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CPPD Epidemiology and Pathogenesis

Announcer:

You're listening to ReachMD. This episode of *Living Rheum*, titled "CPPD Epidemiology and Pathogenesis" is sponsored by Novartis US Clinical Development and Medical Affairs. The speakers have been compensated for their time. This program is intended for healthcare professionals. Here's your host, Dr Jason Liebowitz.

Dr Liebowitz:

Calcium pyrophosphate deposition disease, or CPPD disease, is often mistaken as simply a variation of gout, but it's much more complex than that. And understanding what exactly this disease is can help improve care for our patients.

This is ReachMD, and I'm Dr Jason Leibowitz. Joining me to discuss CPPD epidemiology and pathogenesis is Dr Sara Tedeschi. Dr Tedeschi is an Assistant Professor of Medicine at Harvard Medical School and Associate Physician at Brigham and Women's Hospital. She also serves on the American College of Rheumatology Committee on Quality of Care. Dr Tedeschi, thanks for being here today.

Dr Tedeschi:

I'm excited to be here and to be able to nerd out about one of my favorite rheumatologic disorders.

Dr Liebowitz:

I'm excited as well. So, to start us off, Dr Tedeschi, can you clarify the terms used to refer to the condition of CPPD?

Dr Tedeschi:

I would be happy to. CPPD disease is an arthritis that's caused by calcium pyrophosphate crystals. Until recently, CPPD disease had been referred to generally as pseudogout, which is a term that originates from an early description of this disease in which patients presented with an acute gout-like arthritis, but their synovial fluid crystal analysis revealed crystals that were resistant to digestion by uricase, and they did not have gout.

In 2011, the European Alliance of Associations for Rheumatology, which is EULAR, reformulated all terminology related to CPPD disease to be more descriptive, and this is to account for the different manifestations of CPPD. The term pseudogout, I think historically, has conjured up this picture of an acute inflammatory arthritis, but there are many other manifestations of CPPD disease, including a chronic inflammatory arthritis that can appear very similar to rheumatoid arthritis, as well as osteoarthritis with chondrocalcinosis in unusual joints, potentially with different and unusual features of osteoarthritis.

It should also be noted that chondrocalcinosis is a radiographic manifestation. In and of itself, it's not a disease. And I think this is an important distinction because sometimes people will tell patients that they have chondrocalcinosis and patients don't know, is this the disease itself or is this just a finding? And it's really just a finding that could support a diagnosis of CPPD disease.

Dr Liebowitz:

Thank you, that's very helpful, and does indeed clarify a topic that's confusing to many clinicians. So with that background in mind, can you give us a sense of the epidemiology of this disease?

Dr Tedeschi:

Sure. CPPD disease has been estimated to affect 4 to 7% of the adult populations in Europe and the United States, especially among

older patients. Now, it should be noted that this prevalence estimate is based on studies of radiographic chondrocalcinosis, so a radiographic finding. And the prevalence of each of the different manifestations of CPPD is not known. It's notable that radiographic chondrocalcinosis is not a very sensitive marker of calcium pyrophosphate deposition. So this is probably an underestimate, in fact.

The average patient who has CPPD is generally in their 60s to 70s. It's very uncommon for a person younger than 60 to have CPPD. And radiographic surveys have demonstrated that the prevalence of cartilage calcification or chondrocalcinosis, it increases with age, and there's not thought to be a major sex predominance in CPPD.

Dr Liebowitz:

Wonderful. Now, if we dive a little deeper into this, can you give us a sense of the pathogenesis of CPPD disease?

Dr Tedeschi:

Yes. CPPD occurs when calcium pyrophosphate crystals form outside of articular cartilage. And this is facilitated by articular cartilage vesicles. Pyrophosphate is generated in all cells when ATP breaks down. And in the extracellular matrix of the chondrocytes, this pyrophosphate complexes with calcium to create calcium pyrophosphate crystals. There are several transmembrane enzymes such as ANKH that modulate the levels of extracellular ATP and, therefore, extracellular pyrophosphate. And in some rare familial forms of CPPD, *ANKH* is mutated. There are also extracellular matrix factors that regulate the formation of these crystals. When the crystals are present in the synovial space, they can produce inflammation, but they also have adverse biomechanical consequences and direct catabolic effects on the joint tissues. And these factors ultimately contribute to cartilage damage.

Dr Liebowitz:

Thank you. That's a wonderful summary. What can you tell us about the mechanisms of these different forms of CPPD?

Dr Tedeschi:

Well, first, let's focus on familial CPPD, which is rare, but it often manifests in patients when they're early adults, which is very different from the vast majority of people with CPPD when they're having the disease onset in their 60s or 70s. There are two genetic loci that are associated with familial CPPD. The first is in the *ANK* gene, which is also called *CCAL2*, and this is on chromosome 5p. Mutations in *ANK* are inherited in an autosomal dominant pattern, and this is likely a gain of function in mutation that leads to increased extracellular pyrophosphate concentration in the context of the cartilage. And then recently, the *CCAL1* locus on chromosome 8 has been identified to be osteoprotegerin, also called *TNFRSF11B*. And this gene was described in a family with early onset osteoarthritis and chondrocalcinosis.

Dr Liebowitz:

Wonderful. And to bring this all together, what can clinicians do to improve our understanding of CPPD?

Dr Tedeschi:

First, we need to increase provider awareness of CPPD disease. I think that there are many patients who are diagnosed with seronegative rheumatoid arthritis, and yet they're not responding to typical therapies for rheumatoid arthritis, and potentially they could have something like chronic inflammatory arthritis due to CPPD.

Second, the development of classification criteria for CPPD will facilitate research into this disease. Currently, the American College of Rheumatology and EULAR are cosponsoring development of classification criteria, and so this will be an exciting step forward for future research into this disease, such as development of large cohorts, potentially being able to leverage machine learning, to help understand the different manifestations of CPPD.

I think also our increased and growing understanding of the genetics and epigenetics of CPPD have the potential to shed light on some of the other mechanisms that may be in play at this disease, especially in the large group of patients that do not have early onset disease. Establishing a biorepository of people with CPPD would be one important example of ways that we can help understand the pathogenesis of this type of arthritis.

Dr Liebowitz:

Excellent. Well, with those considerations in mind, I want to thank my guest, Dr Sara Tedeschi, for helping us better understand the epidemiology and pathogenesis of CPPD. Dr Tedeschi, it was a great pleasure speaking with you today.

Dr Tedeschi:

Thanks for indulging me on this topic.

Announcer:

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