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Case Report

Diffuse calcium pyrophosphate deposition disease with hypertension in an elderly female with Gitelman syndrome: case report and literature review

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Abstract: Gitelman syndrome (GS) is an inherited tubulopathy characterized by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria, and normal or low blood pressure. Calcium pyrophosphate deposition disease (CPPD) develops due to longstanding hypomagnesemia secondary to GS. Concomitant diffuse CPPD with hypertension in GS patients has not been reported previously. We describe an elderly female patient with a 10-year history of polyarthralgia and 6-month history of fatigue. She had a 1-year history of hypertension. Serum electrolytes revealed hypokalemia and hypomagnesemia. Arterial blood gas analysis showed decompensated metabolic alkalosis. Urinary electrolytes analysis suggested renal potassium and chloride wasting along with hypocalciuria. Thiazide test showed the fractional excretion of urinary chloride increased by 0.642% (normal >2.3%) after thiazide challenge. This indicated a functional defect in the sodium chloride co-transporter (NCCT) in the distal convoluted tubule. Compound heterozygous mutations in *SLC12A3* were revealed. One missense mutation was c.571G>C in exon 4, which led to p.Ala191Pro, and another splice-site mutation was c.506-1G>A in intron 3. X-rays showed diffuse CPPD. Accordingly, the diagnosis of GS with diffuse CPPD and hypertension was eventually established. Potassium chloride, spironolactone, and potassium magnesium aspartate were administered to correct electrolyte disturbances, and perindopril was administered to control hypertension and retain potassium. Fatigue and joint pain were improved.

Keywords: Calcium pyrophosphate deposition disease, gitelman syndrome, hypomagnesemia, hypertension

Introduction

Gitelman syndrome (GS) is a rare salt-losing tubulopathy associated with loss-of-function mutations in *SLC12A3*, which encodes the thiazide-sensitive sodium chloride co-transporter (NCCT) in the distal convoluted tubule. Its clinical manifestations include fatigue, paralysis, and arthralgia, which is sometimes asymptomatic [1]. In some patients, calcium pyrophosphate deposition disease (CPPD) might develop owing to long-term and profound hypomagnesemia. However, arthritis resulting from CPPD is easily misdiagnosed as gout and less commonly misdiagnosed as rheumatoid arthritis (RA). Gitelman's mutations in the NCCT protect patients from hypertension. However, some reports recently suggested that the development of secondary hypertension may be an unexpected feature in the aging GS population [2, 3]. Here, we report a female patient with GS who had diffuse CPPD and hypertension, which had been misdiagnosed as RA for 10 years.

Case description

A 66-year-old female patient arrived at our clinic and complained of having polyarthralgia for 10 years and fatigue for 6 months. She suffered from swelling and moderate pain in the bilateral wrists and knees that began ten years ago. She had a long history of recurrent arthritis and was diagnosed with rheumatoid arthritis (RA) at a local hospital. She was administered intermittent meloxicam for many years but received poor therapeutic effect. Six months

