

Imaging of chondrocalcinosis: calcium pyrophosphate dihydrate (CPPD) crystal deposition disease – imaging of common sites of involvement

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ABSTRACT

Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease is characterised by the accumulation of pyrophosphate dihydrate crystals in articular and periarticular tissues and it can be classified as sporadic, hereditary or secondary. The diagnosis frequently rests on radiographic findings. Computed tomography scanning can detect well mineralised deposits in joints and also ultrasound may be useful in detecting CPPD crystal deposits. About MRI recent studies have demonstrated the utility of high field in depiction of CPPD crystal deposits.

The aim of this review is to focus on the clinical-classificative and radiological aspects of CPPD, particularly the contribution of the different imaging techniques.

Introduction

Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease is characterised by the accumulation of pyrophosphate dihydrate crystals in articular and periarticular tissues. Various terms have been utilised to describe this arthropathy. Chondrocalcinosis (CC) is a pathologic and radiographic term denoting calcification of cartilage within joints including both hyaline articular cartilage and fibrocartilage. Pseudogout is a clinical term used for an acute inflammatory process in a joint(s) mimicking a gout attack. Pyrophosphate arthropathy is a term that has been used to describe the peculiar pattern of joint destruction associated with CPPD crystal deposition disease (1); it is similar to osteoarthritis (OA) and cartilage calcification may be absent on radiographs (2).

The prevalence of symptomatic CC in the population remains uncertain. Sev-

eral epidemiological studies have used radiographic calcification as the diagnostic criterion (3). A community study in England (1727 subjects, mean age 63.7 years) reported 7% as prevalence of CC, with no difference between men and women, and an age, sex and knee pain standardised estimate for those aged >40 years of 4.5%. There was an important association with age and the prevalence increasing from 3.7% in those aged 55–59 years, to 17.5% in those aged 80–84 years (4). In a Spanish primary care-based study (5) the prevalence of CC, as detected by radiographs of both knees and wrists, was 10% in subjects aged ≥60 years. The prevalence of CPPD deposition in osteoarthritic joints is much higher when synovial fluid is examined for crystals. At the time of joint replacement, 25–43% of SF from patients undergoing total knee arthroplasty contains CPPD crystals (6-8).

CPPD crystal deposition disease can be classified as sporadic, hereditary, or secondary (9). The sporadic or idiopathic form usually occurs in middle-aged and elderly patients and there appears to be no predominance in either men or women (10-12). Aging is the most important risk factor for CC, which frequently associates with OA. CC does not appear to be a risk factor for more rapid cartilage degradation. In patients with CC <55 years, a primary metabolic disorder or a familial predisposition should be considered (13).

The hereditary forms usually have a female predominance and occur at a relatively early age. These patients often have more severe arthropathy (14). Molecular genetics studies have identified two genetic locations for familial CC: 1) CCAL1, related to a mutation in the long arm of chromosome 8

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(8q) and associated with severe OA; 2) CCAL2, in families from the UK, France and Argentina, resulting from a mutation on the short arm of chromosome 5 (5p) (15). The responsible gene at the CCAL2 locus has been identified as the ANKH (ankylosis human) gene, which codes for a transmembrane protein (ANKH) that regulates transport of inorganic pyrophosphate (PPi) out of cells. ANKH variants may increase transcription of the gene to result in an increase in extracellular PPi, which is a critical determinant of mineralisation. ANKH mutations may also influence chondrocyte maturation (16). Recent reports suggest that there is a coordinated interrelationship between ANKH and another key participant of Pi and PPi metabolism represented by sodium/phosphate cotransporter PiT-1. CPPD-associated ANKH mutation might disrupt this protein interactions.

