CPPD: Managing a Prevalent Predicament

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Calcium pyrophosphate deposition disease is many times more common than rheumatoid arthritis, but rarely studied and difficult to diagnose. Here an expert rheumatologist offers the basics for management today and prospects for the future.

Source: Rheumatology Network

Calcium pyrophosphate deposition disease (CPPD), which stems from the deposition of calcium pyrophosphate (CPP) crystals in articular hyaline and fibrocartilage cartilage, is a common cause of both acute and chronic arthritis in elderly patients. It will become increasingly prevalent as the population ages.

Conservative estimates judge that CPPD now affects at least 10 million Americans. However, although it was described in the early 1960s in both Europe and the US,[1,2] fifty years later we know remarkably little about the pathogenesis of CPPD, have few randomized trials of therapies, and consequently have no proven management strategies. Fewer than 3000 references pertaining to CPPD appear in Ovid from 1962 through 2015, notably few of them randomized trials. (In contrast rheumatoid arthritis, which is only about 15% as prevalent as CPPD in the US, has over 100,000 citations.) CPPD can be a challenge to diagnose accurately, and is often overlooked in patients with a chronic polyarticular pattern of arthritis.[3] (About 25% of patients thought to have typical osteoarthritis have CPP crystals in their synovial fluid at the time of knee joint replacement.) The similar acute mono- or oligoarthritis known as pseudogout, in contrast, is usually not missed. CPPD is also associated with a unique group of metabolic disorders including hemochromatosis and hyperparathyroidism. It occurs in both sporadic and familial forms.

Why is CPPD so poorly understood?

• Elderly patients often have several reasons for joint pain, and sorting these out can be difficult.
• The lack of effective therapy may discourage a careful clinical diagnosis of CPPD.
• CPP crystals are small, weakly birefringent, and difficult to find under polarizing light microscopy.
• Diagnostic tests are nuanced and easy to misinterpret.
• Perhaps most importantly, the lack of clear well-validated diagnostic criteria has hampered progress in this disease.

How do we differentiate CPPD from other common forms of arthritis? This is a critical issue for those of us caring for patients with CPPD.

• Acute CPPD (also known as pseudogout) often presents very much like acute gouty arthritis. It can be diagnosed by observing CPP crystals in synovial fluid from the affected joint (Figure 1). Suspect acute CPPD when the involved joint is not typical of gout, such as a shoulder or wrist.
• Important: Remember that the presence of synovial fluid crystals does not rule out septic arthritis.
• The chronic polyarticular forms of CPPD are typically more challenging to diagnose. They often mimic osteoarthritis with or without inflammatory “flares” but can also present with a symmetric inflammatory arthritis resembling rheumatoid arthritis.
Like gout, in the absence of the ability to “crystal-prove” a patient, certain patterns of chronic arthritis suggest CPPD:

- a joint distribution different from that of typical OA, such as involvement of the shoulders, wrists and 2nd and 3rd MCPs
- characteristic radiographic features including tendon calcification and severe joint destruction.5

What are the imaging criteria for diagnosing CPPD?

The Ryan and McCarty diagnostic criteria for definite CPPD include observation of positively birefringent rhomboid-shaped crystals in synovial fluids of affected joints, in addition to the presence of radiographic chondrocalcinosis (Figure 2).3 That said, while chondrocalcinosis itself is a clue to the presence of CPPD, it should not be relied on to confirm the disease; it detects only about 40% of patients with CPPD.

- Careful examination of synovial fluids under polarizing light will often confirm the diagnosis.
- Conventional radiography can detect chondrocalcinosis.
- CT scanning detects calcification and is particularly useful for spinal involvement.
- MRI lends little additional information.
Figure 2. The arrow denotes dense linear deposits typical of chondrocalcinosis.

- Ultrasound imaging may not be able to fully distinguish between gout and CPPD.⁶
- Advanced imaging with newer techniques holds out some promise for new tools to improve diagnosis.

**How and why do CPP crystals form in cartilage?**
The etiology is still not fully understood. In the current paradigm requires, high levels of extracellular inorganic pyrophosphate in cartilage play a role analogous to that of urate in gout.

The transmembrane protein known as ANK has been shown to be involved in chondrocyte pyrophosphate production,⁷ and mutations of this protein occur in some kindreds with familial CPPD. Articular cartilage vesicles likely act as sites of crystal formation in the extracellular matrix, and factors inherent in the chondrocyte phenotype and its matrix also modulate CPP crystal formation.

Just as delineating causation was pivotal to development of new gout treatments, defining the factors that produce CPP crystals in cartilage may lead to new therapies for CPPD.

**How CPP crystals affect existing OA?**
CPP crystals contribute to joint degeneration though several pathways. Calcium-containing crystals have direct effects on resident articular cells, such as synoviocytes and chondrocytes. They are mitogenic for synovial cells and elicit catabolic cytokines and prostaglandins from chondrocytes.⁸ Their presence in hyaline and fibro-cartilage such as the meniscus of the knee leads to altered biomechanics and accelerates joint damage. CPP crystals can also induce a vigorous inflammatory response, likely by signaling through the innate immune system.⁹

**How can we treat CPPD?**
**Acute CPPD** (pseudogout): Typically treated very much like acute gout, and probably responds in a similar manner.

- Low dose oral colchicine and NSAIDs may be effective, but are often poorly tolerated or contra-indicated in the elderly population most susceptible to CPPD.
- Intra-articular corticosteroids, subject of the only clinical trial in acute CPPD, shortened acute attacks.¹⁰
- Systemically administered corticosteroids are also effective in acute CPPD.
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Chronic CPPD: There are few therapies, and the lack of good studies renders all of them unproven.
- **Hydroxychloroquine** has been studied in a poorly characterized patient cohort.\(^\text{11}\)
- **Methotrexate** was initially met with enthusiasm, but a small clinical trial from Europe which demonstrated no effect.\(^\text{12}\) Although this study was negative, methotrexate may still have a role in treating CPPD.\(^\text{13}\)
- We will often try a combination of **prednisone and low dose colchicine**, but the efficacy of this regimen has not been proven.
- Similarly, **anakinra and other IL-1β antagonists** may improve acute inflammation and prevent future attacks, but remain un-studied in any type of clinical trial.\(^\text{14}\)

The take-home message:

CPPD is common and understudied. 
Suspect CPPD in elderly patients with unusually distributed or very severe polyarticular chronic arthritis, as well as in those with pseudogout-like presentations.
Diagnostic challenges exist but are surmountable. The first step in improving management of patients with CPPD is making an accurate diagnosis.
While we await new and more effective therapies, combinations of anti-inflammatory drugs may be useful for patients with CPPD.

References:
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