Calcium pyrophosphate deposition disease: clinical manifestations

C. Ferrone, R. Andracco, M.A. Cimmino
Clinica Reumatologica, Dipartimento di Medicina Interna, Università di Genova, Italy

SUMMARY
Calcium pyrophosphate deposition (CPPD) disease is an arthropathy caused by calcium pyrophosphate dihydrate (CPP) crystal deposits in articular tissues, most commonly fibrocartilage and hyaline cartilage. According to EULAR, four different clinical presentations can be observed:
1) asymptomatic CPPD;
2) osteoarthritis (OA) with CPPD;
3) acute CPP crystal arthritis;
4) chronic CPP inflammatory crystal arthritis.
Acute CPP crystal arthritis is characterized by sudden onset of pain, swelling and tenderness with overlying erythema, usually in a large joint, most often the knee, wrist, shoulder, and hip. Occasionally, ligaments, tendons, bursae, bone and the spine can be involved. CPPD of the atlanto-occipital joint (crowned dens syndrome) can cause periodic acute cervico-occipital pain with fever, neck stiffness and laboratory inflammatory syndrome. Chronic inflammatory arthritis is characterized by joint swelling, morning stiffness, pain, and high ESR and CRP. The relationship between OA and CPPD is still unclear. The main problem is whether such crystals are directly involved in the pathogenesis of OA or if they are the result of joint degeneration. Diagnosis is based on evaluation of history and clinical features, conventional radiology, and synovial fluid examination. Non-polarized light microscopy should be used initially to screen for CPPD crystals based upon their characteristic morphology, and compensated polarized light microscopy, showing the crystals to be weakly positive birefringent, is recommended for definitive identification, although this last pattern only occurs in about 20% of samples. The main goals of CPPD therapy are control of the acute or chronic inflammatory reaction and prevention of further episodes.

Key words: CPPD, calcium pyrophosphate, synovial fluid, pseudogout.

DEFINITION
Calcium pyrophosphate deposition (CPPD) disease is an arthropathy caused by calcium pyrophosphate dihydrate (CPP) crystal deposits in articular tissues, most commonly fibrocartilage and hyaline cartilage (1, 2). Risk factors include aging, osteoarthritis (OA), previous joint trauma/injury, metabolic disease and familial predisposition. The importance of CPP-associated arthritis is also related to its frequency, being the third most common form of inflammatory arthritis (3). CPP formation occurs almost exclusively in the articular and periarticular tissue, usually near the surface of chondrocytes. Fibrocartilage, hyaline cartilage, synovium, joint capsule and ligaments are frequently affected. CPPD is generally a disease of the elderly, often categorized into sporadic, familial and secondary varieties, including hyperparathyroidism, hemochromatosis, and hypomagnesemia (4).
There are two familial forms of CPPD crystal deposition disease: the first one is a relatively benign form characterized by polyarticular distribution, including the knee, wrist, shoulder, elbow, hip and ankle, with recurrent episodes of acute CCP crystal arthritis without chronic deforming arthropathy. This form occurs in people under 50 years of age. The second form occurs in patients aged over 50 years and is more destructive, with oligoarthritis involving knees, wrists, shoulders, and hips as well as deforming and progressive OA.
**CLINICAL FINDINGS**

According to the recent EULAR recommendations for CPPD (1), four different clinical presentations can be observed:

- **Asymptomatic CPPD:** this is CPPD with no apparent clinical correlates, also called lanthanic variant. It may consist of an isolated cartilage calcification (CC), or OA with CC without CPPD symptoms. Radiological CC is not always due to CPP deposition (5) and is often an incidental finding following imaging for other reasons. The prevalence of radiographic CC in the general population varies between 10 to 15% in those aged 65 to 75 years, and increases to more than 40% in subjects aged over 80 years (6,7). In most of these older individuals, concomitant OA is present and it is often not easy to understand the clinical implications of these findings.

- **OA with CPPD:** CPPD can be found by imaging techniques (conventional radiography, computed tomography, or ultrasonography) or by histological examination in a joint that also shows changes in OA. Differentiating between this condition and asymptomatic CC in a joint with pre-existing OA is obviously very difficult and should rely on the coexistence of CPPD and OA symptoms in the former.

- **Acute CPP crystal arthritis:** better known by the old term of pseudogout, is an acute onset, self-limiting synovitis triggered by CPP crystals. Characteristic features are the rapid development of severe joint pain, swelling and tenderness that reaches its maximum within 6-24 h and lasts for 7-10 days. The pain is acute, very intense but self-limiting. In the attack, arthritis can be mono or polyarticular, migratory or additive, monolateral or bilateral. It is a major cause of acute monoarticular arthritis in the elderly.