There has been much speculation regarding the association between certain diseases and CPPD crystal deposition disease. Many of these “associated disorders” have proved to be a chance occurrence two diseases, because CPPD crystal deposition disease is such a common disorder of the elderly and many of the reported associated diseases (including osteoarthritis, diabetes mellitus, and hypertension) are also prevalent in this age group. The four H’s—hyperparathyroidism, haemochromatosis, hypomagnesaemia, hypothyroidism—have shown strongest association with CPPD crystal deposition disease (17). The association between CC and hypomagnesaemia has been reported principally in patients with Gitelman’s or Bartter syndrome (18), and rarely in individuals with hypomagnesaemia due to causes other than renal genetic disorders (19). Given the relatively high prevalence of CC in patients with hypomagnesaemia, hyperparathyroidism and haemochromatosis aged ~ 55 years, and because sporadic CC is rare at this age, it seems reasonable to screen for these conditions in patients <55 years, especially if they have florid polyarticular CC. After the age of 55 years, hyperparathyroidism should be investigated in all patients with CC because both conditions are more common in this age

group (20). There are several reports of an association between CC and severe hypophosphatasia. The young age of patients in some reports makes a true association likely (20). Other metabolic and endocrine diseases that have been reported to predispose to CPPD disease are gout, ochronosis, familial hypocalciuric hypercalcaemia, X-linked hypophosphataemic rickets, Wilson’s disease and acromegaly, but their validity remains unclear (20). The associations between diabetes mellitus and hypothyroidism with CC, first suggested on the basis of observational studies, were subsequently discounted by controlled studies involving age-matched controls (20, 21).

Some of the other disorders for which there may be a likely association with arthropathy include acromegaly, hypermobility syndrome, familial hypocalciuric hypercalcaemia, haemosiderosis, hypophosphatasia, gout, Bartter syndrome, and amyloidosis (14).

Ryan and McCarty proposed several diagnostic criteria for the diagnosis of CPPD crystal deposition disease (22) based on the premise that CPPD crystals are the specific feature of the disease and including radiographic clues suggested by Resnick *et al.* (23) and Martel *et al.* (24). According to these criteria, a case is definite if CPPD crystals are demonstrated in tissues or synovial fluid by definite means (for example, chemical analysis) or if crystals are demonstrated by compensated polarised light microscopy and typical calcifications are seen on radiographs. In this last case, if only one of these criteria is found, a probable diagnosis is made.

CPPD crystals are detectable under polarising light microscopy and their presence in synovial fluids remains the gold standard for the diagnosis of CPPD deposition disease.

Clinical presentations of CC can vary but according to McCarty (22) five clinical common patterns of CC have been described: asymptomatic, pseudo-gout, pseudo-rheumatoid, pseudo-osteoarthritic, and pseudo-neuropathic joint disease pattern. Asymptomatic (lanthan) is usually associated with radiographic findings of chondrocalcinosis in the absence of clinical mani-

festations. Acute pseudogout is characterised by acute monoarticular or oligoarticular arthritis. Pseudoosteoarthritis involves the metacarpophalangeal (MCP) or the proximal interphalangeal (PIP) joints and spine, as occurs in patients with primary osteoarthritis. Pseudorheumatoid arthritis is characterised by symmetrical inflammation of the PIP and MCP joints and must be differentiated from true rheumatoid arthritis. Pseudoneuropathic joints is a severe destructive arthropathy.

Imaging modalities

Conventional radiography

The test of choice for diagnosing CPPD deposition disease is synovial fluid examination, but the diagnosis frequently rests on radiographic findings of chondrocalcinosis. The arthropathy can also precede radiographically detectable cartilage calcifications, because these may not always be dense enough to be visualised on conventional radiographs, or it may be difficult to identify if the joint is severely deranged. The sensitivity of plain radiographs for chondrocalcinosis may be as low as 39% and a role for other, newer imaging modalities has been sought.

Computed tomography

Computed tomography (CT) can detect well mineralised deposits in joints, but is rarely used to image painful joints. (25). The advantages of using CT over plain film include tomographic imaging for localisation abilities, high resolution for characterisation of crystal deposition and increased tissue contrast (26) (Fig 1a-b).

