Case Report

Hypomagnesemia and Chondrocalcinosis in Short Bowel Syndrome

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ABSTRACT. Chondrocalcinosis is a result of deposition of calcium pyrophosphate dihydrate (CPPD) crystals in cartilage and fibrocartilage. Chondrocalcinosis is usually sporadic but has also been associated with a variety of metabolic diseases including hypomagnesemia. Reported cases of hypomagnesemia associated chondrocalcinosis were mostly due to renal genetic disorders such as Bartter's or Gitelman's syndrome. We describe 3 patients with chronic hypomagnesemia induced by short bowel syndrome who developed symptomatic chondrocalcinosis. CPPD crystals were identified by polarizing light microscopy in one patient. The underlying intestinal pathology was radiation enteritis in 2 patients and mesenteric arterial thrombosis in the third. Our observations strengthen the hypothesis of a role for magnesium in CPPD crystal deposition disease. (J Rheumatol 2005;32:2434–6)

Key Indexing Terms:
CHONDROCALCINOSIS
SHORT BOWEL SYNDROME
HYPOMAGNESEMIA
MALABSORPTION

The hallmark of chondrocalcinosis is the deposition of calcium pyrophosphate dihydrate (CPPD) crystals in articular and fibrocartilage. Chondrocalcinosis may present as acute synovitis (pseudo-gout) or chronic arthropathy or may be asymptomatic[1]. Sporadic chondrocalcinosis is the most frequent form of the disease and is age related. There is evidence indicating that CPPD crystal deposition disease may be associated with several conditions such as hemochromatosis, hypophosphatasia, hyperparathyroidism, and hypomagnesemia[2].

Reported cases of hypomagnesemia with chondrocalcinosis were mostly secondary to renal leakage of magnesium (Mg) due to genetic disorders such as Bartter or Gitelman's syndrome[3] or induced by drugs such as tacrolimus[4].

Hypomagnesemia may also occur in the setting of intestinal malabsorption. It is particularly frequent in patients with large intestinal resection, in whom management of hypomagnesemia is difficult as most Mg salts have a laxative effect[5]. To our knowledge, no definite case of CPPD crystal disease associated with such a condition has been reported. We describe 3 cases of chondrocalcinosis in patients with chronic hypomagnesemia induced by short bowel syndrome (SBS).

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CASE REPORTS

Case 1. A 56-year-old woman was admitted to our department for recurrent attacks of acute arthritis of the knee. Her history was marked by an ovarian cancer diagnosed in 1976. Surgical treatment consisted of hysterectomy and ovariectomy combined with adjuvant chemotherapy, and pelvic radiotherapy was secondarily applied. An extensive resection of the small bowel was performed in 1985 because of stenosis as a result of radiation therapy, leading to SBS. This SBS was managed by oral nutrition and regular supplementation with vitamins, minerals, and trace elements.

Physical examination revealed effusion of the left knee, but was otherwise normal, including body temperature. Knee arthrocentesis was carried out and CPPD crystals were observed in the synovial fluid by polarizing light microscopy. Radiographs showed chondrocalcinosis in the knees and pubic symphysis (Figure 1). Table 1 shows the most significant laboratory findings. Severe serum hypomagnesemia was documented on several occa-

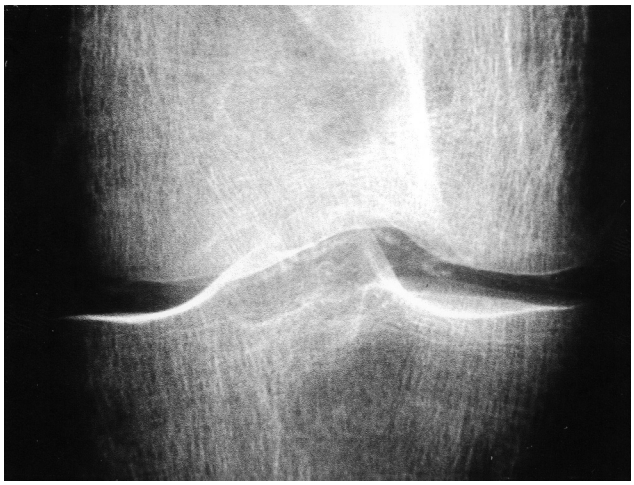

Figure 1. Extensive chondrocalcinosis with characteristic calcifications in cartilage and menisci of the knee in Patient 1.

