy with an enzyme solution containing transglutaminase-1-liposomes has convincing effects on scaling and on restoring epidermal architecture in transglutaminase-deficient lamellar ichthyosis.

To sum up, ichthyosis research has helped us to gain a much better understanding of the mechanisms involved in epidermal differentiation, and ichthyoses can be regarded as diseases of the epidermal barrier. We are beginning to understand how deficiencies in epidermal barrier constituents, such as filaggrin and corneodesmosin, and the lack of a serine protease inhibitor (LEKTI) can give rise to a non-cohesive stratum corneum and contribute to allergic

sensitization and atopic diseases. At the same time, we are witnessing the rediscovery of the usefulness of bathing and bath additives, such as sodium bicarbonate, as an efficient low technology strategy for combating excessive scaling, and the introduction of topical retinoids for the treatment of scaly skin. Ichthyosis really keeps surprising us.

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