Magnetic resonance imaging

Current Magnetic Resonance Imaging (MRI) techniques, such as low field MRI (1.5 Tesla), have been largely disappointing as imaging modalities in this disease (26). MRI is particularly poor at distinguishing meniscal tears from CPPD crystal deposits, as both appear as signal voids. Suan *et al.* (28) set out to determine the utility of a newer MRI technique known as high field MRI (4 T) and compare it with arthroscopy, conventional radiography and several newer CT methods in CPPD deposition

disease. They found that high field MRI was better at detecting CPPD deposits than low field MRI, although the actual presence of CPPD deposits in the tissue was not confirmed. In their case series, high-field MRI demonstrated a greater number of involved articular surfaces and meniscal bodies than CT, radiography, and arthroscopy, suggesting that MRI may be more sensitive to imaging CC in the knee. CC located within the articular cartilage appeared as linear and punctate hypointense regions.

Ultrasound

Ultrasound (US) is a very sensitive and specific technique for detecting calcifications of soft tissues, (29-30) but only few studies have described sonographic evidence of articular and periarticular changes caused by CPPD disease (31-35). Filippucci *et al.* (36) demonstrated that US can detect a higher number of inflamed knee joints than clinical assessment in these patients and the most frequent finding was joint effusion; they also detected synovial hypertrophy and crystal deposition in joint cartilage. Frediani *et al.* (37) tried to define the US aspect of CPPD calcifications in order to propose ultrasonographic criteria for the differentiation of CPPD deposits and hyperechoic deposits of another nature. They then tried to verify the relationship between the presence of CPPD calcifications in cartilage and periarticular tissues detected with US and the presence of CPPD crystals in the synovial fluid and compare the US findings with the radiographic findings. They considered as CPPD calcifications all hyperechoic deposits that presented one of the following patterns:

- Thin hyperechoic bands, parallel to the surface of the hyaline cartilage (frequently observed in the knee)
- A "punctate" pattern, composed of several thin hyperechoic spots, more common in fibrous cartilage and in tendons (Fig. 2)
- Homogeneous hyperechoic nodular or oval deposits localised in bursae and articular recesses (frequently mobile) (Fig. 3).

