NOTE

A Case of Gitelman's Syndrome with Chondrocalcinosis

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Abstract. A 45-year-old Japanese woman, treated for Bartter's syndrome for 14 years, presented with complaints of numbness in her extremities and polyarthralgia. She was diagnosed to have Gitelman's syndrome with chondrocalcinosis, which were effectively treated with spironolactone and magnesium supplementation. Gitelman's syndrome is a primary renal tubular disorder characterized by hypomagnesemia and hypocalciuria with normal calcemia. The persistent hypomagnesemia is one of the causes of chondrocalcinosis, and many cases of Bartter's syndrome with hypomagnesemia are associated with chondrocalcinosis attributed to a tubular magnesium defect. We summarize the reported cases with Bartter's syndrome and chondrocalcinosis, referring to the possibility of Gitelman's syndrome.

Key words: Bartter's syndrome, Chondrocalcinosis, Gitelman's syndrome, Hypomagnesemia
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BARTTER'S syndrome, first reported in 1962, is characterized by hypokalemia, metabolic alkalosis, hyperreninemia, hyperplasia of the juxtaglomerular cells and normal blood pressure [1]. Gitelman's syndrome was initially reported as a "familial disorder characterized by hypokalemia and hypomagnesemia" in 1966 [2]. These disorders had been often confused because of their similar clinical features, but urinary calcium levels have been clinically useful in separating patients with primary hypokalemic metabolic alkalosis into two groups, i.e. classic Bartter's syndrome and Gitelman's syndrome [3]. Recently the pathogenesis of Gitelman's syndrome has been reported to be mutations of the gene encoding thiazide-sensitive Na-Cl cotransporter [4].

In addition, hypomagnesemia has been associated on several occasions with calcium pyrophosphate deposition disease (CPPDD,

chondrocalcinosis). Since the first report in 1978 of the association between Bartter's syndrome and chondrocalcinosis, 25 cases have been published [5–19]. Because all the data in these reports showed hypomagnesemia and hypocalciuria, they might indicate Gitelman's syndrome, not Bartter's syndrome.

In this paper, we describe a patient with Gitelman's syndrome and chondrocalcinosis who has been successfully treated with spironolactone and magnesium supplementation.

Case Report

A 45-year-old Japanese woman was admitted to our hospital in December, 1994 for evaluation of numbness in her extremities and dyspnea. There was no family member with similar symptoms or renal disease, and her parents were nonconsanguineous. She grew up normally and had no childhood history of tetany. There also was no history of vomiting or gastrointestinal disease, or abuse of diuretics, laxatives or other medications.

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Hypokalemia had been first revealed in 1980 when she initially experienced dyspnea and numbness in her extremities. Because of hyperreninemia, hyperaldosteronism, the resistance to the pressor effects of angiotensin II, and hyperplasia of her juxtaglomerular cells, she had been diagnosed as having Bartter's syndrome in the former hospital. Since she came to our hospital with complaints of palpitation, numbness and dyspnea in 1982, she has been treated with spironolactone (25 mg/day) and potassium supplementation (32 mEq/day). Although her serum potassium concentration was slightly increased and maintained at 2.9–3.3 mEq/l with medication, mild numbness and dyspnea continued with gradual progression. The dose of spironolactone could not be increased to more than 50 mg/day, because prolongation of menstruation was found to be due to the drug. Meanwhile, hypomagnesemia was discovered in 1986.

Since 1990 she had been suffering from recurrent episodes of pain in her knees, shoulders and elbows; these attacks, lasting several days, were accompanied by a fever and improved by the administration of non steroidal anti inflammatory drugs. In 1992 chondrocalcinosis was found to be due to calcification in the joint spaces in her knees and symphysis pubis.

On physical examination, her height was 150.3 cm and weight 39.2 kg. Her blood pressure was 92/60 mmHg. Trousseau's sign and Chvostek's sign were both absent.

Laboratory data on admission revealed total serum protein, 6.8 mg/dl; serum albumin, 4.5 mg/dl; creatinine, 0.5 mg/dl; blood urea nitrogen, 10 mg/dl; and uric acid, 4.1 mg/dl. Serum values included the following: sodium, 137 mEq/l; potassium, 2.8 mEq/l; chloride, 102 mEq/l; magnesium, 1.2 mEq/l (normal 1.6–2.1 mEq/l); calcium, 5.0 mEq/l; ionized calcium, 2.64 mEq/l (normal 2.27–2.63 mEq/l); and phosphate, 1.4 mEq/l. Urinary potassium was 55.8 mEq/day; urinary chloride, 138.6 mEq/day; urinary magnesium, 7.7 mEq/day; and urinary calcium, 0.54 mEq/day. The endogenous creatinine clearance was 119.9 ml/min. The molar urinary calcium/creatinine ratio was 0.04. On hormonal examination, the plasma renin activity was 37.3 ng/ml/h; aldosterone, 45 ng/dl; angiotensin I, 2760 pg/ml (normal <500 pg/dl); angiotensin II, 160 pg/ml (normal 9–47 pg/ml);

and intact PTH, 27 pg/ml. The intravenous infusion of 72 mEq magnesium (3.6 g magnesium sulfate) caused the serum magnesium level to transiently increase to 2.2 mEq/l before decreasing to 1.5 mEq/l the next day. The urinary excretion of magnesium was 33 mEq/day, suggesting that the renal magnesium wasting was responsible for the hypomagnesemia. Radiographs revealed chondrocalcinosis of the menisci in the knees (Fig. 1) and symphysis pubis (Fig. 2).

