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Case Report

Gitelman's Syndrome Associated with Chondrocalcinosis

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Gitelman's syndrome (GS), a hereditary disease characterized by hypokalemia, hypomagnesemia, and hypocalciuria, is a salt-losing renal tubulopathy. Herein, we describe a case of a 28-year-old woman diagnosed with atypical GS accompanying chondrocalcinosis. One year ago, she presented with vomiting, hypokalemic metabolic alkalosis, and hypocalciuria, and was tested by diuretic challenge test. As a result, she was diagnosed with atypical GS with normomagnesemia and treated with spironolactone and potassium supplementation. Meanwhile, acute arthritis of the right 1st metatarsophalangeal joint occurred. On the radiographies of the knees, chondrocalcinosis was observed. To the best of our knowledge, this is the first report in Korea of GS with chondrocalcinosis. Antialdosterone therapy or magnesium supplementation is effective in preventing the progression of chondrocalcinosis; thus, early diagnosis and treatment of GS are important. **(J Rheum Dis 2016;23:266-270)**

Key Words. Gitelman syndrome, Chondrocalcinosis, Hypokalemia, Alkalosis

INTRODUCTION

Gitelman's syndrome (GS), which is characterized by hypokalemia and hypomagnesemia, is a salt-losing renal tubulopathy with an autosomal recessive trait [1]. This disorder has often been confused with Bartter's syndrome (BS), which has hypokalemic metabolic alkalosis, hyperreninemia, and normal blood pressure. However, the urine calcium level has been clinically helpful in the differential diagnosis between classic GS and BS [2].

The prevalence of GS is 1/40,000, and it is usually diagnosed at an adult age [3]. The common symptoms are paresthesia, muscle weakness, fatigue, tetany especially accompanied by diarrhea and vomiting, and though rare, sudden cardiac arrest could be seen [3].

Chondrocalcinosis is a common arthritic disorder of the elderly, and the prevalence is about 10% in the general population. Prevalence increases with age [4]. Moreover, there are several other factors associated with increasing calcium pyrophosphate deposits in the joints as follows: trauma, genetics, excess iron, and several metabolic diseases, such as hyperparathyroidism, hypophosphatemia, hypomagnesemia, and GS. Although several cases of GS accompanying chondrocalcinosis has been reported in foreign countries [5,6], to our knowledge, it has not been reported in Korea yet.

The leading cause of GS is mutations in the *SLC12A3* gene which codes the thiazide-sensitive Na/Cl cotransporter on the apical membrane of the distal convoluted tubule in the kidneys. Previously, more than 180 mutations in *SLC12A3* have been reported, whereas 12% of GS was negative for mutation of the *SLC12A3* gene [7].

We describe here a patient diagnosed as GS with normomagnesemia accompanied by chondrocalcinosis, even though the genetic test for the *SLC12A3* mutation was negative.

CASE REPORT

A 28-year-old Korean woman who is a vegetarian ballet

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dancer has been habitually taking non-steroidal anti-inflammatory drugs (NSAIDs) for arthralgia or headache. One year ago she had nausea and vomiting and was admitted to a local clinic, in which blood tests showed hypokalemia, metabolic alkalosis, hypocalciuria, and azotemia. She was, then, referred to the department of nephrology in Hanyang University Hospital for Rheumatic Diseases to evaluate and manage her problems. There was no family history of electrolyte disorders or renal diseases. She had no history of tetany in her childhood. There also was no history of diarrhea and no abuse of diuretics, laxatives, or other medications except for NSAIDs. On physical examination, her height was 163.4 cm and weight 45.1 kg. Her blood pressure was measured as 118/64 mmHg and pulse as 80 beats/min. Pathological findings were not observed in the physical examination.

Electrocardiogram showed a decrease in the T-wave amplitude, ST-segment depression, and U waves (Figure 1). The patient's laboratory data at first admission, April 2014, are summarized in Table 1. To investigate the cause of hypokalemic metabolic alkalosis, a thiazide and furosemide loading test was performed, respectively. The former was negative, and the latter was positive (Table 2). Taken together, she was diagnosed with GS and treated with spironolactone and potassium supplementation. After being discharged from hospital, she has been treated consistently at an outpatient clinic for one year; however, her medication compliance was not good.

