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Separating Fact from Fiction: The Realities of CKD-aP

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Dr. Pollock:
Chronic kidney disease-associated pruritus, or CKD-aP, is an underreported and underdiagnosed condition. It affects the quality of life of a significant proportion of patients with advanced kidney disease undergoing dialysis. Despite its prevalence, there are limited treatment options available for these patients. So today, we'll separate fact from fiction in CKD-associated pruritus.

This is CME on ReachMD, and I'm Dr. Carol Pollock.

Dr. Lanot:
And I am Dr. Antoine Lanot.

Dr. Pollock:
So let's approach this topic by first discussing the pathophysiology of CKD-associated pruritus. So, Antoine, what are the underlying mechanisms that contribute to the occurrence of the itch in people with CKD? And how common is this condition in patients with kidney failure undergoing dialysis?

Dr. Lanot:
Well, the pathophysiology of CKD-aP is complex, and its understanding has progressed in recent decades. Now we have 4 axes that are thought to cause pruritus in CKD patients.

The first one is the uremic axis. Uremic toxins accumulate in the plasma of CKD patients, and it has long been emphasized that some of these toxins could form crystals in the skin, thereby acting as exogenous pruritogens. However, it is worth noting that no such crystal has ever been found in skin biopsies. Moreover, in a DOPPS [Dialysis Outcomes and Practice Patterns Study] survey, no association was retrieved between pruritus and any of the phosphocalcic metabolism products, including phosphate.

The second axis is a peripheral neuropathy. Contrary to what happens in allergies, the histamine pathways are not involved in CKD-aP; some other pathways like the CO-H pathways mediate the signal. We know now that these pathways are overexpressed and overactivated in patients suffering from CKD-aP.

There is a third axis which involves the opioid receptors, kappa and mu. These receptors are located on the nerves' fibers, and while the mu receptors are pro-pruritogens, the Kappa receptors are anti-pruritogens. In CKD, there is an imbalance between the kappa and the mu receptors in favor of mu.

Finally, the fourth axis involves the immune system. Opioid receptors are located on several immune cells. The imbalance in favor of mu promotes an activation of these cells toward a TH-1 profile and therefore a pro-inflammatory state. This implies the release of various cytokines known to be able to activate the pruriceptors.

Concerning the prevalence of CKD-aP, this is a frequent condition with moderate to severe pruritus affecting from 25% to 50% of HD [hemodialysis] patients, depending on the series. However, this is an underestimate in diagnosis. In a DOPPS study published in 2017, we had 17% of the patients nearly always bothered by itching, who did not report itching to healthcare staff. In addition, 69% of medical directors of HD units underestimated the prevalence of pruritus in their own unit. So however frequent it is, this is an underestimated and an underreported diagnosis.

Dr. Pollock:
Well, that's an excellent summary of the cause of CKD-associated pruritus. I think it's clear from what you've said that there is a completely different pathophysiology in CKD-associated pruritus versus in the general population.

Dr. Lanot:
Yes, indeed, the pathways are totally different.

So, Carol, now that we have a better understanding of the pathophysiology and prevalence of CKD-aP, let's look at its effects. How does the itch impact our patients' quality of life? And how can we quantify the itch intensity and itch-related quality of life?

Dr. Pollock:
We know that itch can be quite often generalized, it can also be localized, and it's associated with visible skin lesions. So there are often scratch marks, but when it becomes chronic, then there is a prurigo nodularis that develops that is quite unsightly for patients. We recognize that people have, as you've said, a lot of comorbidity. They are bothered significantly in more than 50% of cases, and that's underreported. And it's associated with worse health-related quality of life amongst dialysis patients, whether or not we look at the burden of kidney disease, the symptoms, the physical components, or indeed the mental components. And we know that people are depressed, they feel embarrassed about their itching, it makes it difficult to concentrate, difficult to work, they avoid interaction with people because of the issues related to itch. They also then develop disturbed sleep. And disturbed sleep means that they are sleepy during the day and potentially unable to work or focus on family and friends as they would otherwise like to. So when we look at how we assess the severity of itching, we do this by looking at what's called the Worst Itch Numeric Rating Scale [WI-NRS]. And this is really a single question that asks whether or not people can rate their itch severity by circling the number that best describes your worst level of itch in the last 24 hours. So it goes from 0 to 10.

This has been validated in tests that have been undertaken in several studies of CKD-associated pruritus, in particular, the KALM studies. So it is useful to do in clinical trials, where multiple aspects of testing are done. But when we use it in a clinical setting, a simple test is the best test. And the Worst Itch-related Numerical Rating Scale, being a single question is most likely to be of use. When they looked at this testing tool in the KALM studies, a greater than 3-point improvement from baseline in the weekly mean of the WI-NRS score is a clinically meaningful change. So when we look at this, this was much improved by the use of difelikefalin, which we will get around to. There's also quality-of-life-related tools. And these are the Skindex, which is a primary quality-of-life tool. There are other tools. But I think that the WI-NRS and the Skindex seem to be 2 tools that are fairly easily used in clinical practice to rate severity and quality of life.