In all cases, calcifications had a sparkling appearance and created posterior

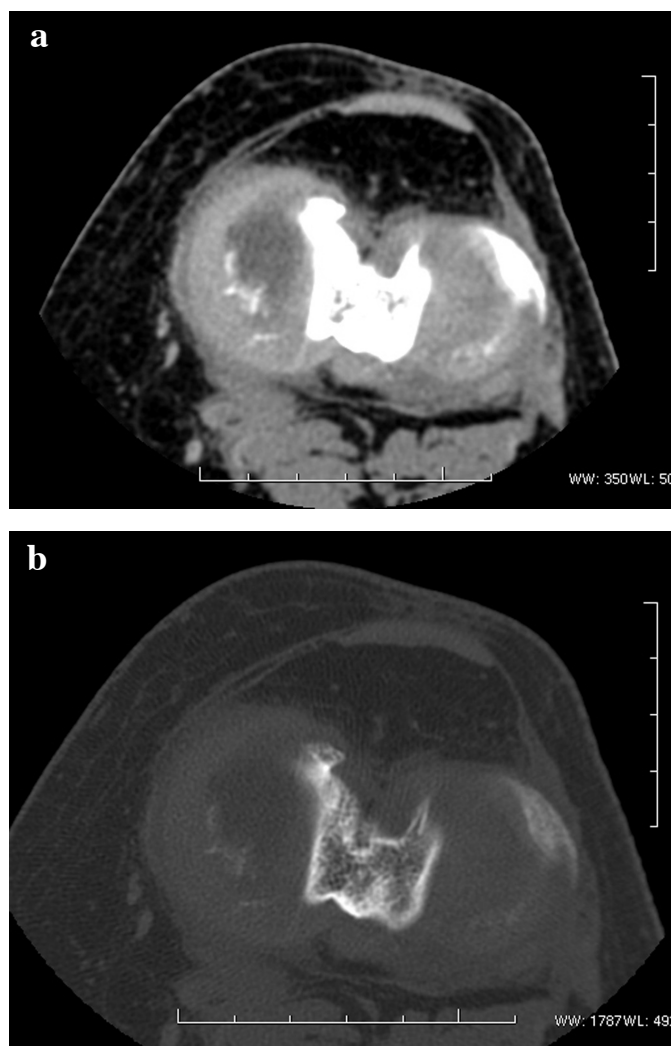


Fig. 1a-b. Computed Tomography (CT) axial plane of the knee with soft tissue (a) and bone reconstruction (b) algorithm shows calcification of menisci and medial femoral-tibial cartilage joint.

shadowing only when they reached dimensions >10 mm. In contrast, calcifications that presented a hypoechoic appearance with posterior shadowing even at an early stage (2–3 mm in diameter) were considered as crystalline deposits of another nature, probably due to hydroxyapatite crystal deposition disease.

US is a very sensitive and specific technique for detecting calcifications. In some cases calcifications detected by US may not be found in standard plain radiographs, because of the localisation of the deposit or the technique used.

Common sites of involvement

The joints most frequently involved are knee, wrist, symphysis pubis, and hip. Unlike OA the glenohumeral joint and elbow often are involved (14). Other sites of involvement are spine and temporomandibular joints.

Tofhaceous pseudogout is a rare presentation of CC disease with soft-tissue calcified mass. Based on case reports para-ischial region, lesser trochanter, mitral valve, infratemporal fossa (38), iliopsoas myotendinous junction are unusual presentation of CC, sometimes difficult to differentiate from tumoural calcinosis. Some reports (39) emphasised radiological similarities with benign or malignant cartilaginous lesions and to avoid misdiagnosis is often necessary to identify the CC crystal components on biopsy fragments. Atypical bilateral case of CC localised in the first metatarsophalangeal joint bilaterally with no radiographic evidence was recently reported (40) in patients with pseudogout. The presence of calcium pyrophosphate dihydrate crystals was sometimes demonstrated only with chemical analysis of the surgi-

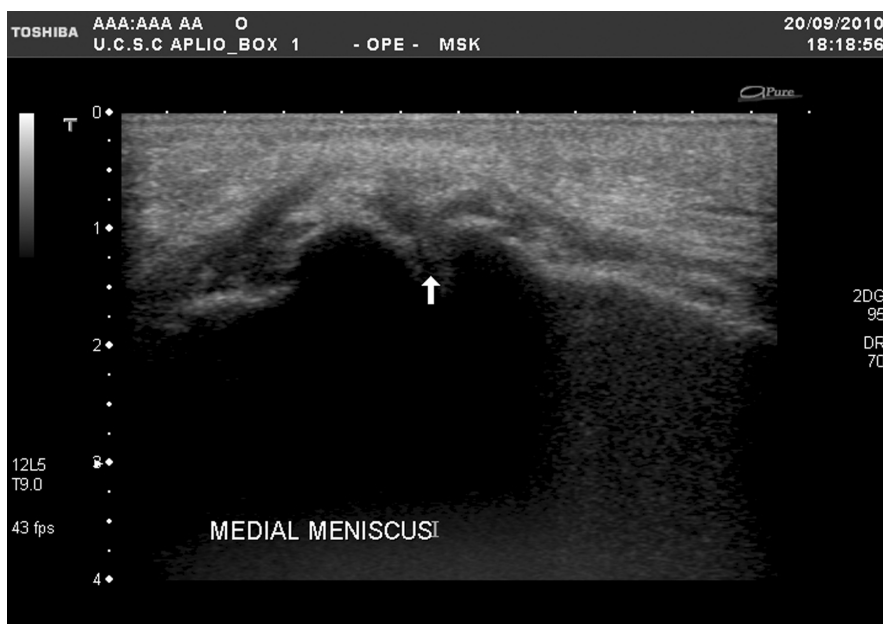


Fig. 2. Longitudinal US scan of the medial aspect of the knee shows a narrowing of the articular space with hyperechoic medial meniscus due to calcification.