Table 1. Results of laboratory investigations

Variable		Reference range
Serum biochemistry		
Sodium (mmol/L)	137.9	135-145
Potassium (mmol/L)	2.82	3.5-5.5
Urea (mmol/L)	7.0	2.8-7.2
Creatine (μmmol/L)	45	40-88
Fasting blood glucose (mmol/L)	5.6	3.89-6.11
Calcium (mmol/L)	2.15	2.08-2.6
Phosphate (mmol/L)	1.27	0.81-1.45
Magnesium (mmol/L)	0.45	0.77-1.03
Albumin (g/L)	37.5	35.0-52.0
Uric acid (μmol/L)	309	154-357
Alanine aminotransferase (U/L)	19	< 34
Aspartate aminotransferase (U/L)	25	< 35
Endocrinology		
Intact parathyroid hormone (pg/ml)	28.17	15.0-65
h-throid stimulating hormone (mIU/L)	1.47	0.35-4.94
Aldosterone (standing, ng/L)	174.4	70-300
Plasma renin (standing, μg/L/h)	5.77	0.10-6.56
Angiotensin II (standing, ng/L)	89.0	50.0-120.0
Serum cortisol (8 am, nmol/L)	217.86	185-624
Serum cortisol (4 pm, nmol/L)	144.67	
Adrenocorticotropin (8 am, pg/mL)	11.8	7.2-63.3
Adrenocortitropin (4 pm, pg/mL)	7.9	
Arterial blood gas analysis		
pH value	7.484	7.350-7.450
$PaCO_2$ (mmHg)	42.0	36.0-44.0
Actual bicarbonate (mmol/L)	31.20	22.0-26.0
Base excess (mmol/L)	7.40	-3.0±3.0
Standard bicarbonate (mmol/L)	31.10	22.0-26.0
Urinalysis		
PH value	7.0	4.5-8.0
Urinary volume (mL per day)	2000	800-1800
Vanillyl mandelic acid (μmol/24 h)	21.40	0.1-68.6
Potassium (mmol/24 h)	116.8	25-100
Sodium (mmol/24 h)	109	130-260
Chloride	414.2	150-250
Calcium to creatinine ratio (mmol/mmol)	0.016	>0.2

before her visit, fatigue developed. Persistent hypokalemia was identified at a local hospital, which was not corrected by oral and intravenous potassium supplement. She had a one-year history of hypertension but did not take antihypertensive drugs. She had no familial history of hypertension or hypokalemia and did not consume diuretics, laxatives, or licorice. She had no episodes of anorexia, vomiting, or diarrhea. On physical examination, her blood pressure (BP) was 153/88 mmHg and several repeated measurements revealed invariably elevated BP and a body mass index (BMI) of 23.46 kg/m^2. There was swelling and tenderness in the bilateral wrists and knees, but no deformity was found. Serum electrolytes revealed hypokalemia, hypomagnesemia, and hypocalcemia. Arterial blood gas analysis showed decompensated metabolic alkalosis. Urinary electrolyte analysis suggested renal potassium and chloride wasting along with hypocalciuria (**Table 1**). All laboratory results were consistent with GS. A thiazide test was performed to evaluate the function of NCCT as previously described [4]. The fractional excretion of urinary chloride increased by 0.642% (normal >2.3%), supporting the diagnosis of GS. To further confirm the diagnosis of GS, genetic testing was performed. Compound heterozygous mutations in *SLC12A3* were revealed. One missense mutation was c.571G>C in exon 4, which led to p.Ala191Pro (**Figure 1A**). Another splice-site mutation was c.506-1G>A in intron 3 (**Figure 1B**), which was already a known pathogenic mutation from previous reports [5, 6]. Accordingly, a diagnosis of GS was eventually established. The patient had multiple arthralgia, and subsequent X-ray examination showed marked chondrocalcinosis (CC) in one interphalangeal joint, partial metacarpophalangeal joints, and bilateral wrists (**Figure 2A-C**), shoulders (**Figure 2D**, **2E**), knees (**Figure 3A-C**), hips (**Figure 4**) and Achilles tendons (**Figure 5A-C**), and. Antinuclear antibodies as well as rheumatoid factor and anti-cyclic citrulline polypeptide antibodies were all negative. Therefore, the possibility of RA was excluded. According to her symptoms and our investigations, the patient was diagnosed as having GS with diffuse CC

