Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

Beneath the skin of PPKs

*Attendees at UCD's Charles Institute Seminar Series heard a presentation from **Prof Edel O'Toole** on the current clinical science in treating palmoplantar keratodermas*

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert practical advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology.

The fourth presentation in the series was delivered by Prof Edel O'Toole, Clinical Academic and Centre Lead at the Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine, UK.

A graduate of University College Galway, Prof O'Toole has decades of experience working in the UK and US and she delivered a presentation titled 'The Palmoplantar Keratodermas (PPKs)', which focused on the different types of PPK, associated characteristics, and genetic testing, among other aspects.

Prof O'Toole, who was described by Prof Tobin as "one of the most gifted clinical researchers in Europe today", provided attendees with a number of case studies to illustrate the differing clinical characteristics of a range of skin disorders caused by genetic mutations, including an overview of rare PPKs.

"Aquagenic keratoderma is actually quite common and you may know it as being associated with cystic fibrosis (CF)," said Prof O'Toole. "In a normal hand, the appearance is very subtle; you can perhaps see just a few papules, but when the hand is exposed to water, the appearance becomes far more marked. It has been suggested that it should be regarded as a CFTR-related disorder, similar to congenital absence of the vas deferens, bronchiectasis or pancreatitis." CF genetic testing will only identify 95 per cent of mutations, said Prof O'Toole, so physicians should always be wary that if they see a patient with aquagenic keratoderma, they may also be a carrier of a CF mutation.

Genetic mutations

Prof O'Toole also provided an overview of the characteristics of focal keratodermas, which present on the weight-bearing areas of the feet with varying callus sizes, as well as describing the five subgroups of pachyonychia congenita (PC) caused by mutations in five different genes. "The pain is not proportional to the calluses, as some of the people with the smallest calluses seem to experience the greatest amount of pain," she explained. Prof O'Toole also briefly outlined the genetics and characteristics of subungual hyperkeratosis, which can be quite variable in patients with keratin 6A mutations.

Palmar keratoderma is less common in patients with PC apart from patients with keratin 16 mutations and can present as linear calluses along the palms or fingers of the hand, she told the attendees. Oral leukokeratosis is another feature of PC and is most severe with the PC keratin 6A

Prof Edel O'Toole

mutation, explained Prof O'Toole, and can present with hoarseness in the first year of life, with laryngeal leukokeratosis, but may rarely also present with breathing difficulties.

Cysts occur in all types of PC but are most severe in patients with keratin 17 mutations, said Prof O'Toole. "Difficulties in infants usually occur in babies with PC-K6a mutations, so they may have problems with feeding and sucking, with worrying crying, and this is called 'first-bite pain'", explained Prof O'Toole. "It lasts for 15-to-25 seconds and is thought to be related to the salivary glands and it is even worse between the ages of four and 12, when it is often misdiagnosed as an ear problem." These young patients will often present with severe pain just in front of their ear for 25 seconds or so, she added.

For babies, parents can do a number of things to alleviate symptoms, such as enlarging the teat hole in a feeding bottle, use of a syringe for feeding, or making formula feeds slightly thicker, she told the seminar.

'Full house' of PC

"PC-K6a is the 'full house' of PC," Prof O'Toole continued. "These patients have wedge-shaped nails, focal keratoderma and leukokeratosis. In general, all 20 nails are affected and quite often, they also have follicular hyperkeratosis. It's also very early-onset, so generally, the abnormal nails are present in the first month or two of life and the calluses appear as soon as the child starts to walk. Often, there is very severe plantar pain early, at age four or five."

Patients with the PC-K17 mutation have the most extensive cysts and 76 per cent have a history of natal teeth, so they are born with two front teeth at birth that fall out and normal teeth grow to replace them, explained Prof O'Toole. "They may experience less-severe plantar pain and their nail involvement can also be less severe. A few of these patients may have leukokeratosis, but quite a few have follicular hyperkeratosis. The main problem these patients have is with cysts," she said. "Some of these patients may have 300-to-400 cysts."

Prof O'Toole continued: "With PC-K6b, it is a little less severe. These patients generally have affected toenails, 50 per cent have affected fingernails, and only 8 per cent have all 20 nails involved. They have milder keratoderma and milder pain and there is a later onset."

