Case Report

Chondrocalcinosis Secondary to Hypomagnesemia in Gitelman's Syndrome

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ABSTRACT. Chondrocalcinosis can be associated with hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia. Gitelman syndrome (GS), an inherited disorder due to loss of function mutations of the gene encoding the distal convoluted tubule Na-Cl cotransporter (NCCT), is characterized by hypokalemia metabolic alkalosis, hypomagnesemia, and hypocalciuria. A 53-year-old man, with history of recurrent joint effusions and pains affecting knees and wrists, had transient episodes of muscle pain, weakness, cramping, and fatigue over a one-year period. Laboratory tests showed hypokalemia, metabolic alkalosis, hypocalciuria, and hypomagnesemia related to genetically proven GS. Radiographs of affected joints revealed calcium pyrophosphate dihydrate deposition. This observation points out the necessity to look for Mg depletion (and especially GS) in the biological investigation of chondrocalcinosis. Additionally, the association between GS (NCCT inactivation) and high bone mineral density provides a new insight into the possible role of thiazides in osteoporosis management. (J Rheumatol 2005;32:1840–2)

Key Indexing Terms:
CHONDROCALCINOSIS | MAGNESIUM | INORGANIC PYROPHOSPHATE
GITELMAN SYNDROME | OSTEOPOROSIS | Na-Cl COTRANSPORTER

Calcium pyrophosphate dihydrate (CPPD) is a weakly positive, birefringent crystal that can be found in hyaline cartilage, fibrocartilage, and other soft tissue structures. CPPD deposition is the most frequent form of crystalline arthropathy. It is common in aging, and its incidence can reach 20% in individuals over 80. Although the asymptomatic form is the most frequent, crystal deposition is responsible for a spectrum of clinical manifestations that can mimic gout, rheumatoid arthritis, severe osteoarthritis with or without acute exacerbation, or even neuroarthropathy[1-5]. Mostly idiopathic in the elderly, its occurrence in the young adult can be secondary to a familial form of chondrocalcinosis or associated with metabolic diseases such as hyperparathyroidism, hemochromatosis, hypophosphatasia, or hypomagnesemia[1-5].

Gitelman syndrome (GS), an autosomal recessive inherited disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria, can be associated with CPPD crystal deposition[6]. First described as the hypocalciuric and hypomagnesemic variant of Bartter syndrome[7], GS is now well characterized at the genetic, biologic, and clinical level[8-11]. Chondrocalcinosis is a major outcome of the disease. In addition, recent studies have shown that GS is associated with higher bone mineral density (BMD) than normal[12-13].

We present the case of a middle-aged man with genetically proven GS revealed during investigations for chondrocalcinosis, with documented high BMD with z scores > 2.5 at both lumbar spine and femur.

CASE REPORT

A 53-year-old white man had repeated episodes of pain and swelling in his knees and wrists since the age of 32 years. Joint effusions had never been aspirated and were considered as gouty arthritis because the plasma uric acid level was once elevated. He was treated with allopurinol. At the age of 52 years, severe hypokalemia was discovered because he experienced transient episodes of muscle pain, weakness, cramping, and fatigue. There was no history of vomiting or gastrointestinal disease, and abuse of laxatives or diuretics was denied. The systolic blood pressure was decreased at 100 mm Hg. Laboratory tests showed severe hypokalemia (2.64 mmol/l, normal 3.50–4.50), metabolic alkalosis and hypomagnesemia (0.54 mmol/l, normal range 0.70–1.40) with preserved urinary potassium and magnesium excretion. Urine calcium excretion was decreased and the fasting urine calcium/creatinine ratio was 0.02 (normal > 0.20). Plasma renin activity was increased (273 mU/l, normal 10-50), with normal aldosterone level. The lack of high aldosterone level in spite of high renin was related to the inhibitory effect of hypokalemia on aldosterone secretion. GS was suspected and confirmed by analysis of the gene encoding the distal convoluted tubule Na-Cl cotransporter (gene locus *SLC12A3*) which showed a homozygous loss of function mutation. Radiographs revealed CPPD in the menisci of the knees, pubic symphysis, and triangular fibrocartilage of the wrists. Bone density, measured by dual x-ray absorptiometry (QDR 4500,

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Accepted for publication May 5, 2005.