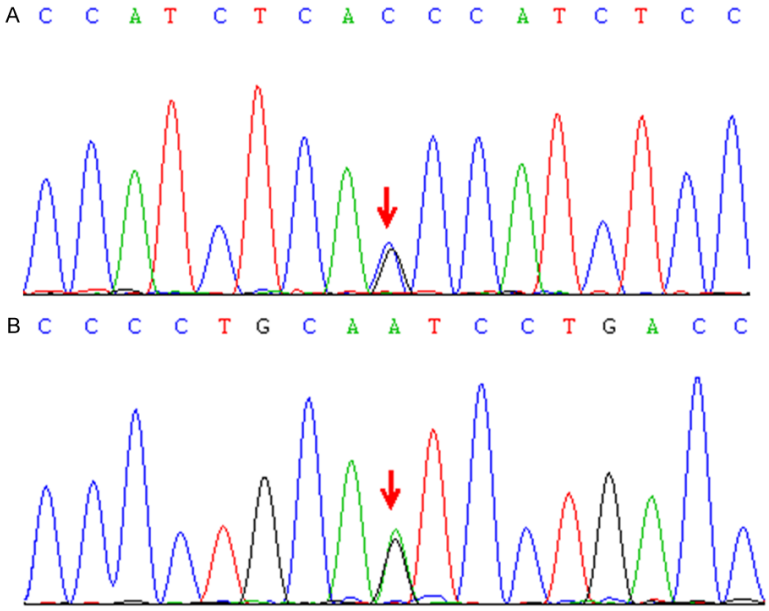

Figure 1. A. Polymerase chain reaction (PCR) fragment of the mutated sequence of the thiazide-sensitive NaCl-cotransporter (NCCT). The red arrow indicates a novel missense mutation of c.571G>C in exon 4 of *SLC12A3*, which led to p.Ala191Pro. B. Polymerase chain reaction (PCR) fragment of the mutated sequence of NCCT. The red arrow indicates a splice-site mutation of c.506-1G>A in intron 3 of *SLC12A3*.

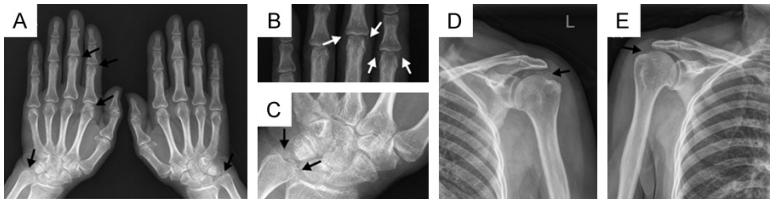

Figure 2. Anteroposterior projection of both of the patient's hands (A); calcification of one metacarpophalangeal joint, two proximal interphalangeal joints, and the bilateral wrists is shown. The magnified anteroposterior projection of the left hand (B); linear calcification is present around the first and second proximal interphalangeal joints. The magnified anteroposterior projection of the left hand (C); calcification of the disk of the triangular fibrocartilage complex. Anteroposterior projection of the left (D) and right (E) shoulder. The arrows show cartilage and supraspinatus tendon calcification of the bilateral humerus.

and hypertension. Potassium chloride (4.0 g/day), spironolactone (40 mg/day), and potassium magnesium aspartate (0.9 g/day) were prescribed to correct electrolyte disturbances and perindopril (4 mg/day) was prescribed to control hypertension. In the next nine months, fatigue and joint pain were improved even though the serum potassium (3.1-3.3 mmol/L) and magnesium (0.49-0.65 mmol/L) levels did not achieve the normal range. Moreover, she could even climb one flight of stairs without flaring of joint pain. However, no improvement in CC was found in multi-joint radiography.

Discussion

We describe an exceptional case of a female patient with arthralgia and hypertension. Genetic testing revealed compound heterozygous mutations in *SLC12A3*. X-ray analysis showed diffuse CC. Other causes of CC such as hyperparathyroidism, haemochromatosis, and hypophosphatasia were all excluded; therefore, we presumed that her CC resulted from CPPD secondary to hypomagnesemia owing to GS. Chronic calcium pyrophosphate (CPP) crystal inflammatory arthritis (one form of CPPD) was consistent with her recurrent flares of joint pain. The patient also had hypertension rather than normotension or hypotension. Literature review revealed only 25 cases of CPPD induced by GS and 21 cases of hypertension combined with GS (as shown in **Tables 2**-**4**). To our knowledge, this is the first case of GS with diffuse CPPD and hypertension to date.