- **Chronic CPP crystal inflammatory arthritis:** chronic inflammatory arthritis associated with CPPD, oligoarticular or polyarticular, often resembling seronegative rheumatoid arthritis (RA). This form may present as destructive arthropathy; it can be more or less destructive than primary, erosive OA.

Acute CPP crystal arthritis is characterized by acute onset of pain, swelling and tenderness with overlying erythema. The attacks usually involve a large joint, most often the knee, wrist, shoulder, and hip. The small joints of the hand can be also involved. Because CPPD can theoretically affect every joint, also uncommon locations of acute CPP crystal arthritis, such as the acromion-clavicular (8) and temporomandibular joints (9) have been described. Acute attacks of CPPD can occur in periarticular structures like ligaments, tendons, bursae and also in bone (10). The axial skeleton can be occasionally involved with CPP deposits in the intervertebral disks, posterior longitudinal ligament, facet joints, ligamentum flavum, and sacroiliac joints that correspond radiographically to linear calcification and, sometimes, to spinal ankylosis (11). Calcified deposits in the ligamentum flavum, facet joints, lateral masses, and posterior longitudinal and atlanto-occipital ligaments can remain asymptomatic or be associated with periodic acute cervico-occipital pain with fever, neck stiffness and laboratory inflammatory syndrome. Therefore, CPPD of the atlanto-occipital joint should be considered among the differential diagnoses when acute episodical pain occurs at the base of the skull. This clinical entity, named crowned dens syndrome from the characteristic CT appearance (see chapter on imaging), should be differentiated from meningitis, spondylitis, and polymyalgia rheumatica. It occurred, when investigated by CT, in 51% of 49 patients with CPPD (12). The eye is another unusual site for CPPD crystal deposition as described in a woman with the Gitelman variant of hypomagnesemia (13). Patients with CPPD disease may present with episodes of hemarthrosis, often after a trauma to the knee. In fact, the attack may be precipitated by trauma or it may occur after surgery. In addition, also other conditions have been observed to precipitate acute attacks, such as serious medical illnesses like pneumonia, strokes, and myocardial infarction.
Pregnancy, arthroscopic surgery, the use of parenteral pamidronate, granulocyte colony stimulating factor, and intra-articular injections with sodium hyaluronate have been associated with acute arthritis flares (2). Bisphosphonates are non-hydrolysable PPI analogs and cartilage supersaturation with PPI is crucial to the pathogenesis of CPPD (14). The mechanism of the rare association between bisphosphonates infusion and acute crystal arthritis is not known, although it can be hypothesized that these drugs could interfere with PPI catabolism in the articular cartilage or with the dissolution of CPP crystals by alkaline phosphatase. In our experience, this side effect of bisphosphonates does not necessarily recur with subsequent administrations of the same drug, suggesting that other unknown causes might be at work. Intra-articular injections of hyaluronic acid can rarely cause acute synovitis. It has been reported that, occasionally, acute CPPD arthritis can be triggered by these compounds (15,16). This process is probably secondary to acute neutrophilic inflammation and disruption of the cartilage matrix integrity with the subsequent release of CPP crystals. Alternatively, preparations of hyaluronan, which contain phosphates that could induce a local drop in joint fluid calcium, might facilitate crystal shedding. It has not been proven that hyaluronan preparations can trigger the formation of new crystals. Occasionally, fever may be a prominent manifestation of CPPD, but also other systemic features, such as confusion, disorientation, nuchal rigidity, and leukocytosis, have been reported in individual cases. CPPD is rare under the age of 50 years, and when it occurs, familial CPPD should be suspected. The incidence of CCP crystal arthritis increases dramatically with age, being the most common cause of inflammatory arthritis in the elderly. Clinical features, although suggestive for this diagnosis, are not diagnostic per se and require further proof, including demonstration of crystals in the synovial fluid, radiological evidence of CC, and prompt response to colchicine. The latter increases the likelihood of the diagnosis but are of course not conclusive. It can happen that synovial fluid samples aspirated from joints with radiographic CC are negative for crystals at microscopy, but the extent of this phenomenon and its causes are poorly understood. Differential diagnosis includes, as expected, gout, but also septic arthritis and other forms of acute monoarthritis, such as psoriatic or Lyme arthritis.