Meanwhile, from her last visit, she had been suffering from acute arthritis of the right 1st metatarsophalangeal (MTP) joint with swelling, heating, and redness. She denied having a history of trauma. The patient's laboratory data at the latest admission are summarized in Table 1. We took X-rays of both knees (Figure 2A) and feet and ultrasonographic examination of the right 1st MTP joint (Figure 2B). After that, we performed arthrocentesis of the right 1st MTP joint, but no crystals were observed during the polarizing microscopy. Furthermore, dual-energy computed tomography of her feet was used to determine the presence of tophi. There was no evidence of tophi. However, the radiographies showed chondrocalcinosis of the menisci in the knees. The pain was controlled by an extended-release tramadol hydrochloride 75 mg/acetaminophen 650 mg fixed-dose combination tablet instead of NSAIDs because she had chronic kidney disease induced by the long-term use of NSAIDs.

For a precise diagnosis, after obtaining consent from the patient, we performed direct sequencing of *SLC12A3* on chromosome 16q13 (Samsung Medical Center, Seoul, Korea), but no mutations were detected. Now, she is doing well without any musculoskeletal symptoms with antialdosterone therapy and potassium supplementation.

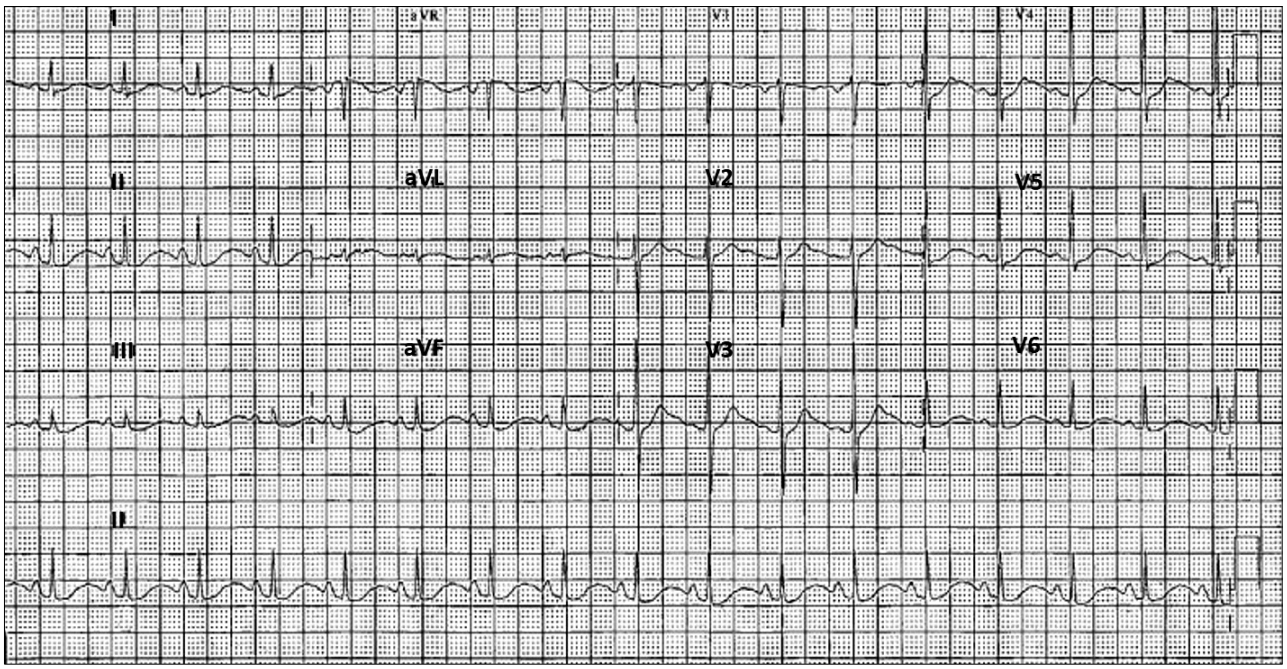

Figure 1. A 12-lead electrocardiogram (ECG) from a 27-year-old woman with hypokalemia. ECG demonstrates flatten T-waves, depressed ST-segment changes, and prominent U waves.