The blood pressure of patients with GS is typically low, particularly among patients with GS who have severe hypokalemia and hypomagnesemia [1, 7]. However, Balavoine *et al* showed for the first time that hypertension was present in patients with GS. Among those patients with hypertension who lacked a familial history of hypertension, half were obese. The patient in our study also had no familial history of hypertension or obesity. In 2013, Berry *et al* found that 15 patients with GS had hypertension. Normotensive patients were significantly younger than the hypertensive ones. Berry *et al* also found no significant difference in median renin levels between hypertensive

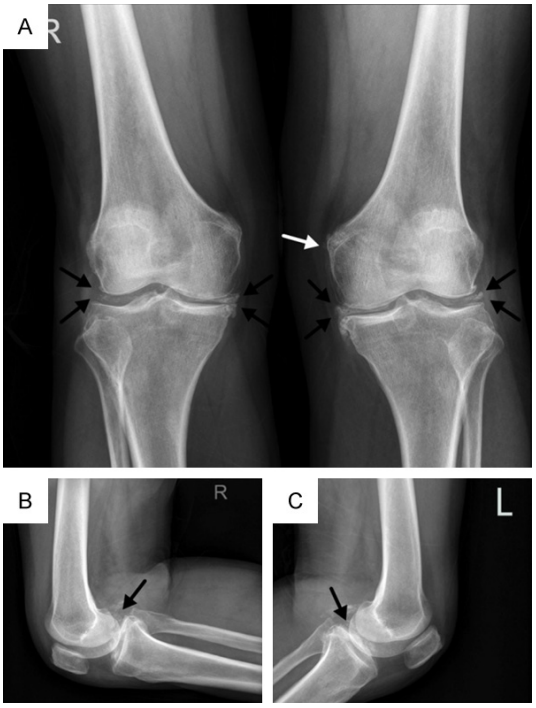

Figure 3. Anteroposterior (A) and lateral (B, C) projections of the patient's knees. Extensive chondrocalcinosis of the fibrocartilage of the medial and lateral menisci (black arrows) is present on the anteroposterior and lateral radiographs. Linear calcification of the medial collateral ligament (the white arrow) is evident on the anteroposterior and lateral projections.

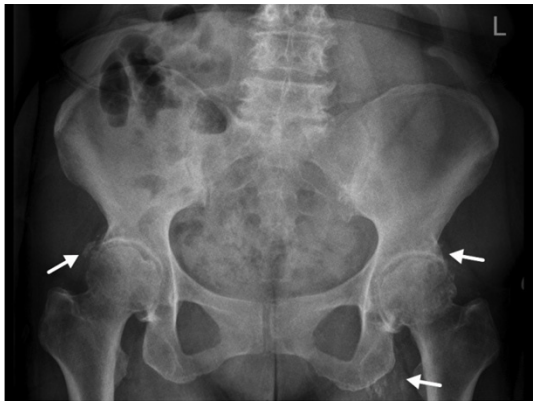

Figure 4. Anteroposterior of the pelvis. Calcification is present around the bilateral hip and left ischial tuberosity.

and normotensive subjects [3]. The pathogenesis of hypertension in patients with GS remains elusive. Berry *et al* hypothesized that ongoing stimulation of the renin-angiotensin-aldosterone system resulted in chronic vasoconstriction, leading to a situation in which