Treatment with increasing doses of spironolactone (50 mg/day) and oral magnesium (magnesium oxide 0.3 g/day) was started, along with continuation of the potassium supplementation. Although the serum potassium level increased to greater than 3 mEq/l, the serum magnesium level did not change. Weekly intravenous drip infusion of magnesium sulfate (32 mEq) was therefore initiated. Despite persistent hypomagnesemia, the polyarthralgia improved and the high fever had been reduced (Fig. 3).

Discussion

Our patient manifested all of the characteristic findings of Bartter's syndrome, including the laboratory examination and renal histology done by biopsy. In addition, hypomagnesemia due to renal magnesium wasting and hypocalciuria were

Fig. 1. Chondrocalcinosis of the menisci in the knee.

present. These features are compatible with Gitelman's syndrome, that was first described by Gitelman in 1966 [2]. Patients with Gitelman's syndrome tend to have a milder and later developing course, manifesting renal magnesium wasting and hypocalciuria [3].

Fig. 2. Chondrocalcinosis of the symphysis pubis.

Renal magnesium wasting is defined as the urinary excretion of more than 1 mmol/day of magnesium in the presence of hypomagnesemia (plasma magnesium < 0.7 mmol/l) [20]. Sixty-five percent of magnesium reabsorption takes place in the ascending loop of Henle, driven by the electrical gradient generated by the active reabsorption of chloride. Hypomagnesemia with renal magnesium wasting is demonstrated not only in all patients with Gitelman's syndrome, but also in 20–39% of those with Bartter's syndrome which might have involved Gitelman's syndrome in previous reports [20, 21].

Nevertheless, these two syndromes may be differentiated by the laboratory examination of the calcium excretion. The patients whose calcium excretion is consistently reduced (molar urinary calcium/creatinine ratio < 0.10) are diagnosed as having Gitelman's syndrome, while the patients whose calcium excretion is normal or increased (molar urinary calcium/creatinine ratio > 0.20) are diagnosed as having Bartter's syndrome [3]. The differences in calcium excretion may result from

Fig. 3. The clinical course of our patient, a 45-year-old Japanese woman with Gitelman's syndrome and chondrocalcinosis.

different sites of tubular involvement. As calcium and magnesium are absorbed in parallel in Henle's loop, Bartter's syndrome, with its defect at this site, manifests as hypercalciuria and magnesium wasting. As calcium and magnesium transport can be dissociated in the distal convoluted tubule, which is the site of the defect in Gitelman's syndrome [3, 22–24], these patients manifest magnesium wasting and hypocalciuria. Simon *et al.* demonstrated a wide variety of non-conservative mutations in the gene encoding renal thiazide-sensitive Na-Cl cotransporter (TSC) in the patients with Gitelman's syndrome and proposed that the mutant alleles result in a defect in normal TSC function [4], although our patient wasn't been performed gene analysis. The mechanism of the defect causing hypomagnesemia and hypocalciuria is unclear, but the physiological features of Gitelman's syndrome appear to be derived from a mutation in TSC, because these same effects are seen in patients taking thiazide diuretics, specific inhibitors of TSC [4].

There are reports indicating that concentrations of ionized calcium are normal [25] or low [26] with a normal level of PTH and an association between hypocalciuria and a reduction in fractional excretion of ionized calcium in patients with Gitelman's syndrome. Colussi *et al.* suggested the possibility of an abnormal ionized calcium-PTH relationship related to hypomagnesemia [25].

Our patient had polyarthralgia due to chondrocalcinosis for ten years after revealing hypokalemia. Twenty-five cases of Bartter's syndrome with chondrocalcinosis including familial presentation have been reported since 1978 [5], and hypomagnesemia was always presented in these cases (Table 1). The mean age at revealing hypokalemia in these cases was 42.8 years old, which is a late presentation for Bartter's syndrome. The fact that all the patients (except one), with urinary calcium had hypocalciuria, also indicated that these cases had a high possibility of Gitelman's syndrome not Bartter's syndrome.