Table 1. Significant laboratory data (normal values) at time of chondrocalcinosis diagnosis (blood and urine chemistry test).

Indicator	Patient 1	Patient 2	Patient 3
Magnesium, mmol/l (0.74–0.90)	0.56	0.62	0.41
Urinary Mg excretion, mmol/day (0.6–2)	0.4	2.6	1.8
Calcium, mmol/l (2.35–2.5)	2.27	2.16	2.18
Phosphorus, mmol/l (0.85–1.45)	0.99	0.88	0.41
Transferrin saturation, % (20–40%)	28	12	34
25OH vitamin D, ng/ml (8–35)	33.8	17.5	28.7
Vitamin A, mg/l (0.32–0.90)	—	0.67	0.62
Vitamin E, mg/l (7–13)	6.2	12.8	7.2
Copper, µmol/l (12.7–22)	12.7	15.9	8.1
Selenium, µmol/l (0.9–1.5)	1.2	1.23	1.26
Zinc, µmol/l (12.5–18)	11.9	20.2	14.9

sions. Complete blood cell count, hepatic function, serum iron and ferritin levels, total iron binding capacity, and parathyroid hormone were normal.

Case 2. Patient 2 was a 73-year-old woman who had been taking home parenteral nutrition since 1998. In 1971 she had been successfully treated for ovarian cancer by chemotherapy and radiotherapy. She progressively developed a malabsorption syndrome due to radiation enteritis and extensive resection of small bowel performed in 1993. Despite suitable enteral nutrition, she required continuous parenteral nutrition with vitamins, trace elements, and Mg supplementation.

In 2004, she presented with acute synovitis of her right ankle and bilateral gonalgia. Radiographs revealed extensive calcifications in cartilage of knees and pubic symphysis. Her medical record showed that despite supplementation she frequently experienced profound hypomagnesia. Significant laboratory findings are indicated in Table 1.

Case 3. This patient, a 45-year-old man, has been managed by longterm home parenteral nutrition in the nutrition support department of our hospital. His intestinal history began suddenly in 1994, when he experienced a severe mesenteric arterial thrombosis due to aortic dissection. This led to large-scale resection of the small intestine and SBS that required parenteral nutrition. In 2000, he complained of noninflammatory pain of both knees. Examination disclosed no synovial fluid effusion and normal range of motion. Radiographs of both knees revealed typical chondrocalcinosis. He denied having acute episode of arthritis. Laboratory findings showed regular serum hypomagnesemia (Table 1) despite Mg supplementation.

DISCUSSION

We describe 3 patients with articular chondrocalcinosis and short bowel syndrome. CPPD crystals were observed in one of them by polarizing light microscopy. Two patients were relatively young, a finding supporting the hypothesis of nonsporadic chondrocalcinosis. Our patients had longstanding hypomagnesemia, which is the most likely explanation for their chondrocalcinosis. Diagnosis of hemochromatosis was excluded because of normal or low values of transferrin saturation in all patients. Mg deficiency appeared as a consequence of malabsorption due to SBS, as none of the patients was taking drugs known to induce Mg leakage, and low urinary Mg concentration excluded the hypothesis of renal Mg wasting.