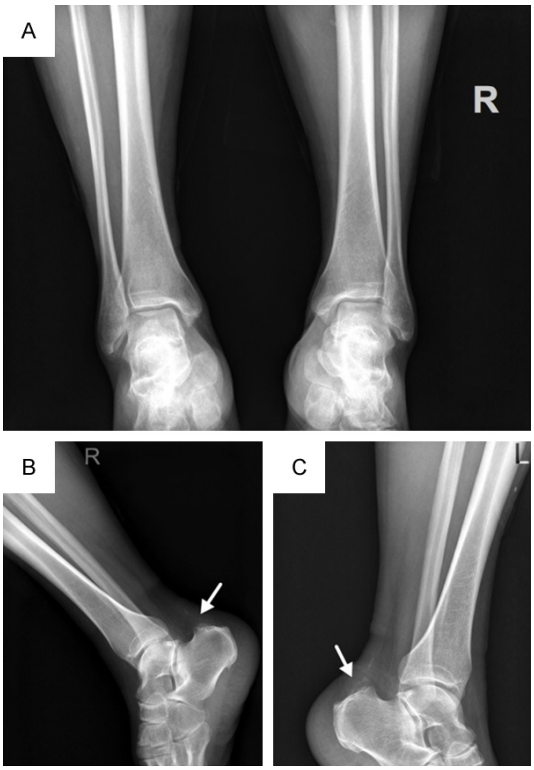

Figure 5. Anteroposterior (A) and lateral (B, C) projections of the patient's ankles. Calcification of the Achilles tendons is present.

hypertension supervenes. They also found that hypertensive patients with GS are more likely to have mutations in the C-terminal domain of *SLC12A3*. Accordingly, they also postulated that the C-terminal domain was vital for NCCT function, which is mediated through its role in altering the encoded protein, resulting in the loss of cotransporter function. More severe electrolyte wasting may give rise to more exaggerated compensatory mechanisms (stimulation of the renin-aldosterone axis) and the subsequent development of hypertension. However, the present patient's renin level was normal and the mutation site was located in the N-terminal domain of *SLC12A3* rather than the C-terminal domain. Thus, we cannot use the above model to explain the pathogenesis of hypertension. These findings collectively suggest that older age may be the only probable risk factor of hypertension for the present patient. Therefore, arterial hypertension does not exclude the diagnosis of GS in adults [1].

CPPD is arthritis caused by CPP crystals, which is clearly a disease of aging and is rare in

Table 2. Patients with Gitelman syndrome presenting with calcium pyrophosphate deposition disease or with hypertension

Research author	Research article title	GS with CPPD (percentage)	GS with hypertension (percentage)
Punzi L, et al, 1998	Chondrocalcinosis is a feature of Gitelman's variant of Batter's syndrome. A new look at the hypomagnesemia associated with calcium pyrophosphate dehydrate crystal deposition disease	4/4	0/4
Hisakawa N, et al, 1998	A case of Gitelman's syndrome with chondrocalcinosis	1/1	0/1
Garcia Nieto, V, et al, 2003	Chondrocalcinosis and hypomagnesaemia in a patient with a new mutation in the gene of the thiazide-sensitive Na-Cl cotransporter	1/1	0/1
Gupta, et al, 2005	Sclerochoroidal calcification associated with Gitelman syndrome and calcium pyrophosphate dihydrate deposition	1/1	0/1
Ea HK, et al, 2005	Chondrocalcinosis secondary to hypomagnesemia in Gitelman's syndrome	1/1	0/1
Volpe A, et al, 2007	Familiar association of Gitelman's syndrome and calcium pyrophosphate dehydrate crytal deposition disease-a case report	3/3	0/3
Gutierrez M, et al, 2010	Gitelman syndrome, calcium pyrophosphate dihydrate deposition disease and crowned dens syndrome. A new association?	1/1	0/1
Gutierrez M, et al, 2010	Gitelman syndrome associated with chondrocalcinosis: description of two cases	1/2	0/2
A S Balavoine, et al, 2011	Phenotype-genotype correlation and follow-up in adult patients with hypokalaemia of renal origin suggesting Gitelman syndrome	3/26	4/26
R V Poussou, et al, 2011	Spectrum of mutations in Gitelman syndrome	2/24	0/24
Rim PC, et al, 2011	Chondrocalcinosis and hypo- magnesemia in a 26-year-old woman.	1/1	0/1
Saban Elitok, et al, 2012	Chronic hypokalaemia in a hypertensive patient	0/1	1/1
Koçkara AŞ, et al, 2013	Gitelman's syndrome associated with chondrocalcinosis: a case report	1/1	0/1
Miriam R. Berry, et al, 2013	Unexpected clinical sequelae of Gitelman syndrome: hypertension in adulthood is common and females have higher potassium requirements	0/36	16/36
Brambilla G, et al, 2013	It is never too late for a genetic disease: a case of a 79-year-old man with persistent hypokalemia	1/1	0/1
Ohkubo K, et al, 2014	A novel mutation of CLCNKB in a Japanese patient of Gitelman-like phenotype with diuretic insensitivity to thiazide administration	1/1	0/1
Iqbal Z, et al, 2016	Chondrocalcinosis and Gitelman syndrome	1/1	0/1
Iqbal Z, et al, 2016	Case report: Cervical chondrocalcinosis as a complication of Gitelman syndrome	1/1	0/1
Zabotti A, et al, 2016	Gitelman syndrome disclosed by calcium pyrophosphate deposition disease: early diagnosis by ultrasonographic study	1/1	0/1

