

## LESSON OF THE MONTH

## Calcium pyrophosphate crystal deposition is not always 'wear and tear' or aging

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### Case 1

A 54 year old man gave a two year history of a painful right hip, fingers, and wrists. There was no past medical history of note. On examination there were bilateral, bony, metacarpophalangeal (MCP) joint swellings and painful restriction of movement in his right hip. The remainder of the examination was unremarkable. It was thought, at the initial presentation, that the clinical and radiographic features (fig 1) were consistent with osteoarthritis and he was treated symptomatically. A further rheumatology opinion was sought two years later as his symptoms were progressive. Because of the history and radiographic features further investigations were requested. Radiographs of his knees confirmed chondrocalcinosis and calcium pyrophosphate dihydrate (CPPD) crystals were identified in synovial fluid aspirate by compensated polarised light microscopy. The serum ferritin concentration was found to be increased at 1200 µg/l. The  $\gamma$ -glutamyl-transferase was 65 (10-50 U/l) and the alanine aminotransferase 65 (5-40 U/l), the remainder of the liver function tests were normal. A liver biopsy confirmed haemochromatosis. Regular phlebotomy was instituted. Eight months later his serum ferritin and liver function tests had returned to normal. The arthropathy, however, remained symptomatic, requiring regular topical agents, analgesics, and education in pain management. He eventually required a right hip arthroplasty. Screening of family members identified an asymptomatic affected sister who subsequently underwent phlebotomy.

### Case 2

An otherwise fit 55 year old woman gave a 20 year history of recurrent episodic pain and swelling in her right knee and left shoulder occurring once or twice a year. Each episode lasted one to two weeks, but between episodes she was asymptomatic. There was no family history of joint disease. General and locomotor examination was unremarkable. Radiographs taken five years previously by a general physician showed widespread chondrocalcinosis (fig 2) but at that time no other investigations had been performed. A rheumatology opinion was sought because of increasing frequency of the episodes. On referral to our unit aspiration of her currently

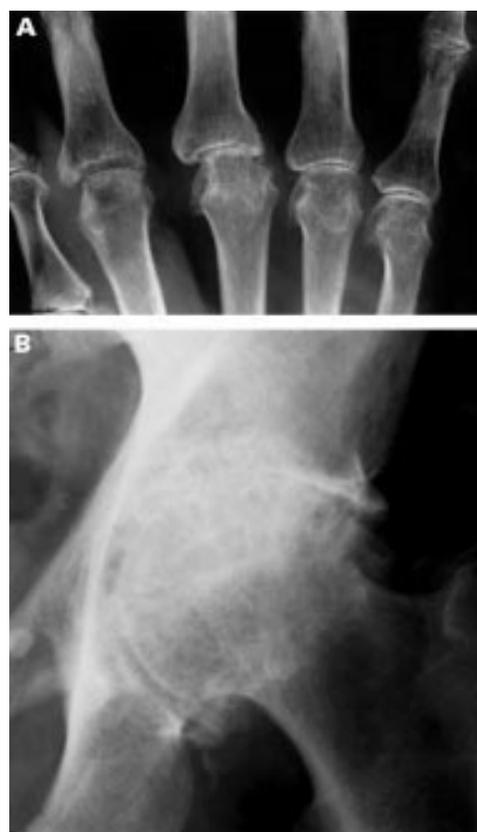


Figure 1 (A) Hand radiograph showing pronounced eccentric loss of joint space at the MCP joints, with sclerosis, osteopenia, and radial 'hook' osteophytes. (B) Hip radiograph showing attrition of the femoral head with ring cysts. These features are typical of haemochromatosis.

asymptomatic right knee confirmed CPPD crystals. A limited biochemical screen was performed, which revealed persistent hypomagnesaemia of 0.46-0.50 mmol/l (0.7-1.0). The patient was normotensive and had a normal serum potassium. There was no history of diuretic use. Twenty four hour urinary electrolyte analysis revealed a magnesium of 1.86 mmol/l (3.0-4.2), potassium of 47 mmol/l (40-120), calcium of 2.5 mmol/l (2.5-7.5), phosphate of 19.7 mmol/l (15-50), and creatinine of 6.3 mmol/l (7.5-12.5). The urinary magnesium concentration was inappropriately high compared with the serum concentration, in keeping with isolated renal wasting of magnesium. A diagnosis of hypomagnesaemia

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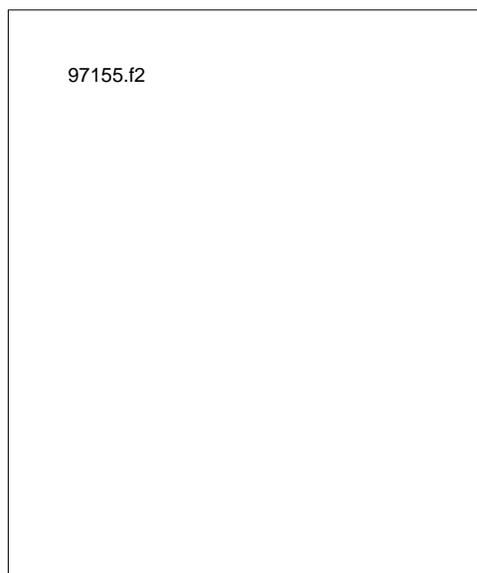


Figure 2 Hip (A) and knee (B) radiographs showing florid chondrocalcinosis with no structural arthropathy.

resulting from an isolated renal tubular defect was made. The patient was given oral magnesium carbonate supplementation and the serum concentrations improved to 0.6 mmol/l (0.7–1.0) with a concurrent reduction in the frequency of episodes of pseudogout. All screened family members had normal magnesium values.

