Introduction to Ichthyosis (EDD) and Underlying Causes

CME Series on Epidermal Differentiation Disorders — Presented by Dr. Amy Paller

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Welcome to introduction to Ichthyosis or EDD and underlying causes. Part of First's CME series on epidermal differentiation disorders or ichthyosis. Presenting this topic is Doctor Amy Paller. Doctor Paller is the Walter J. Hamlin professor and chair of dermatology and a professor of pediatrics at Northwestern University Feinberg School of Medicine, an author of 800 scientific articles and leading textbooks.

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She is an expert on genetic skin disorders, including ichthyosis or epidermal differentiation disorders. Doctor Paller runs a basic science laboratory, a clinical research unit, and the Northwestern University Skin Biology and Diseases Resource based center. We'll be talking today about an overview of ichthyosis, which is a subset of EDDs. And we'll be talking about their underlying causes.

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There'll be others in this series that will give you more details about each of these forms of ichthyosis, and what you should know about their treatment. These are my disclosures. I do a lot of work in the clinical research and bench research arena. And as you can see, I've highlighted companies that are involved right now with ichthyosis research.

01:15

We have several learning objectives today to recognize the common forms of ichthyosis, and the potential impact of this group of disorders on quality of life. To understand the new classification for ichthyosis or EDDs and why it was developed, realize the reason that the genetic changes leading to ichthyosis affect the barrier and consider the mechanisms by which potential interventions in the future could lead to improvement.

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Now the ichthyoses are disorders of the epidermal barrier. And I've shown you hear some schematics that include the epidermal barrier. The epidermal barrier prevents us from drying out by limiting water loss through the outer layer of skin, the epidermis. And that water loss is transepidermal water loss then, or TEWL. The epidermal barrier protects from potential triggers of allergic reactions.

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Toxins, detergents, ultraviolet light, microorganisms, and trauma, including itch.

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All of these ichthyoses are genetic scaling disorders that are involved with the deficiency or ineffective functioning of our skin barrier. So why does this disruption in the skin barrier cause ichthyosis? When protein and lipid components of the barrier are not functioning, then the skin becomes leaky, its barrier is not good, and the body compensates by causing the skin to thicken, to flake and to become red.

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To protect us against our environment. That function of the epidermal barrier is measured through transepidermal water loss or TEWL. So what does ichthyosis look like? There are many variations in the appearance of ichthyosis that allows us using clinical means to subdivide our patients into groups, but they all involve variations in scaling and most of them in how red the skin is.

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For example, one type we'll talk about later with scaling skin, especially on the legs, and thickening and linear markings on the palms and soles. Another with scaling that is accentuated on the neck, but there's minimal skin redness. Here's another with a very distinctive type of scale that looks corrugated and overlie skin redness. A baby born with bright red skin and flaking of scale or desquamation this child has more of a shingle like scaling of her entire body, and this child with ichthyosis has bright red, thickened skin with mild peeling.

04:00
But regardless of all of these different sorts of appearances to ichthyosis. All of these subtypes have scaling and increased loss of water through the skin, which causes dryness.

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Now, the good news is that anyone in the United States, or even beyond, can get involved in the National Ichthyosis Registry. First has partnered with this registry to try to help us find genes and do research. This registry, if one signs up, allows for free diagnosis to find the underlying gene and also different research panels. In fact, there's a 72 gene panel that's available that allows us to find the vast majority.

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There have been 1500 genetic diagnoses made with pathogenic variants in 91% of patients enrolled in the registry, who were then eligible to have this service at no cost. And in fact, this team has found 12 new genes linked to ichthyosis just in the last several years.

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Now, the term epidermal differentiation disorders, or EDDs, is a relatively new umbrella term that includes the ichthyosis includes palmoplantar keratodermas with involvement primarily on the palms and soles, and includes some other scaling disorders. It is a heterogeneous group of more than 100 disorders, each with a different gene underlying it. The nomenclature in the past was

strictly based on clinical appearance, but now the new nomenclature, as with so many other genetic disorders, incorporates the name of the gene that is altered and its functional group.

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The intent is to find pathogenesis based therapies, therapies that would most likely then be the most effective with the fewest side effects for our patients with ichthyosis.

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The new classification eliminates eponyms. So many different forms of ichthyosis have been named after a historical person that we don't even know anymore, that are not helpful in helping us to really understand the features and the basis for the genetic problem.

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EDDs are divided into nonsyndromic or nEDDs, syndromic or sEDDs, and palmoplantar or pEDD forms.

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This is the way these new names look. For example among the nonsyndromic or nEDDs is filaggrin nEDD which has been called ichthyosis vulgaris and TGM1-nEDD which has been largely called lamellar ichthyosis. Among the sEDDs are SPINK5-sEDD or Netherton syndrome. And here's another NSDHL-sEDD-CHILD, including the mnemonic that tells you that this individual has congenital hemi dysplasia with ichthyosis and limb defects and includes that in the name in addition to the gene.