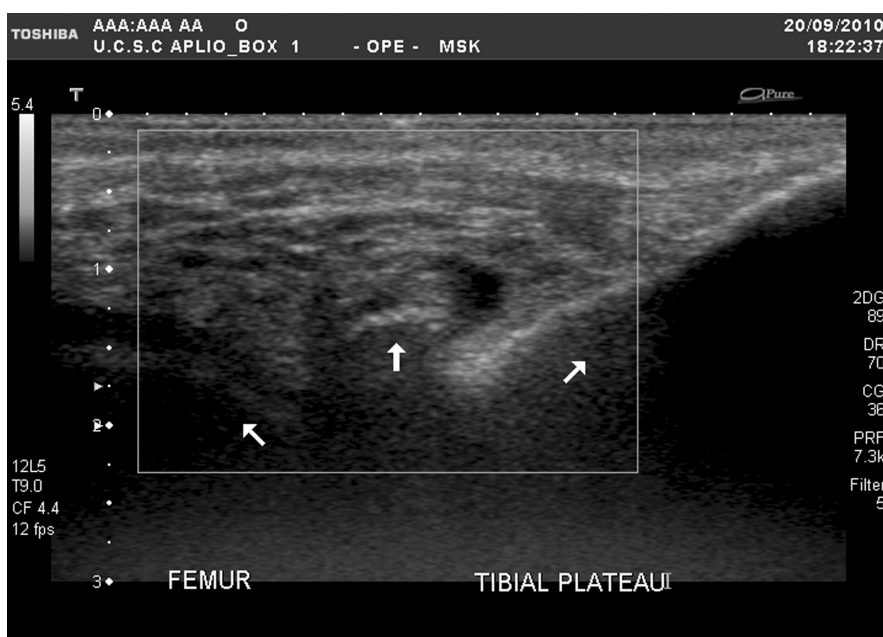


Fig. 3. Longitudinal US scan of the anterior aspect of the knee shows a loose articular body in anterior synovial recess, as indicated by central arrow.

cal samples. CC disease of the wrist is characterised radiologically by the presence of chondrocalcinosis of the triangular fibrocartilage between the distal ulna and the carpal bones, but CC also may progress and be seen in the ligaments between the various carpal bones, particularly in the scapholunate and lunotriquetral joints but also on the metacarpal heads and in the interphalangeal joints. Rare re-

ported cases (41) reported CC tophus exceptionally localised in a finger. Calcifications of the adductor tendons are not uncommon in CC. Moreover there is a high correlation between the existence of this tendon calcifications and the extension and intensity of calcific deposits in other articular areas. Better knowledge of this entity could avoid enlarged surgery as it has been done on some occasion.

Knee

The knee is very commonly the initial site of clinical symptoms and radiography characteristically shows disproportionate patello-femoral osteoarthritis. The most common locations for chondrocalcinosis in the knee are the menisci; less commonly the articular cartilage is involved. (42).

Disproportionate narrowing of the patellofemoral joint is a characteristic finding that is seen occasionally. The medial and lateral compartments frequently are of normal width. Meniscal and hyaline cartilage may be calcified (Fig. 4). Chondrocalcinosis is thought to be secondary to post-traumatic or degenerative meniscal changes, or both types of changes (43). The synovium, capsule, ligaments, and tendons also may be calcified. Intra-articular bodies occasionally are seen in association with degenerative changes of the cartilaginous and subchondral regions (14). S. Kaushik *et al.* (44) have studied MR imaging of knee menisci and showed MR imaging sensitivity and specificity for detection of meniscal tear is decreased in the presence of meniscal chondrocalcinosis. Chondrocalcinosis appeared as a high-signal-intensity region on T1-weighted, intermediate-weighted, and inversion recovery sequences (Fig. 5 a-b) and can be confused with a meniscal tear. Radiographic correlation with the MR imaging examination can help prevent overdiagnosing meniscal tears. (42).