### Discussion

The metabolism of inorganic pyrophosphate (PPi) and mechanism of CPPD crystal formation is complex and not fully understood. PPi is a by product of multiple intracellular biosynthetic reactions<sup>1</sup> with nucleoside triphosphates (NTP) the major substrates. PPi cannot passively cross membranes (being a phosphate ester), however, chondrocytes possess ectoenzymes (as NTP pyrophosphatase), which con-

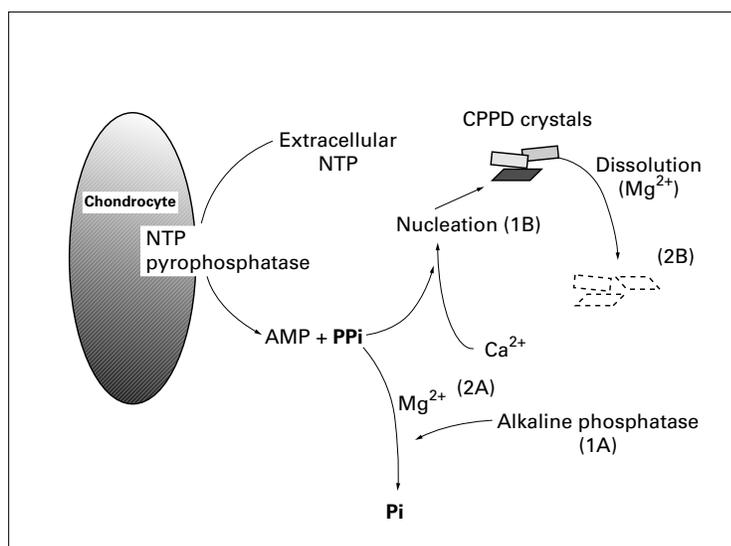


Figure 3 Metabolism of PPi and formation of CPPD crystals in haemochromatosis (1) and hypomagnesaemia (2). (1A) Inhibition of alkaline phosphatase by iron, resulting in high values. (1B) The nucleation activity of iron in CPPD crystal formation. (2A) Impaired complexing of PPi with  $Mg^{2+}$  leading to reduced processing to orthophosphate (Pi). (2B) Reduced dissolution of crystals by a  $Mg^{2+}$  dependent pathway.

vert leaked NTP to nucleosides and extracellular PPi. Extracellular PPi is then complexed with magnesium and rapidly processed to orthophosphate (Pi) by pyrophosphatases, principally alkaline phosphatase (fig 3).

CPPD crystal formation is influenced both by a high ionic product ( $Ca^{2+} \times PPi$ ) and 'tissue factors' (promoters or inhibitors) relating to crystal nucleation and growth. Increased synovial fluid concentrations of PPi occur in asymptomatic knees of patients with untreated, haemochromatosis, hypomagnesaemia, and hyperparathyroidism<sup>2</sup> supporting an influence on PPi metabolism and an increased ionic product. The postulated mechanisms of CPPD crystal formation in haemochromatosis and hypomagnesaemia are shown in figure 3. Both conditions result in high PPi values.

There are two common clinical manifestations of CPPD crystal deposition disease: (1) chronic pyrophosphate arthropathy, characterised by structural abnormalities of osteoarthritis with CPPD deposition; and (2) pseudogout—acute synovitis associated with intra-articular CPPD deposition. The target site for both is usually the knee but compared with 'primary' osteoarthritis, chronic pyrophosphate arthropathy may involve atypical sites such as the wrist, shoulders, and ankles.

CPPD deposition is most commonly sporadic, with a female preponderance and increasing association with age. Chondrocalcinosis caused by CPPD is a common asymptomatic radiographic manifestation in the elderly. CPPD commonly also occurs in association with osteoarthritis (chronic pyrophosphate arthropathy). However, rare familial forms of CPPD, with or without structural change, are described<sup>3</sup> and genetic linkage to a locus on chromosome 5p has been identified in one family.<sup>4</sup> CPPD deposition may also rarely result from underlying metabolic abnormalities such as hyperparathyroidism, haemochromatosis, hypophosphatasia, hypomagnesaemia, Wilsons disease, and hypothyroidism.<sup>5–10</sup> Although monoarticular CPPD may occur in the context of joint damage (for example, after meniscectomy), CPPD, especially florid polyarticular CPPD, is rare under age 55 in the absence of metabolic or familial predisposition.