07:20
And then we have the palmoplantar EDDs, including what used to be called Pachyonychia congenita And now in this case, KRT6a-pEDD-PC, and another which used to be called Vohwinkel syndrome, LOR-pEDD, reflecting the fact that the gene is loricrin now the most common clinical types are shown here by far most common ichthyosis vulgaris, with fine scaling, especially on the legs and these hyper linear palms.

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These patients have a very high risk of developing atopic dermatitis, X-linked ichthyosis. Next most common with dark inherent scales and a risk of learning disabilities, as well as attention deficit disorder and autism.

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And then the plate like scaling of lamellar ichthyosis. These are the most common form of babies born with a collodion membrane. And can have these large dark scales that on the face can pull the eyelids open to such an extent that one has ectropion, as shown in this image here. We have what's been called harlequin ichthyosis in the past, always due to changes in the ABCA12 gene with bright red thickened skin that is very cracked in the newborn period and can lead to residual deformities because of the incredible tightening of skin.

08:55

What's been called epidermolytic icthyosis largely variance in keratin one and keratin ten with early blistering, and then a progressive compensatory response that leads to marked thickening and scaling of skin, especially over joint areas. In those who have the keratin one form, we see this extensive involvement of the palms and soles not in the keratin ten form to any such degree.

09:24

And then we have what's been called Netherton syndrome or SPINK5-sEDD with early bright red skin, with desquamation that transitions in the majority to a more localized wall-like scaling, as shown here at the bottom. These patients also have short, brittle hair and most have atopic associations, especially food allergies and among the forms of ichthyosis, all of which we've now shown are related to increased risk of allergies.

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Netherton has the most severe atopic associations.

09:59

So finally, I want to talk a bit about how skin changes in ichthyosis affect the skin barrier from a basic science standpoint. So the stratum corneum, as shown here on the right, is the outer “cornified” layer of skin. We think about the cells in the stratum corneum which are corneocytes or flattened keratinocytes as the bricks each surrounded by a dense protein envelope or the cornified envelope.

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And then we think about the mortar between these bricks as the highly structured lipids or fats between the bricks. The stratum granulosum is immediately below that. And here you can see the granules in the stratum granulosum beneath the dark colored stratum corneum. These granules are largely made up of profilaggrin in the outer skin cells or keratinocytes.

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The profilaggrin is broken down at the junction of the stratum granulosum to the stratum corneum, to form twelve or at least ten filaggrin monomers. Filaggrin also breaks down into proteins that keep skin hydrated and acidified at the surface so that they can be shed. normally.

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The most common form of ichthyosis, which occurs in 1 in 10 people, is generally deletion in filaggrin, and that leads to a deficiency of filaggrin, this haploninsufficiency is thought to be what results then in this dry skin scaling disorder. With the hyper linear palms, most people come into the office and don't even know that they have a form of ichthyosis.

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They think they have dry skin and they may be coming in with atopic dermatitis. Because this is common. Individuals who have this filaggrin nEDD may marry, and then each carries one gene with the deficiency of filaggrin as a result. But because it's common, 1 in 400 individuals will get

copies of the abnormal filaggrin from both of their genes. And in that case, we'll have what's a recessive rather than a dominant disorder and a much worse phenotype.

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Now the stratum corneum major protein is keratin. And primarily in the cell layers above the basal cell layer. We're talking about keratin one and keratin ten. They form a network of filaments, as you can see at the right that is beautifully arrayed from the nucleus to the border of the cells and provide structural integrity. This network of filaments, aggregates with the granules with a lot of filaggrin And as I just mentioned, made in the stratum granulosum and the filaggrin monomers bundle with the keratin in the stratum corneum.

13:16

Now when you don't have normal keratin, the abnormal keratin in this dominant disorder incorporates into the filaments and leads to cell instability as well as inflammation and blistering. You can see this baby born with a keratin ten abnormality, covered with blisters, as well as some thickening and scaling of skin. What we see under the microscope when we do a biopsy is a collapse of the differentiated epidermis.

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As you can see, the basal cells are nicely arrayed and then everything over that is lysine. And that's why this appearance has been called epidermal lytic over time. It's compensatory mechanism. Our patients get this thick scaling of skin, which as I mentioned before, involves palms and soles. If it's keratin one, because keratin one partners with keratin nine and not much with keratin ten in palms and soles.

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The stratum corneum also is the site where filaggrin promotes cell flattening and enables tight linking of proteins by an enzyme called transglutaminase one, which gives mechanical stability to the barrier. You can see that a deficiency of trans contamination one prevents the tight cross-linking required for barrier function. So we start with a baby who has this shiny collodion membrane of thickened but poorly functioning barrier.

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And over time, over the first month, that collodion membrane peels. And then over the first three months, we see the typical large lamellar scaling of this form of ichthyosis caused by deficiency of transglutaminase 1. Now, the cornea sites and the lipids between the cells are really what form the stratum corneum barrier.