With regards to the PC-K6c, Prof O'Toole told the meeting: "These patients have focal keratoderma, and in general they have one or two nails affected; 24 per cent have cysts and they have milder keratoderma, milder pain, and a low incidence of natal teeth. This is definitely under-diagnosed, or can be diagnosed as something else, such as hyperkeratotic eczema or EB simplex."

There is a milder form of Olmsted syndrome caused by mutations in TRPV3, which can be mistaken for PC. Distinguishing features include inflammation of the lips and considerable erythema around the calluses, Prof O'Toole explained. Patients of African ethnicity may present with a focal, painful plantar keratoderma known as focal acral hyperkeratosis. Tylosis is also an important condition to be aware of, as these patients have a 95 per cent lifetime risk of oesophageal cancer, she added. These patients will present with focal keratoderma and follicular papules, as well as oral leukokeratosis and nail abnormalities, making the condition easy to confuse with PC. However, these patients will have a strong family history of oesophageal cancer. Autosomal recessive nail dysplasia can also be a differential diagnosis, she told the attendees, where an infant will present with significantly thickened nails.

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"Striate keratoderma can have various causes," Prof O'Toole pointed out. "It can be caused by mutations in keratins... definitely in keratin-1 or desmoplakin. This is one instance where biopsy can be of value in PPK, because you can decide whether it's a desmosomal gene or a keratin gene because if it is caused by a defect in the desmosomes, you will have loss of cell-cell adhesion between the keratinocytes and the epidermis, also known as acantholysis."

Warning sign

Prof O'Toole provided a brief overview of the various recessive PPKs with cardiomyopathy and outlined some work done by she and her colleagues on autosomal-dominant keratodermas accompanied by woolly hair, which is caused by mutations in desmoplakin. "You can see that all the affected people have woolly or curly hair, but there is considerable variation in how curly or woolly these patients' hair can be," she explained. "The warning sign there for a dermatologist is, if you see someone with a keratoderma, and they have curly hair, it would be good to know whether the rest of the family also have curly hair, or if they are the only ones. This is definitely something to bear in mind," said Prof O'Toole, who presented a number of case studies to illustrate the potential for this type of variation.

Prof O'Toole concluded her presentation by telling attendees: "We should consider a diagnosis of PC when patients present with focal keratoderma and plantar pain," she said. "We should also consider desmosomal gene mutations in patients with keratoderma with woolly hair and screen for cardiomyopathy. With late-onset PPKs, these are very often inflammatory, so patients will present at age 45 or 50 years, for example.

"Starting with a low dose of acitretin is very important — if patients start on 10 mg on alternate days, or 10 mg per day if it's a big person, that's the sort of dose I would start with and then work up to the maximum tolerated dose, rather than barging in with 25 mg or 35 mg, as the patient may end up with blistering and severe pain," said Prof O'Toole.

"In inflammatory dermatoses, it is also important to rule out tinea. For the future, personalised medicine will make genetic testing necessary for all."

During a lively Q&A session following Prof O'Toole's presentation, the question was raised of diversity of clinical features highlighted by Prof O'Toole in her presentation. She was asked whether genetic hyperkeratosis and other types of related disorders seem to get better with age. Prof O'Toole replied: "That is not generally the case with PPK, for example. With PC, the patient's condition becomes worse as they get older, but as their age progresses — 70 or 75 years old, for instance — they often improve a little. Generally speaking, other keratodermas remain the same, while in some cases, they can get worse."

Prof Tobin posed the question as to whether, in the context of altered mutations and potentially altered protein, these are ever seen as antigenic or autoreactive by a person's immune system. Prof O'Toole responded: "In PC, for example, it has been shown by RNA sequencing that if you sequence PC skin, you see an 'alarmin' response, as if there's a very impaired barrier, so there is a lot of inflammation. There have been some thoughts [by researchers] that inhibiting that inflammation may also help to control the pain — NSAIDs do actually help to control the pain somewhat. There has also been some work done on the EGF receptor, and it is thought that perhaps some drugs targeting this receptor may also work in PC," Prof O'Toole remarked.

Relife has had no input into the content of the series or article.