Table 1. Biochemical data of patient

Parameter	At first admission (April 2014)	At latest admission (April 2015)	Reference range
Serum chemistry			
Sodium (mEq/L)	136	138	135～145
Potassium (mEq/L)	2.1	2.4	3.5～5.5
Chloride (mEq/L)	82	87	96～110
Magnesium (mg/dL)	1.9	2.4	1.5～2.5
Calcium (mg/dL)	9.6	9.4	8.4～10.4
Phosphate (mg/dL)	3.0	4.5	2.5～4.5
Uric acid (mg/dL)	9.6	9.3	2.2～8
Osmolality (mOsm/kg)	285	290	280～300
BUN (mg/dL)	37.6	24.2	7～20
Creatinine (mg/dL)	1.22	1.08	0.6～1.4
eGFR	56	70	
AST (U/L)	23	25	5～40
ALT (U/L)	22	20	5～45
ALP (U/L)	81	84	30～110
Ferritin (ng/mL)	101.3	-	13～150
Urine chemistry	(24 h urine)	(Spot urine)	
Sodium (mEq/d)	146.0	179	40～220 (25～250)*
Potassium (mEq/d)	37.6	84.7	25～120 (12～129)*
Chloride (mEq/d)	45.1	59	110～250 (0～300)*
Magnesium (mg/d)	77.1	-	7.3～12.2
Calcium (mg/d)	13.9	-	100～300
Osmolality (mOsm/kg)	315	622	400～800
Urine pH	8.5	8.5	5.0～8.0
Arterial blood gas analysis			
pH	7.56	-	7.35～7.45
$PaCO_2$ (mmHg)	56.6	-	32～45
PaO_2 (mmHg)	85.6	-	83～108
HCO_3^- (mmol/L)	49.2	-	21～28
Base excess (mmol/L)	23.9	-	−2～2
Endocrine test			
Plasma renin activity (ng/mL/h)	34.78	-	0.15～2.33
Serum aldosterone level (ng/dL)	11.0	-	1.3～14.5
TSH (μIU/mL)		1.33	0.27～4.2
Free T4 (ng/dL)		1.57	0.93～1.7
PTH-intact (pg/mL)		86.6	15～65

ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transferase, BUN: blood urea nitrogen, eGFR:estimated glomerular filtration rate, PTH: parathyroid hormone, TSH: thyroid-stimulating hormone. *Spot urine reference range.

DISCUSSION

In hypokalemic patients, vomiting, diarrhea, and diuretic and laxative usage history should be taken into account. If these causes are excluded, a hereditary tubulopathy should be considered. The common clinical findings of GS or BS are hypokalemic metabolic alkalosis, normal blood pressure, loss of salt, and increased levels of plasma renin and aldosterone [8]. The overlapping biochemical parameters between GS and BS make it difficult to differentiate one from the other.

Clinically, assessments of renal excretion of calcium and diuretic challenge are used to biochemically distinguish between GS and BS [2]. Although patients with GS and BS usually have normal serum calcium levels, those with BS commonly have normal or increased urinary calcium excretion (urine calcium/creatinine ratio >0.20) and those with GS have consistently reduced calcium excretion (urine calcium/creatinine ratio <0.10) [2]. Furthermore, diuretic challenge has been used to investigate the tubular site and underlying causes of hypokalemic tubular disorders, and different responses present as a different mo-

Table 2. Thiazide and furosemide loading test*

Parameter	Basal	Thiazide loading	Furosemide loading
FE_{Na}			
Base	1.85	1.45	3.08
Max	1.03	0.18	10.63
ΔFE_{Na}	−0.82	−1.27	7.55
FE_K			
Base	46.62	29.63	26.61
Max	31.02	16.76	73.43
ΔFE_K	−15.6	−12.87	46.82
FE_{Cl}			
Base	1.03	0.7	1.75
Max	0.57	0.13	14.57
ΔFE_{Cl}	−0.46	−0.57	12.82
C_{Cl}	0.34	0.41	4.14

Sodium and chloride clearances were markedly increased after furosemide loading, but not affected by thiazide loading. FE_a: Solute fractional clearance (%) = $[(U_a \times P_{cr})/(P_a \times U_{cr})] \times 100$. ΔFE: The difference between maximal excretion at any time after diuretics (thiazide or furosemide) administration and FE (base): $\Delta FE = FE\ (max) - FE\ (base)$. *Fractional electrolyte clearance before (base) and its maximal increase levels (max).