Chronic inflammatory arthritis is characterized by chronic oligoarthritis or insidious polyarthritis with joint swelling, morning stiffness, pain, and high sedimentation rate and CRP. The differential diagnosis includes RA (pseudo-rheumatoid arthritis) and all the forms of chronic arthritis of the elderly. When the shoulders are involved, also polymyalgia rheumatica should be considered in the differential diagnosis (17). Based on clinical assessment, patients with CPPD who presented with symptoms mimicking polymyalgia rheumatica tended to be older than those with polymyalgia rheumatica and had more tibio-femoral OA, more frequent tendon calcifications and a higher prevalence of ankle arthritis. However, the features of these 2 patient populations are largely overlapping and differential diagnosis remains problematic. The relationship between OA and the various types of calcium crystals is still unclear. The main problem is whether such crystals are directly involved in the pathogenesis of OA, or if they are merely a byproduct of joint degeneration. Some investigators believe that OA with secondary CC is a distinct entity from idiopathic CPPD. This distinction is supported by differences in the biochemical profile of enzyme activities involved in ATP and PPI metabolism in the joints of elderly patients with idiopathic CPPD and OA. An over-exuberant TGFβ-driven repair response to a primary joint damage induced by OA, with increased PPI production as a manifestation of the reparative chondrocyte phenotype, could be at work. It is not clear whether CPPD is primary to cartilage degeneration or whether OA precedes CPPD. A recent study has analyzed the association between CC and OA in a community-based popu-
Calcium pyrophosphate deposition disease: clinical manifestations

Randomly selected individuals older than 60 years were radiologically assessed for OA and CC of the knees. Radiological changes in OA were more common in subjects with CC than in those without. Interestingly, OA was also more common in the hands of individuals with CC. The association between CC and OA reached statistical significance in the lateral tibial femoral compartment and the first three, left metacarphopalangeal (MCP) joints in this study. The MCP joints are a less common localization for primary OA than the proximal and distal interphalangeal joints, a fact suggesting that in this study there was increased CPPD in the MCP joints, even without clear radiological CC. It has been hypothesized that idiopathic CPPD of aging may be a distinct age-related disease from OA, perhaps related in part to differences in subchondral bone structure. In addition, also unusual joints can be involved when CPPD and OA occur simultaneously. The involvement of the scaphoid-trapezium joint has been advocated as predictor of CPPD in patients with or without hand OA (19). Scaphoid-trapezium joint OA was more severe in patients with CPPD and its presence conferred an increased risk of CPPD diagnosed by the identification of radiological CC and positive synovial fluid examination. As reported above, the interpretation of clinical features is not always simple due to the multifaceted presentation of CPPD. Imaging of CPPD is discussed elsewhere in this issue of Reumatismo. Synovial fluid aspiration and examination for crystals is the gold standard for diagnosis. This is primarily based upon microscopic demonstration of CPP crystal deposits in synovial effusions. Fresh synovial fluid should be examined after centrifugation, to increase the concentration of CPP crystals. These are 1-20 µm long and can be visualized under regular microscopy as square or rectangular structures which are found free in the synovial fluid or ingested by macrophages. CPP crystals are pleomorphic with rhomboid, rectangular, acicular, and rod shaped forms. When examined by compensated polarized light microscopy, the crystals may show a weak positive birefringence (3). Because of this only weak birefringence, which probably occurs only in a minority of the crystals, many laboratories may miss CPP crystals using polarized light microscopy, emphasizing the importance for an observer experienced in crystal identification to examine the fluid. Examination of 10 synovial fluids from patients with acute knee CPPD by 2 experienced observers showed that only about 20% of all CPPD crystals identified by ordinary non-polarized light microscopy were birefringent when examined by uncompensated polarized light microscopy (23). It is, therefore, possible that some CPPD crystals may be missed if a search for these crystals in synovial effusions is only conducted under polarized light microscopy. In fact, poor inter-laboratory reproducibility and inter-observer
agreement have been reported. In a typical clinical setting; synovial fluid analysis has 12% sensitivity in the detection of CPP crystals (24). When readers received intensive training, sensitivity for detecting the presence of CPP and monosodium urate (MSU) crystals increased to 95% and specificity to 86%. The trainees were, however, better at identifying MSU than CPP crystals. Unfortunately, none of the examined fluids in this study contained corticosteroid or cholesterol crystals, which can be misidentified as CPP crystals. False-negative rates in identifying CPPD crystals are particularly high (25). Although non-polarized light microscopy should be used initially to screen for CPPD crystals based upon their characteristic morphology, compensated polarized light microscopy showing the crystals to be weakly positive birefringent is recommended for definitive CPPD crystal identification. Occasionally, infection or other crystals, such as MSU or basic calcium phosphate, may coexist with CPP. Differential diagnosis with MSU crystals is usually easy because of the different form and the opposite birefringence. Differentiation from crystals of long-acting glucocorticoids injected in the joint to treat synovitis is more difficult. Occasionally, diagnosis may be made after arthroscopy for acute or chronic knee joint involvement. Deposition of linear or punctate white material in the articular cartilage or meniscal fibrocartilage can be observed (26). In a few occasions, despite negative radiographs and crystal search in synovial fluid aspirates, CPP crystals could be demonstrated by arthroscopic visualization and confirmed by microscopic evaluation of joint lavage fluids (27).