Wrist and hand

The radiocarpal articulation has severe degenerative changes. When symptomatic, the clinical presentation may be pain and swelling in the wrist or thumb, decreased strength and range of motion, dorsal wrist synovitis and wrist stiffness. CPPD may become symptomatic after wrist trauma, having been previously asymptomatic (45).

In 14% of cases, carpal tunnel syndrome (CTS) is the initial presentation. This may be acute (46) and the combined presence of CTS and dorsal wrist synovitis should raise suspicions of CPDD and lead to a wrist x-ray.

In the wrist, the lunotriquetral ligament has been shown in some reports to be a

more common site of calcification than the triangular fibrocartilage (TFC), although the TFC is frequently calcified (Fig. 6). Hyaline cartilage calcification is most frequent between the scaphoid and lunate. There often is associated radiocarpal joint space narrowing and radiocarpal compartment changes may be seen occasionally in patients with gout or occupation-related degenerative disease. A scapholunate advanced collapse (SLAC) pattern of arthritis, is the most common form of structural joint damage in the wrist in patients with CPPD crystal deposition disease. There is often narrowing of the radioscapoid and capitohamate joint spaces. The radiolunate space is generally spared. Narrowing of the metacarpophalangeal joints (especially the second and third) also is frequent in CPPD crystal deposition disease with sparing of or only mild changes in the interphalangeal joints. The metacarpophalangeal joint may also reveal sclerosis, cyst formation, and subchondral collapse, particularly of the metacarpal head. There is also the Missouri metacarpal syndrome, a disease that affects manual labor, that have similar changes in the metacarpophalangeal joints. Capsular calcification is occasionally identified in CPPD crystal deposition disease, especially about the metacarpophalangeal joints (2).

Symphysis pubis and hip

Frequently calcification and occasional severe erosive changes can be detected in the fibrocartilaginous joint of the symphysis pubis. Considerable bone fragmentation is occasionally seen in patients with CPPD crystal deposition disease. In the hip, calcification is seen in both fibrocartilage of the acetabular labra and hyaline cartilage. The calcified acetabular labrum presents as a small radiodense triangle along the peripheral aspect of the acetabulum superolaterally. CC is often apparent in the hyaline cartilage leading to a radiodense curvilinear line that parallels the femoral head. Surrounding tendons, including the rectus femoris, hamstrings and adductor insertion, may also calcify. Narrowing of the hip joint is commonly superolateral, in a pattern similar



Fig. 4. Plain film radiograph of the knees in AP view shows calcification of menisci and articular cartilage.