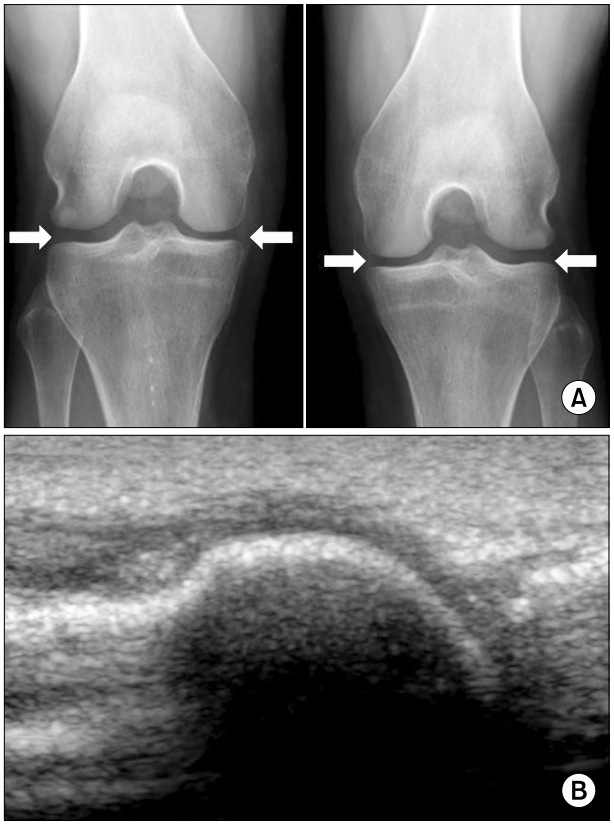

Figure 2. Chondrocalcinosis in radiographies of the patient's knees (A). Arrows show amorphous radiopaque densities along both medial and lateral menisci. Ultrasonographic examination of right 1st metatarsophalangeal joint (B) showed no evidence of crystal deposition like double contour sign.

lecular background for these disorders and their genetic heterogeneity [9]. That is to say that, in patients with normotensive hypokalemic alkalosis, a blunted thiazide response could predict a very high sensitivity and specificity of the GS genotype.

Sixty to 70% of BS patients have normomagnesemia, while most patients with GS have hypomagnesemia [2]. However, normomagnesemia has been reported in some who were diagnosed with GS [10,11] like our patient. We think of that the possible causes of normomagnesemia in our patient could be related to the intake of foods with high magnesium content and to reduced renal function. Even so, the causes of normomagnesemia in patients with GS have remained elusive.

Genetic mutations have been reported in more than 80% of GS cases [7]. Thus, genetic testing has become a useful tool to diagnose monogenetic tubular disorders that are characterized by hyperreninemic hypokalemia and alkalosis. However, in our patient, no mutations in the *SLC12A3* gene were detected. The possible reasons for an unidentified genetic mutation could be as follows [12]: 1) the mutation could be missed by the widely used PCR polymorphism analysis; 2) detection analysis based on individual exons will not detect large heterozygous deletions, and 3) mutations could be present in the gene-regulatory regions, such as promoters, or in non-coding regions.

In general, chondrocalcinosis is strongly associated with age and osteoarthritis [4,13]. If chondrocalcinosis occurs under the age of 50 years, we should consider a hereditary or metabolic disorder. For hereditary renal tubulopathies, twenty-five cases of BS accompanying chondrocalcinosis have been presented since 1978, but even so, the fact that most of the patients had hypocalciuria implies that these cases had a high possibility of GS not BS [5]. GS has a variety of clinical manifestations; however, those do not correlate with the degree of laboratory abnormalities. In some patients, the only evidence could be the chondrocalcinosis [3]. So far, it is not clear how hypomagnesemia induces the development of chondrocalcinosis in GS. However, because magnesium functions as a cofactor for pyrophosphatase, magnesium deficiency decreases the activity of pyrophosphatases and increases synovial fluid concentrations of inorganic pyrophosphates

which could induce the nucleation of calcium pyrophosphate dehydrate crystals [13]. Therefore, magnesium supplementation has the effect of preventing the progression of chondrocalcinosis. Antialdosterone therapy also has the effect of restoring the electrolyte balance, such as hypokalemia and hypomagnesemia through an effect on potassium secretion and magnesium reabsorption [14].

Although the clinical course of GS is thought to be good [15], we should remember that GS could be accompanied with complications such as chondrocalcinosis, tetany, paralysis, rhabdomyolysis and sudden cardiac arrest [3].

SUMMARY

Herein, we present a 28-year-old patient with atypical GS with normomagnesemia and chondrocalcinosis who has hypokalemic metabolic alkalosis, hypocalciuria, and a reduced thiazide test result. We suppose that chondrocalcinosis could be underestimated in GS. In addition, when chondrocalcinosis occurs at an early age, a metabolic disorder should be considered. Because magnesium supplementation and/or antialdosterone therapy can prevent the progression of chondrocalcinosis as well as complications of GS, early diagnosis and treatment are very important.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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