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In between these cells are special ultra long chain fats called esterified omega hydroxy ceramides. These are also linked to this tightly linked protein network and becomes the scaffold then for other intercellular lipids. And it is transglutaminase 1, as we just talked about, that is also involved in linking the cornified envelope to these special ultra long ceramides.

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So let's look at the lipid barrier components. We have three major fats ceramides the most prevalent cholesterol next most prevalent and then free fatty acids. And these are all aligned in a specific way with the ceramides closest to the cells. Building on that scaffold I just mentioned of the essential ultra long chain omega hydroxy ceramides, and then cholesterol, which binds to ceremide, and then to the free fatty acid.

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And this all together forms sheets of highly organized lipids.

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This is a patient with a disorder that is in ceramide synthesis. And these individuals tend to have red finally scaling skin. But they also are born with a collodion membrane. Just as individuals who have TGM1-nEDD. And these large lamellar scales that look quite different. Here's a fun fact for you that I think most don't realize. When we think about ceramides in skin, we may be thinking that there's one thing, but in fact, there are about seven to more than 1000 unique ceramides in skin.

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So when we're putting on ceramide containing moisturizers, we are adding ceramides to skin, but not anywhere near the unique ceramides in skin, of which about 70% are deficient in ichthyosis. Now, also in this area are lamellar bodies. And in fact, these lipids that populate the areas between the cells in the stratum corneum are stored in these lamellar bodies in addition to some enzymes, and these are secreted into the intercellular space as the stratum granulosum to stratum corneum interface.

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A very important transport protein is ABCA12, and it's required for the release of these various enzymes and the lipids, and thus not only to provide the lipid barrier, but also for desquamation. Because the kallikrein are enzymes within them, are critical for desquamation or the natural peeling that cycles our skin.

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When one has a deficiency of ABCA12 transport protein, then one cannot get these lipids in to form the barrier, and one cannot appropriately desquamate. And that leads to a severe erythrodermic form of ichthyosis that's been called in the past harlequin ichthyosis. And of course, also for those with milder changes, more of a collodion phenotype.

18:47

Now the stratum corneum homeostasis requires this cell for surface layer peeling called desquamation, and it requires a more acidic pH. This is regulated by a cascade of kallikreins, which are then released from the lamellar bodies through the ABCA12 transport protein and are then functional in breaking down proteins, but also if we don't have them in causing inflammation, they're inhibited by LETKI, which is the product of SPINK5 serine protein inhibitor.

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And when we have a deficiency of SPINK5, we have a syndromic form of ichthyosis, which leads to inflammation of the skin in addition to a very poor barrier, and in fact, also some hair breakage abnormalities that are thought to relate to the deficiency of kallikrein 14.

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Corneocyte desquamation is also regulated by steroid sulfatase, which cleaves cholesterol sulfate and then forms cholesterol. Cholesterol sulfate competitively inhibits proteases that break down desmosomes between the cells. And so if you have too much cholesterol sulfate, you can't have normal desquamation.

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And by the way, the deficiency of placental steroid sulfatase, which is a function of the baby, is associated with failure to progress at delivery. So boys who have steroid sulfatase deficiency, which is encoded on the X chromosome, can have a disorder called STS-sEDD, This occurs in 1 in 1500 males. Two brothers are shown here with their scaling or ichthyosis, and one of the clues to diagnosis is asking the mother about her delivery, and in most cases you will hear that she was either induced by oxytocin or underwent a C-section because of the failure to progress after her bag broke.

21:10

Now, I mentioned the SPINK5-sEDD, I mentioned the SDS-sEDD, these are syndromic EDDs, and in fact there are 51 syndromic EDDs. And in each case, there are other organs affected in the majority of individuals. This is from a wonderful publication that talks about syndromic EDDs, but you can see that the that most of these actually have neurologic features, 71% and ophthalmologic features in about 50%.

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And interestingly, about 40% have hair abnormalities.

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Finally, I want to just mention burdens beyond the skin. There are the physical burdens of itch, pain, overheating because of poorly developed sweat glands, fissuring because of the thickened skin that cracks, and the infection risk that comes with having inflamed skin and a poor skin barrier. There are a variety of systemic effects that can be seen.

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Fluid and temperature regulation issues, particularly in neonates, growth and nutritional challenges, ocular complications, and hearing issues, sometimes sensorineural in some of these syndromic types. But for many, many really more of a conduction problem because of the shedding of the skin within the ear canal. And then there's of course the psychosocial burden, the high visibility of disease, social stigma and the impact on quality of life.

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And we'll be learning more about all of these in future modules that you'll hear. And finally, you'll also hear more about treatments for ichthyosis. There is no FDA approved treatment.

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We still use the same therapies we've been using for the last several decades. Emollients, keratolytics to reduce scale, retinoids, particularly for some forms with increased scaling, and infection prevention. What's so important to emphasize is that multidisciplinary care is key. Emerging therapies are rapidly moving forward, whether we're talking about targeted biologics, pathway-directed treatment, or gene therapy approaches.

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And with that, I thank you for your attention.