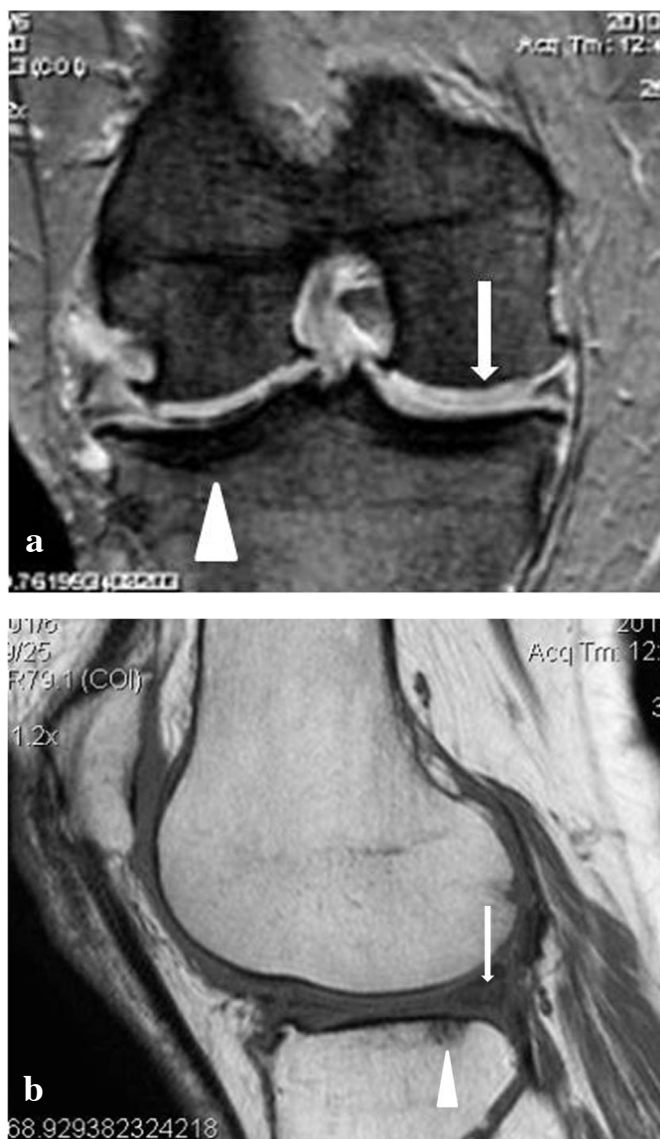


Fig. 5a-b. Magnetic Resonance Imaging (MRI) (a) GE T2* coronal view shows linear hypointensity on lateral tibial plateau (arrow head) associated with hyperintense menisci (arrow) due to calcification of the fibrocartilage and of the cartilage joint. (b) T1-weighted image on sagittal plane shows a diffuse lateral meniscus hyperintensity (arrow) due to calcified degeneration and it is also presents a subchondral defect (arrow head).

to OA. Alternatively, the hip joint may reveal concentric narrowing with axial migration, simulating the appearance of an inflammatory arthropathy. (2).

Glenohumeral joint and elbow

In the glenohumeral joint, CPPD crystal deposition disease resembles osteoarthritis with subchondral bone for-



Fig. 6. Plain film radiograph of right wrist in AP view shows presence of calcification of cartilage of radio-carpal joint and triangular fibro-cartilage (TFC). There is also a subchondral cyst in the distal radius.

mation, cysts and osteophytes. Tendinous, capsular and bursal deposits are occasionally seen. Rotator cuff tears are common in patients with CPPD crystal deposition disease. The “Milwaukee shoulder syndrome” is a rapidly progressive, destructive arthritis characterised by recurrent large effusions, rotator cuff tear, and destruction of cartilage and subchondral bone. There is a prevalence in older women often with a history of trauma to the affected shoulder. Elbow calcification and contractures are occasionally detected. The extensor, flexor, biceps and triceps tendons may calcify. CPPD crystal deposition disease is accompanied by joint space narrowing, resorption of the proximal portion of the ulna and radius, subchondral sclerosis and cyst formation, and bone fragmentation. Surrounding bursae including the olecranon and radio-bicipital bursa can contain CPPD crystals. Elbow osseous resorption in the proximal portions of the radius and ulna, joint space narrowing, extensive sclerosis, cyst formation and bone fragmentation are visualised (2).