In both the patients we describe, CPPD crystal associated arthropathy was the presenting manifestation of a metabolic abnormality. The first patient presented with chronic arthropathy, the second with recurrent attacks of pseudogout. Symptomatic arthropathy is a well recognised presenting feature of haemochromatosis<sup>11</sup> and chondrocalcinosis occurs in 15–30% of screened patients.<sup>7</sup> Although the arthropathy is similar to that of idiopathic pyrophosphate arthropathy, it may be suggested by its early onset, predominant involvement of MCP joints, 'hook-like' radial osteophytes, absence of scapho-lunate dissociation, juxta-articular osteopenia, and the presence of ring cysts. Rapid subchondral attrition of the femoral head is also characteristic (fig 1). Haemochromatosis is caused by a recessive gene on chromosome 6 close to the HLA-A locus,<sup>12</sup> leading to iron retention.

Homozygosity for haemochromatosis in the white population occurs in 3 to 5 persons per 1000 and the carrier frequency is 1 in 10 to 1 in 15.<sup>13,14</sup> Early detection and treatment with phlebotomy, as in our patient, can prevent premature death from complications of chronic liver disease, hepatocellular carcinoma, or heart failure.<sup>15</sup> The arthropathy, however, does not usually improve and damage to the synovial membrane and cartilage seems to be permanent.<sup>11</sup> Screening of asymptomatic family members is important as life threatening complications can be avoided by institution of appropriate treatment.

The second patient had a less common abnormality of magnesium metabolism caused by an isolated renal tubular defect.<sup>9</sup> Correction of the metabolic abnormality in this case reduced the frequency of pseudogout attacks. In this instance, screening of family members did not uncover asymptomatic affected persons.

#### The lesson

- In patients with young onset (< 55 years) CPPD deposition, especially polyarticular chondrocalcinosis or atypical osteoarthritis, familial and metabolic predisposition should be considered.

- An appropriate biochemical screen should include: serum calcium, alkaline phosphatase, magnesium, ferritin, and thyroid function tests.

- Screening of family members may be indicated if haemochromatosis, hypomagnesaemia or hypophosphatasia are confirmed.

- 1 Russell RGG. Metabolism of inorganic pyrophosphate (PPi). *Arthritis Rheum* 1976;19:465-78.
- 2 Doherty M, Chuck A, Hosking D, Hamilton E. Inorganic pyrophosphate in metabolic diseases predisposing to calcium pyrophosphate crystal deposition. *Arthritis Rheum* 1991;34:1297-303.
- 3 Doherty M, Hamilton E, Henderson J, Misra H, Dixey J. Familial chondrocalcinosis due to calcium pyrophosphate dihydrate deposition in English families. *Br J Rheumatol* 1991;30:10-5.
- 4 Hughes A, McGibbon D, Woodward E, Dixey J, Doherty M. *Human Mol Genet* 1995;4:1225-8.
- 5 Hamilton EBD. Diseases associated with CPPD deposition disease. *Arthritis Rheum* 1976;19:353-7.
- 6 Dodds WJ, Steinbach HL. Primary hyperparathyroidism and articular cartilage calcification. *Am J Roentgenol Rad Ther Nucl Med* 1968;104:884-92.
- 7 Hamilton EBD, Bomford AB, Laws JW, Williams R. The natural history of arthritis and idiopathic haemochromatosis: progression of the clinical and radiological features over ten years. *Q J Med* 1981;199:321-9.
- 8 Chuck AJ, Patrick MG, Hamilton E, Wilson R, Doherty M. Crystal deposition in hypophosphatasia: a reappraisal. *Ann Rheum Dis* 1989;48:57-60.
- 9 Milazzo SC, Ahern MJ, Cleland LG, Henderson DRF. Calcium pyrophosphate deposition disease and familial hypomagnesaemia. *J Rheumatol* 1981;8:767-71.
- 10 Jones AC, Chuck AJ, Arie EA, Green DJ, Doherty M. Diseases associated with calcium pyrophosphate deposition disease. *Semin Arthritis Rheum* 1992;22:188-202.
- 11 Dymock IW, Hamilton EBD, Laws JW, Williams R. Arthropathy of haemochromatosis. *Ann Rheum Dis* 1970;29:469-76.
- 12 Feder JN, Gnirke A, Thomas W, *et al*. A novel MHC class I like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399-408.
- 13 Leggett BA, Halliday TW, Brown NN, Bryant S, Powell LW. Prevalence of haemochromatosis amongst asymptomatic Australians. *Br J Haematol* 1990;74:525-30.
- 14 Edwards CO, Griffen LM, Goldgar D, Drummond C, Skolnick MH, Kushner JP. Prevalence of haemochromatosis among 11,065 presumably healthy blood donors. *N Engl J Med* 1988;318:1355-62.
- 15 Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long - term survival in patients with hereditary haemochromatosis. *Gastroenterology* 1996;110:1107-19.