Dr. Lanot:
Thank you, Carol, for this great overview of the tools available for pruritus assessment. And as you said, the best test is a simple test. And this is sometimes complicated for the physicians to assess the quality of life of patients because of the complexity of the questionnaires and tests. And nowadays, there is no consensus in Europe. But I think that the SADS [Social Avoidance and Distress Scale] questionnaire has the advantage of being very simple and easy to use in clinical practice. The SADS is the presentation to the patient of 3 scenarios of a typical patient bothered or not by itching. And you can read it to the patient, the 3 scenarios of the patient, the A, B, or C. And to sum it up, the patient A has no problem with itching, the patient B has [a] moderate problem related to itch, and the patient C is very bothered by itching in several ways. And this very simple score has shown good correlation with other scales for the assessment of quality of life.

Dr. Pollock:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Carol Pollock, and here with me today is Dr. Antoine Lanot. We're discussing how to separate fact from fiction in CKD-associated pruritus.

Dr. Lanot:
So now let's turn to treatment. After diagnosing CKD-aP, we often rely on some off-label treatments, but the level of evidence of their effectiveness is somehow low. And there are frequent side effects associated with their use. Could you please elaborate on the drawbacks and adverse effects of these current therapies?

Dr. Pollock:

Of course. So I think everyone with CKD-associated pruritus needs to have attention to their adequacy of dialysis, if you like, so we need to ensure that we optimize their parathyroid hormone, the calcium and phosphate homeostasis. And we recognize that there is no evidence that doing such actually improves their itch. But still, we do that as a matter of first principle. We also then need to look at moisturization of the skin. And then in people who have more severe CKD-associated pruritus, we need to be really instituting itch-specific therapy, which is really difelikefalin, in addition to these universal approaches. Now, if we look at difelikefalin, it is the only agent that has been approved for CKD-associated pruritus.

There are other mechanisms of action in the other treatments that don't really address the specific cause of CKD-associated pruritus. Many of our patients will end up on antihistamines, but there is no evidence that a histaminergic pathway is involved in CKD-associated pruritus. It's associated with side effects, particularly sedation. And in the setting of a lack of benefit, we shouldn't be prescribing these. If we look at centrally acting opioids that have been used to treat particularly peripheral neuropathy, they are associated with the potential for drug dependency and abuse. And they also have limiting side effects such as sedation, dysphoria, and potentially a suicidal risk. If we look at gabapentinoids, they're sometimes used to treat CKD-associated pruritus. And they do have some benefits in very small studies up to, you know, 40 or so patients. So there may be a benefit, but again, there are adverse effects associated with them, particularly with dizziness, somnolence, weight gain, increased suicidal risk, and of course, they're renally excreted. So to use these, dosing is difficult in people on hemodialysis in particular. So I think that when we look at the evidence base, we are really looking at difelikefalin to improve the symptoms and the quality of life in people on hemodialysis with CKD-associated pruritus.

So do you have any additional insights on the unmet treatment needs of these patients?

Dr. Lanot:
Well, indeed there is a real unmet treatment need. For example, the most common first-line treatments are antihistamines. However, in CKD-aP, antihistamines should not be effective, because the neuropathic pathways effects are not histamine dependent. And in fact, as you said, the positive effects sometimes observed with antihistamines is probably due to their sedative effects, which is not something that we want for the patients. The risk of side effects is the main issue when using the current off-label therapies. For example, with gabapentinoids, you said they have a very narrow therapeutic index, cognitive impairment is the main issue with gabapentinoids. So nephrologists are not really prone to use this class of drugs in several countries. The overall vision is, on one side, a frequent but underdiagnosed disease associated with a poorer quality of life. And on the other side, treatments that are not very effective or which present significant risk of side effects, until we get these new treatments, the opioid receptor agonists, which have a very good safety profile and which have shown to be effective in 2 recent clinical trials.

Dr. Pollock:
Yes, I entirely agree with you. And also, you know, the gabapentinoids are excreted by the kidney and difficult to manage in terms of their dosing, etc.

So look, this has been a really excellent conversation, and I'm so pleased to have been able to discuss this with you. But maybe you can share one take-home message with our audience.

Dr. Lanot:
Well, thank you. For me, one of the most important messages would be the need to proactively screen patients with pruritus because of the underreporting and underestimation of this condition.

What would be your take-home message, Carol?

Dr. Pollock:
Look, I think that we really need to be looking at the patient perspective in this. So I think we really need to consider that if we can't add years to a patient's life, then we at least can add life to a patient's years. And I think reducing itch, improving quality of life, actually does add life to remaining years.

So I think that's all we have time for today. So I want to thank our audience for listening, and I really want to thank you, Dr. Antoine Lanot, for joining me and for sharing all of your valuable insights. It was really lovely to speak with you today.

Dr. Lanot:
Thank you very much, Dr. Carol Pollock. The pleasure was all mine.

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