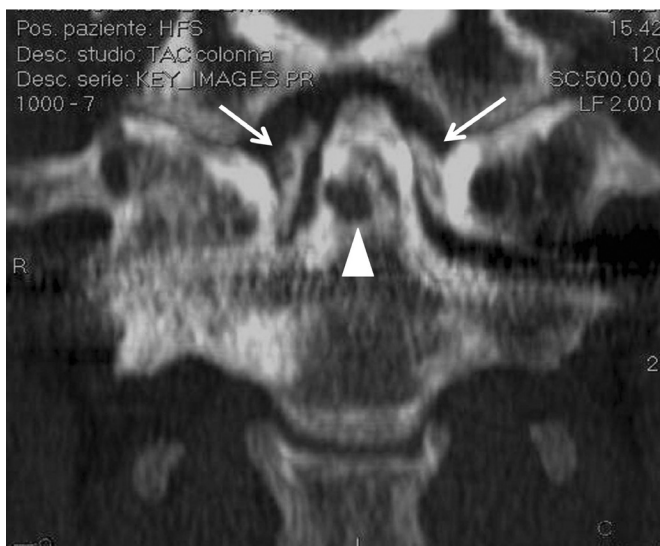
Spine

CPPD crystal deposition disease can



Fig. 7a-b. Plain film radiograph of dorsal spine in AP (a) e LL (b) views, shows diffuse spondylosis with discal calcification and “vacuum phenomenon”.

Fig. 8. Multi Planar Reconstruction (MPR) CT reformat on coronal plane of the atlanto-axial joint shows calcification of alar ligaments (arrows) and degenerative cyst of the odontoid process (arrow head).



produce severe degenerative disk disease that often involves multiple levels (Fig. 7 a-b). The L2-3 disk level is a common site of involvement. CPPD crystals can deposit in either the anulus fibrosus or nucleus pulposus of the

disk or in both structures. Calcification usually begins in the outer fibers of the anulus fibrosus. Previous disk surgery may predispose to CPPD crystal deposition disease (14).

Crystal arthropathy may affect all ar-

eas of the spine. Cervical myelopathy, radiculopathy, spinal stenosis to cauda equina syndrome are various presentations (47).

The ligamenta flava, the longitudinal, supraspinous and interspinous ligaments, the intervertebral disks and the sacroiliac and apophyseal joints are among the most frequent sites of crystalline deposition in the spine.

Calcium crystal deposition disease in the periodontoid area is a peculiar variety of this entity that has gained increasing attention (Fig. 8). Because of the crown-like appearance of the calcifications around the odontoid process on imaging, this manifestation has been called "crowned dens." (48).

As regards clinical findings, although such calcification often remains asymptomatic, it may be associated with attacks of acute neck pain with segmentary stiffness, fever and an increased erythrocyte sedimentation rate, sometimes mimicking polymyalgia rheumatica and/or giant cell arteritis or neurological symptoms (49).

Temporomandibular joints

The temporomandibular joint (TMJ) is more commonly affected in the chronic form than in the acute form.

Symptoms are restricted motion, morning stiffness and contractures. The most frequent complaints of patients with TMJ CPPD deposition disease are pain (66.6% of cases), joint swelling (50%), trismus (36.8%), abnormal occlusion (22.2%), and conductive hearing loss (22.2%). Some patients may be asymptomatic. This unusual location of CPPD may be mistaken for a chondrosarcoma as extensive destruction of the temporal bone may be present. Patients with TMJ CPPD deposition disease may present with degenerative articular changes of the condyle and temporal bone. CT is the best imaging technique to establish the diagnosis and usually demonstrates a calcified mass involving the joint space with degenerative changes of the surrounding bones (articular space narrowing, osteophytosis, subchondral cyst formation). MR features have rarely been described, except in tumoural forms, which demonstrate low signal intensity periarticular formation

on T2-weighted images. Postcontrast T1-weighted images demonstrate inhomogeneous enhancement of the articular mass, probably linked to a foreign body granulomatous inflammation due to periarticular crystal deposits. Low signal intensity periarticular formation may be encountered in other cartilaginous diseases such as amyloid, gout and synovial chondromatosis, as well as post-traumatic sequelae. Diagnosis by MR imaging is difficult, because subtle forms of CPPD deposition disease may be completely overlooked and "tumoural" forms may mimic a cartilaginous malignancy. When the diagnosis is doubtful, conventional radiographs or CT of the wrist or of the knee may contribute to the diagnosis by demonstration of calcium deposition in the menisci (knees) or triangular cartilages (wrist) (50).

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