Hologic, Waltham, MA, USA), was increased both at the lumbar vertebrae (L2–L4) (z score + 2.7 SD) and the upper extremity of the left femur (z score + 3.7 SD) levels. He was the eldest son of 3 brothers from a nonconsanguinous marriage, and family history did not find other cases of GS or chondrocalcinosis. Allopurinol was stopped. Treatment with potassium sparing diuretics (spironolactone, triamterene) and oral potassium and magnesium supplementation was given. Nonsteroidal antiinflammatory therapy was recommended for joint attacks.

DISCUSSION

Chondrocalcinosis in the young adult should alert the physician to check for associated metabolic diseases such as hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia[3-5]. Although the mechanism and pathogenesis of pyrophosphate calcium crystal deposition are not completely understood, recent studies have highlighted the role of extracellular inorganic pyrophosphate (ePPi) in CPPD crystal deposition[4,14,15]. Specifically, excess ePPi generation by chondrocytes leads to CPPD whereas ePPi deficiency leads to hydroxyapatite crystal deposition. Production of ePPi results from PPi-generating nucleoside triphosphate pyrophosphohydrolase (NTPPPH) activity and/or anion transport of intracellular PPi across the cell membrane by ANK protein, a multi-pass transmembrane PPi transporter[16-17]. PPi is hydrolyzed to inorganic phosphate by alkaline phosphatase (ALP) and inorganic pyrophosphatase. Excess accumulation of ePPi relates to factors that increase its production (stimulation of PPi production by chondrocytes by transforming growth factor-ß in aging, increased ANK activity by ANKH mutations in UK, French, and Argentinean families with chondrocalcinosis[17–19]) or decrease its destruction by ALP (reduced ALP levels due to hypophosphatasia, presence of ALP inhibitors such as calcium and iron in hyperparathyroidism and hemochromatosis, or deficiency in ALP cofactors such as magnesium).

Chronic hypomagnesemia can be produced by various conditions including gastrointestinal disorders, diet, laxative abuse, and renal tubular dysfunctions. GS, described in 1966 as the hypomagnesemic and hypocalciuric variant of Bartter syndrome, is secondary to loss of function mutations of the gene encoding the renal thiazide sensitive Na-Cl cotransporter (NCCT)[7-13]. The cotransporter consists of 12 transmembrane domains and an intracellular amino and carboxyterminal region. Most of the mutations are localized in the carboxyterminal region and lead to defective Na and Cl reabsorption in the distal convoluted tubule. Na-Cl wasting results in extracellular volume depletion with activation of the renin-angiotensin-aldosterone system. Elevated aldosterone levels induce hypokalemia and metabolic alkalosis. The inhibition of Na-Cl absorption in the distal tubule also has consequences for calcium and magnesium reabsorption in this segment. As observed during thiazide treatment, GS is associated with increased tubular calcium reabsorption, low urinary calcium excretion, and renal loss of magnesium by mechanisms that remain unclear[20,21].

Patients with GS are either asymptomatic or have symptoms related to hypomagnesemia and hypokalemia such as cramps, fatigue, muscle weakness, carpopedal spasms, tetany, paralysis, and rhabdomyolysis. Severe symptoms are observed only in conditions of profound magnesium depletion (vomiting, diarrhea, fever). Chondrocalcinosis occurs in some patients and is secondary to hypomagnesemia, which decreases ALP activity. As observed in chronic thiazide diuretic administration, several studies have shown an association between GS and high BMD[12,13]. The mechanism leading to this beneficial effect remains unclear. It might be due to the enhanced urinary calcium reabsorption with a positive calcium balance and to hypomagnesemia, which inhibits parathyroid hormone secretion and its bone resorbing activity[13]. Contribution of a direct effect of NCCT on bone cells remains to be established; indeed the NCCT is expressed in human osteoblasts and osteoblast-like cells[22], and thiazide diuretics at high dose inhibit bone resorption by isolated rat osteoclasts[23], although this effect might be due to mechanisms other than NCCT inhibition, such as nonspecific inhibitory effect on bone carbonic anhydrase activity.

In summary GS, an inherited disorder secondary to loss of function mutations of the gene encoding the distal convoluted tubule NCCT, is associated with chondrocalcinosis in the young adult because of chronic hypomagnesemia. Its association with high BMD suggests that the NCCT gene may be a novel determinant of bone mass and confirms NCCT as a possible target in osteoporosis management.

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