What is an EDD? Ichthyosis, a Form of EDD and its Underlying Basis

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

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Welcome to what is an EDD? Ichthyosis, a Form of EDD and its Underlying Basis. Part of First's CME series on epidermal differentiation disorders or ichthyosis. Presenting this topic is Dr. Amy Paller. Dr. 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 over 800 scientific articles and leading textbooks,

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She is an expert on genetic skin disorder, including ichthyosis or epidermal differentiation disorders. Dr. Paller runs a basic science laboratory, a clinical research unit, and the Northwestern University Skin Biology and Diseases resource based center.

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What is an EDD? We'll be talking about ichthyosis, a form of EDD and its underlying basis. These are my disclosures, and I've highlighted those that involve companies that are moving forward with new therapies for ichthyoses and EDDs. Our learning objectives today are to recognize the common forms of ichthyosis and the potential impact of this group of disorders on quality of life.

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To understand the new classification for ichthyosis, a form of EDDs, and why it developed, to realize the reason that the genetic changes leading to ichthyosis affect the barrier, and to consider the mechanisms by which potential interventions in the future could lead to improvement. Ichthyoses are disorders of the epidermal barrier, which, as you know, prevents us from drying out by limiting water loss through the outer layer of skin.

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This water loss is called transepidermal water loss, or TEWL.

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The epidermal barrier protects us from potential triggers of allergic reactions toxins, detergents, ultraviolet light, microorganisms and trauma, including from scratching the ichthyosis are

genetic scaling disorders that all involve a deficiency or ineffective functioning of our skin barrier.

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So why does a disruption of the skin barrier cause ichthyosis? When the protein and lipid barrier of skin is leaky, our body compensates by causing skin to thicken, flake, and become red to protect us against our environment. The function of the epidermal barrier is measured through transepidermal water loss or TEWL. So how does icthyosis look? There are many variations in the extent and the morphology of scaling and redness, from hyper linear palms, and fine flaking to scaling on the neck that looks dirty with minimal skin redness to thick

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corrugated scaling that overlies skin readiness to a baby born with bright red skin and flaking scales, to another child with shingle like scaling of the entire body. And this child with bright red, thickened skin with only mild peeling. Regardless of the appearance, all types have scaling and increased water loss through the skin, causing dryness. I encourage you all to get in touch with the National Ichthyosis Registry and refer any of your patients with ichthyosis.

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This registry has been involved for decades now in providing genetic diagnosis and doing research. Moving it forward. They have a 72 gene panel that allows detection of pathogenic variants in 91% of patients, and those in whom we can't find the variance will have whole exome sequencing and even whole genome sequencing done to try to find the underlying genetic cause.

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This service has provided information that has found 12 new genes linked to ichthyosis and has been very impactful. Now, the epidermal differentiation disorders or EDDs

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include ichthyosis and palmoplantar keratoderma with EDDs as an umbrella term. This is a heterogeneous group of more than 100 disorders, each with a different underlying genetic basis. Of course, we have nomenclature for ichthyosis that in the past was strictly based on clinical appearance, and we're not throwing that away.

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But the new nomenclature incorporates the name of the gene that is altered and its functional group. This type of nomenclature has been incorporated in a variety of different genetic groups of disorders outside of of skin disorders,

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it is intentional because knowing the gene and its functional group is going to be imperative for finding pathogenesis based therapies, which we think will be most effective for our patients and with the fewest number of side effects.

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Many of these therapies will be systemic therapies in the future. Now, the new

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nomenclature for EDDs eliminates eponyms which don't really have too much meaning in informing us about the disorder, even though they do honor historical figures like Netherton, Vohwinkel and Gaucher, etc. we're also eliminating a lot of the terms that have come across as potentially derogatory for our patients.

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They've been divided into non syndromic forms or nEDDs as shown here with some examples. Syndromic forms or sEDDs and palmoplantar forms or pEDDs again with example shown. And at the bottom I list three articles that came out in 2025, in the British Journal of Dermatology, which really are now the go to references because of the large numbers of tables and pictures that can help us to identify clinically the genes that are involved in our patients with ichthyosis.

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Now, the most common clinical types, of course, I hope all dermatologists know. But as a refresher, by far the most common what's been called in the past ichthyosis vulgaris, a derogatory term and now is called filaggrin nEDD. This is, of course, a disorder with fine scaling, especially on the legs and hyper linear palm. But it's important to recognize, because of the high risk of associated atopic dermatitis.

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Less common, but certainly not too rare, is X-linked ichthyosis. Now called STS sEDD with its large, dark, inherent scales and a risk of learning disabilities, attention deficit disorder and even autism, plate like scaling of lamellar ichthyosis, now called TGM1 nEDD, often presents at birth as babies with a collodion membrane that is shed, leading to the compensatory thickening of skin and ectropion of the eyes

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with the eversion of the lids and the risk of eye damage. Because of that tightness around the eyelid area. We have what's been called harlequin ichthyosis, another derogatory term, and now is called ABCA12 nEDD. With this cracking of skin and deformities that occur from the tightening in that early neonatal period, and then what leads to severe red scaling skin.