Mg is an essential element for homeostasis of electrolytes and deficiency is rarely encountered in healthy individuals. Mg homeostasis is regulated by both the gastrointestinal tract and kidneys. Under normal conditions, Mg is mainly absorbed from the small intestine. Two separate transport systems are proposed to participate in the absorption of Mg: a transcellular saturable process and an intercellular passive process. Nevertheless, the kidney is the organ that most closely regulates Mg metabolism. Under conditions of deprivation, both organs increase their fractional absorption of Mg[6].

Hypomagnesemia usually indicates the presence of underlying disease. It may arise from various disorders that lead to reduced intestinal Mg absorption or increased renal Mg loss. Most cases of hypomagnesemia are asymptomatic in clinical practice. Classical features include neuromuscular manifestations (positive Chvosteck's and Trousseau's signs, muscle cramps, tetany, vertigo), and cardiac arrhythmias. Biologically, Mg depletion is frequently associated with hypokalemia and hypocalcemia caused by impaired parathyroid hormone secretion that is usually refractory to calcium repletion[7]. None of our patients had clinical manifestations of Mg depletion, but all 3 had hypocalcemia.

Mg depletion is common in patients with SBS because its main absorptive site, the distal small bowel, has been removed[5]. Treatment of hypomagnesemia can be difficult, as it is not always responsive to oral Mg oxide supplementation alone. Moreover, administration of Mg sulfate frequently leads to diarrhea[8]. To our knowledge, no proved case of chondrocalcinosis occurring in patients with hypomagnesemia related to intestinal loss has been reported. However, Jin-no, *et al* described a patient who presented with pseudo-gout attack of the right knee with hypomagnesemia secondary to isolated Mg malabsorption. Unfortunately, no radiographic or synovial fluid analyses were available and a precise diagnosis is impossible[9].

The association between hypomagnesemia due to renal wasting in the setting of Gitelman's or Bartter's syndrome, and chondrocalcinosis is documented in numerous reports[2,3,10,11]. Young age of patients in most reported cases at onset of CPPD disease strongly supports the link between chronic Mg depletion and chondrocalcinosis. Findings of chondrocalcinosis in patients with hypomagnesemia due to causes other than renal genetic disorders strengthen the hypothesis of a role for Mg in CPPD disease. One report has described 2 patients suffering from chondrocalcinosis with hypomagnesemia while undergoing therapy with tacrolimus, a drug known to induce renal leakage of Mg[4]. Interestingly, a recent study found an association between diuretic use and chondrocalcinosis that might theoretically be explained by increased urinary Mg loss[12].

The therapeutic potential of Mg in patients with pyrophosphate arthropathy is unknown. A 6 month, double blind, placebo controlled trial of magnesium in chondrocalcinosis found a trend toward clinical improvement in patients taking magnesium[13]. In our patients, the finding of chondrocalcinosis associated with hypomagnesemia led us

to increase Mg supplementation. Followup of these patients is not long enough to ascertain the effect on chondrocalcinosis.

The role of hypomagnesemia in the development of chondrocalcinosis is not fully understood. Excess inorganic pyrophosphate is a crucial and necessary precursor for CPPD crystal nucleation. Mg acts as a cofactor in numerous enzyme systems, such as pyrophosphatases. Among them, alkaline phosphatases play a key role by converting inorganic pyrophosphates to orthophosphate. Moreover, *in vitro* study has shown that Mg increases the solubility of CPPD crystals. Thus, hypomagnesemia could favor chondrocalcinosis through intraarticular elevation of extracellular inorganic pyrophosphate and/or reduced saturation product of CPPD[3].

We describe 3 patients with chondrocalcinosis in the setting of hypomagnesemia of gastrointestinal origin, a previously unreported association. The discovery of chondrocalcinosis in our patients has highlighted the need to carefully detect and treat hypomagnesemia in patients already taking Mg supplements who have short bowel syndrome. Our observations imply that patients with SBS who present with acute arthritis should be investigated for serum Mg levels and CPPD deposition disease by radiographs and synovial fluid analysis.

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