It can be hypothesized that, in these patients, sparse crystalline material is more or less tightly adherent to the synovial membrane and is detached from it by the pressure of the irrigating fluid. Previous studies of gout patients demonstrated the presence of MSU crystals in synovial fluids from uninflamed joints between clinical attacks. In parallel to their studies in gout, Martinez-Sanchis and Pascual (28) examined uninflamed joints for the presence of synovial fluid CPP crystals. They also studied the significance of intracellular versus extracellular crystals, and the correlation between pain and the intracellular location of CPPD crystals, or the number of inflammatory cells. Of the 79 patients studied, 52 had pain in the affected knee. About 50% had acute CPP attacks in the past. The synovial fluid analysis revealed a mean white cell count of 301 cells/μl, of which 83% were mononuclear cells and 17% polymorphonuclear leukocytes. Twenty-four percent of the fluids contained crystals. Typically, CPPD crystals were seen inside mononuclear cells. Interestingly, the presence of intracellular crystals did not correlate with pain, and cell counts were only slightly higher in the pain compared to the no-pain group.

### TREATMENT

Due to the variable manifestations of CPPD, differentiated therapeutic approaches are necessary. It is especially important to share with the patient the mechanisms that could be involved in his/her disease and the resulting treatment strategies. Asymptomatic CC does not require any treatment, being usually an age-related feature of the normal population (29). The management of CPPD, which has been recently reviewed in the EULAR recommendations (30), is similar to that of gout (see the relevant chapter in this issue of Reumatismo), with the main goals of therapy being control of the acute or chronic inflammatory reaction, characterized by intense pain, and prevention of further episodes. Rest of the inflamed joint, colchicine, systemic or intra-articular glucocorticoid preparations, and NSAIDs, are the mainstay of therapy of the acute attacks. NSAIDs are effective in acute CPP crystal arthritis but should be used with caution because of the increased risk for renal and gastrointestinal toxicity in elderly patients. At the doses that have been recently confirmed to be effective in the control of the gouty acute attack (0.5 mg to 1 mg daily) (31), colchicine is ef-
Effective and safe in most of the patients. At the same or lower doses of 0.5 mg once daily or on alternate days, it can be helpful in preventing further attacks (32). NSAIDs and colchicine should be preferred to analgesics in OA patients with evidence of associated CPPD. Because many attacks are short-lived, complete aspiration of the joint may be sufficient to significantly relieve pain and discomfort in some patients. Intra-articular injections of long-acting glucocorticoids are particularly effective, although there have been no controlled studies. In difficult joints, ultrasound-guided injections increase the probability of reaching the target and reduce the risk of injection-related side effects. In contrast to gout, there is currently no treatment to reduce the formation of the causative crystals in CPPD. In vitro studies, however, have shown that magnesium can solubilize CPP crystals and inhibit their nucleation and growth (33).

For those who have chronic pain and inflammation, physiotherapy, analgesics, colchicine, and NSAIDs are alternatives for management. For patients who have chronic pseudorheumatoid CPPD disease, hydroxychloroquine at dosages of 200-400 mg daily has been shown to be superior to placebo in one small controlled study (34). Similarly, also methotrexate at low doses of 5-10 mg weekly has been used in the long-term treatment of a few patients affected by pseudo-rheumatoid CPPD (35) with excellent results. This drug could represent a useful alternative in the patient resistant to or non-tolerant colchicine. It is important to remember that all the above reported treatments are based on anecdotal cases or small series of patients (type IIb evidence); a surprising observation given the high prevalence of CPPD.

**CONCLUSIONS**

In contrast with the fact that CPPD is a diffused and apparently well-known condition, the data summarized in this review emphasizes the need for more research in this field. In particular, the relationship between CPP deposition in articular and peri-articular structures and clinical features, the optimal synovial fluid examination protocol, and the need for large treatment trials must be addressed in the future.

**REFERENCES**

5. Fam AG. What is new about crystals other than monosodium urate? Curr Opin Rheumatol 2000; 12: 228-34.