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We have our keratin neuropathy especially if keratin 1 and 10 that present with blistering and lead to progressive scaling and sometimes palmoplantar keratoderma. And what's been called Netherton syndrome, now also known as SPINK5 sEDD with early red skin, that desquamates and often transitions to more localized, wall like scaling and icthyosis linear circumflexa, as well as short, brittle hair.

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Now, we recently published showing that across the spectrum of congenital ichthyosis, there is an increased risk of atopy of all types, but it tends to be worst in Netherton syndrome or SPINK5 sEDD, particularly because of food allergies and anaphylaxis. Let's talk a little bit about basic science and remind about how these forms of ichthyosis are really linked to barrier abnormalities.

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We've got the stratum corneum of course, with its bricks, the cells and its mortar behind highly structured lipids between the bricks. And then we've got below it the stratum granulosum with its tight junctions that keeps the water in. And of course the major protein in the stratum granulosum. And what makes up the granules that we see histologically is the profilaggrin.

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The profilaggrin is broken down at the junction of the stratum granulosum and the stratum corneum, to form 10 to 12 filaggrin monomers. And then, of course, filaggrin also breaks down into proteins that keep the skin hydrated and acidified at the surface so that they can be shed normally, as you know well, ichthyosis vulgaris, now called filaggrin nEDD, occurs in 1 in 10 individuals who have a deletion, most often of the filaggrin gene on one allele, giving them haploinsufficiency and an autosomal dominant disorder.

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But when you've got 1 in 10 individuals, they can marry and create an ensemble recessive situation in 1 in 400 of them by probability, with a much more severe disease. Now, most of our individuals who have filaggrin nEDD come into our offices and think they have dry skin and never realized what caused it, and that it was genetic, and they particularly come in because of atopic dermatitis.

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So we have an opportunity as dermatologists to educate our patients. And hopefully in the future, they'll be therapy with topically applied filaggrin. Now the stratum corneum is made up primarily of keratin in our keratinocytes. And particularly in the suprabasaler areas keratin 1 and 10, which form this dense network of filaments as shown to the right that aggregate with the granules of primarily filaggrin in the stratum granulosum made in the stratum granulosum.

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So in the stratum corneum we have these. This bundling of the keratins and the filaggrin monomers. So what about the keratins there. Well when we have an abnormal keratin allele in an autosomal dominant disorder that in the past has been called epidermalytic ichthyosis, this form of non syndromic epidermal differentiation disorder presents at birth with blistering. And of course this is because when we look histologically at the biopsies we see a perfectly normal basal cell layer.

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But everything above it lysed, or with epidermolysis. Because of the instability of the incorporation of these keratin 1 and keratin 10, primarily keratin molecules that are there in forming the poor filament structure. There's also inflammation. That inflammation is critical to the blistering as well. Now we can see we're back to our appearance, this tremendous corrugated scale that is so typical and tends to be the worst over the joint areas.

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And those who have keratin 1 rather than keratin 10 abnormalities, we see a marked thickening and disabling thickening with fissuring of the palms and soles, because in this palm and sole area, keraton 9, not keratine 10 is the important partner for keratin 1. So keratin 1 is critical there and not keratin ten.

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And that's why we see this marked palmoplanter thickening. Now keratin is important but filaggrin also plays a role in cell flattening and enables tight linking of proteins by transglutaminase1 encoded by the gene TGM1, which gives the mechanical stability to the barrier when there's a deficiency of transglutaminase1 and what used to be called lamellar ichthyosis, babies are born with a collodion membrane.

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This shiny thickening, which actually represents a very poor barrier but is the body's attempt to compensate in the in utero environment now that is shed during the first month or so, and over the next few months we can see this, these large plate like scales in our patients who have these abnormalities. And often issues like the ectropion is shown here as I mentioned before.

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And that is because the transglutaminase is not there to form that tightly cross-linked epidermal barrier. But the transglutaminase is not just involved in linking the protein components of the cornified envelope, it's also thought that it's involved in linking a special ultra long chain group of fats, called esterified omega hydroxy ceramides to the tightly linked protein network, and these esterified omega hydroxy ceramides become the scaffold for other intercellular lipids.

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That I'll talk about in just a minute. So another reason why a deficiency of transglutaminase1 gives a profound barrier issue of ichthyosis. Now the lipid barrier components are, in decreasing order of their prevalence, primarily ceramides, cholesterol and free fatty acids. And they align in a certain way that gives these sheets of highly organized lipids with the ceramides closest to the cells.