Chondrocalcinosis is caused by the release of lysosomal enzymes from polymorphonuclear leukocytes in response to phagocytosis of calciumpyrophosphate-dihydrate (CPPD) crystals. Hypomagnesemia is considered to be one of the causes of chondrocalcinosis. There is *in vitro* evidence suggesting a relationship between

hypomagnesemia and chondrocalcinosis; 1) magnesium is a cofactor for pyrophosphatase and magnesium depletion decreases the activity of pyrophosphatase, increasing the level of pyrophosphate [27], 2) magnesium ions increase the solubility of CPPD crystals [28]. It is not clear whether the tendency to hypercalcemia in the patients with Gitelman's syndrome contributes to the deposition of CPPD crystals. Since our patient had no factor of chondrocalcinosis except hypomagnesemia, persistent hypomagnesemia for over 4 years is considered to be the cause of chondrocalcinosis.

Magnesium supplementation is considered to be effective in inhibiting progression of chondrocalcinosis. Salvarani *et al.* described a patient who showed no progression of chondrocalcinosis (no radiological increase in the calcified deposits and absence of acute attacks of arthritis) after treatment with magnesium supplementation and indomethacin [12]. Smilde *et al.* described familial cases with the longest follow up (about 10 years). The patients kept on magnesium supplementation had remained free of clinical symptoms and regression or no radiological increase in calcified deposits. In contrast, progression had been observed in other patients who refused or stopped magnesium supplementation [18]. On the other hand, antialdosterone therapy is effective in ameliorating hypokalemia and hypomagnesemia in Gitelman's syndrome. Its effects appear to result mainly from a direct tubular effect on potassium secretion and magnesium reabsorption [23]. In our patient, after starting treatment with magnesium supplementaion (oral magnesium oxide and intravenous magnesium sulfate) besides antialdosterone therapy, the severity of acute attacks became milder and the calcification did not increase, although serum magnesium did not reach completely normal levels.

The long-term clinical course and growth of patients with Gitelman's syndrome is considered to be good [29], but we should note that Gitelman's syndrome may be accompanied with a complication due to persistent hypomagnesemia, such as chondrocalcinosis. Long-term hypomagnesemia causes chondrocalcinosis, and antialdosterone therapy and magnesium supplementation is important in protecting against complications.

Table 1. Previously reported cases of Bartter's syndrome with chondrocalcinosis

Source	Sex	Age of onset of arthritis (years)	Age of revealing hypokalemia (years)	Plasma Mg (normal value)	urinary Ca	urinary Ca/Crn
Schwartz <i>et al.</i> 1978 [5]	M	32	52	0.29 mEq/l (0.46–0.89)	—	
Bauer <i>et al.</i> 1979 [6]	M	24	36	0.4 mmol/l	—	
	F		40	0.53 mmol/l (0.75–1.25)	—	
Goulon <i>et al.</i> 1980 [7]	F	37	32	16 mg/l	—	
	M	27	42	14 mg/l (21 ± 4)	—	
Hurault <i>et al.</i> 1981 [8]	F	24	21	0.48 mmol/l (0.78–0.98)	—	
de Bruyne <i>et al.</i> 1982 [9]	M	32	36	0.7 mEq/l (1.5–2.5)	—	
Mayoux-Beuhamou <i>et al.</i> 1985 [10]	F	26	31	0.55 mmol/l		0.015
	F	56	44	0.35 mmol/l (0.74–0.90)		0.10 (0.1–0.3)
Dupond <i>et al.</i> 1989 [11]	F			0.48 mmol/l (0.75–0.90)		0.04 (0.1–0.3)
Salvarani <i>et al.</i> 1989 [12]	M	31	31	0.8 mg/dl (1.6–2.5)		—
Pagès <i>et al.</i> 1991 [13]				0.45 mmol/l 0.43 mmol/l (0.7–1.0)	49 mg/g.crn 22.5 mg/g.crn (70–190)	
de Heide <i>et al.</i> 1991 [14]	F	44	24	0.65 mmol/l (0.85–1.0)	—	
de Fillipi <i>et al.</i> 1992 [15]				0.52 mmol/l (0.70–0.90)	—	
Jones <i>et al.</i> 1992 [16]	F	49	50	0.5 mmol/l (0.7–1.0)	—	
Waitman <i>et al.</i> 1992 [17]	M		60	0.75 mg/dl (1.7–2.4)	—	
Smilde <i>et al.</i> 1994 [18]	F	39	54	0.56 mmol/l	2.80 mmol/day	
	M		56	0.60 mmol/l	2.20 mmol/day	
	M		59	0.60 mmol/l	1.10 mmol/day	
	F		41	0.49 mmol/l	1.16 mmol/day	
	M		37	0.54 mmol/l	1.95 mmol/day	
	M		43	0.49 mmol/l	1.95 mmol/day	
	M		44	0.52 mmol/l (0.80–1.20)	1.82 mmol/day (2.5–7.5)	
Muñoz-Fernández <i>et al.</i> 1994 [19]	M	65	65	1.2 (1.4–2.1)	—	

Ca, Calcium; Crn, creatinine; Mg, magnesium; M, male; F, female.

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