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Building on that scaffold of the ultra long chain omega hydroxy ceramides, then cholesterol binding to the ceramides and the free fatty acids as well. So when one has a deficiency of these long chain ceramides because of abnormalities in ceramide synthesis, one can get red, finely scaling skin in a variety of other forms of ichthyosis that primarily present in the neonatal period, with a colonial membrane as the transglutaminase1 deficiency ones that I just talked about.

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Now, here's a fun fact for you, because I think we think about ceramides as a single lipid, but in fact, there are 700 to more than 1000 unique cermides in skin and most of them are deficient, especially in these deficiencies of ceramide synthesis. So think about our moisturizers with ceremide. They certainly can be helpful and have ceramides within them, but nowhere near the many unique ceramides that are deficient in ichthyosis.

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I want to also mention lamellar bodies in the lipid epidermal barrier, because these lamellar bodies form at the interface of the stratum granulosum and the stratum corneum. They contain lipids including ceramides as well as enzymes, and are secreted through these lamellar bodies into the stratum corneum. Now, ABCA12 transport protein is critical for the release of these lipids, for the release of these enzymes, and thus for desquamation, as well as having this normal lipid barrier.

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And when we have a deficiency of ABCA12 transport protein, we don't get the release of ceramides, we don't get the release of enzymes from the lamellar bodies. And that leads to a poor barrier, secondary inflammation and scaling, and a failure to have adequate desquamation with thickening of skin because of the kallikrein is not being secreted. Well, what's that all about?

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Well, that has to do with not only desquamation,but also the pH of skin. So to have desquamation you have to have a more acidic pH, and that is regulated by kallikreins which break down the proteins of skin. Without them one sees inflammation then. And they're inhibited by LEKTI which is encoded by SPINK5, a serine protease inhibitor. Now Netherton syndrome

an eponym that we'll not use in the future because we'll be using SPINK5 sEDD as a new name.

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But this syndrome is due to the absence of LEKTI because of SPINK5 defects and very high levels of certain kallikreins 5, 7, and the hair related care kallikrein, kallikrein 14. Now there's one more disorder I want to mention here, with respect to the basic science of the barrier. And that's one involving cholesterol. So cholesterol sulfate is cleaved by steroid sulfatase to form cholesterol.

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And it turns out that if you have an accumulation of cholesterol sulfate because you don't have this enzyme, you have competitive inhibition of proteases that break down desmosomes in between our cells, and very important to be broken down to have normal desquamation. So in these individuals with steroids sulfatase deficiency, we can't get normal desquamation of skin. In addition, a deficiency of placental STS, which is a reflection of the baby's STS, is associated with failure to progress at delivery.

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So we can see boys 1 in 1500 males with STS sEDD Because STS is encoded on the X chromosome but is not inactivated in affected female carriers, and these boys have this scaling skin that's typical of STS sEDD. I'm showing two brothers here, but I would encourage you to make sure to take a good history, because the history of a complicated delivery can be a clue to diagnosis.

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With women failing to progress once the bag breaks and they either end up getting on oxytocin or going to C-section to get that baby out. Now, the last two I just talked about of SPINK5 sEDD and STS sEDD are considered syndromic forms because they have other organs involved. And in fact, there are 51 syndromic forms of EDDs.

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As you can see in this nice table, the majority 71% have neurologic involvement under the brain there. And I'm only showing you a subset of these., the full list of 51 in the original article in the British Journal of Dermatology. Almost 50% have ophthalmological involvement. And interestingly, 40% of these sEDDs have hair involvement. Finally, I just want to end by telling you that that those with ichthyosis have tremendous burdens beyond the skin.

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We have the physical burdens of itch, pain, overheating from the reduced ability to sweat, and other developmental abnormality. Fissuring from the thick scale and the fissuring of course, can be quite painful. And then the risk of infection through the abnormal barrier. There are many systemic effects on fluid and temperature regulation, particularly during the neonatal period, and then growth and nutritional challenges.

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Because of the increased requirement in ichthyosis, particularly the erythrodermic forms. Ocular complication and hearing issues, both sensory neural as part of syndromic forms, but also conductive hearing issues because of the scale that blocks the ear canal, and finally the psychosocial burden of a highly visible disease with social stigma and quality of life impact. And we'll hear more about them in an upcoming module.

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I also want to stress that there's not a single FDA approved treatment for ichthyosis. For the last 40 years, we've had emollients, keratolytics, and retinoids to treat selectively for some of the lesser erythrodermic more scaling subtypes. And then, of course, infection prevention. And it takes a village. We need to reach out to our multidisciplinary team of specialists to try to help these patients, particularly those with syndromic forms, but even those with non syndromic forms.

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And I'm excited that the field is rapidly moving just from supportive treatment towards mechanism based treatment with targeted biologics, new pathway directed treatment coming and of course gene therapy approaches. Thank you so much for listening.