patients younger than 60 years of age [8]. According to clinical manifestations, there are three forms of CPPD: acute CPP crystal arthritis (formerly known as pseudogout), osteoarthritis (OA) with CPPD, and chronic CPP crystal inflammatory arthritis. A rare form of polyarticular chronic CPP crystal inflammatory arthritis resembles RA. Flares in this form of CPPD disease often involve joints sequentially, and involvement is less symmetric than that seen in RA [8]. Recognized risk factors for CPPD include aging, OA, and metabolic conditions [9]. Therefore, GS is associated with CPPD mediated by hypomagnesaemia, which is an obligate feature of GS. Hypomagnesemia seems to cause CPPD by increasing formation and reducing the solubility of CPP crystals [10]. Evidence for the association between CPPD and GS mainly comes from anecdotal case reports. As a result, its epidemiology remains unknown [10]. To date, 24 cases with CPPD secondary to GS have been reported. In all reported patients with GS having CPPD, the age ranged from 26 to 80 years. The most common type of CPPD is acute CPP crystal arthritis, and the most common joints involved are the knees [10-13]. Regarding the present patient, the only risk factor for CPPD was hypomagnesemia owing to GS. Therefore, the multiple CC she had was considered to be a radiological manifestation of CPPD resulting from GS. The clinical form of CPPD was also identified as chronic CPP crystal inflammatory arthritis. Among all reported patients with GS having CPPD, she had the highest number of joints involved. However, her initial joint symptoms mimicked RA, and she was misdiagnosed. Hence, we should raise the awareness of CPPD in the GS population.

Therapy for GS consists of administration of deficient electrolytes such as magnesium and potassium. When supplements are not suffi-

Table 3. Demographic and clinic information of patients with Gitelman syndrome presenting with calcium pyrophosphate deposition disease

Research author	Patient	Age	Sex	symptoms	Age of GS onset	Age of CPPD onset	Sites of CPPD	Type of CPPD	K (mmol/L)	Mg (mmol/L)
Punzi, 1998	1	54	F	Arthralgia, arthritis, weakness	45	34	Shoulders, knees	PG-CC	ND	ND
	2	27	M	Weakness	17	ND	Knee	CC	ND	ND
	3	35	M	Weakness, arthritis	25	25	Right knee	PG-CC	ND	ND
	4	37	F	Weakness, arthritis	37	37	Both knees	PG-CC	ND	ND
Hisakawa, 1998	5	45	F	Numbness extremities, dyspnea, polyarthralgia	31	41	Knees, symphysis pubis	PG-CC	ND	ND
Garcia, 2003	6	38	M	Arthritis, fever	ND	18	Knees, pubis, hips	PG-CC	ND	ND
Gupta, 2005	7	49	F	Polyarthralgia	49	ND	Knee, shoulder	PG-CC	3.1	0.3
Ea, 2005	8	53	M	Arthritis, muscle pain, weakness, cramping,	52	32	Knees, symphysis pubis, wrists	PG-CC	ND	ND
Volpe, 2007	9	77	M	Tetany, recurrent presyncope, arthritis	51	53	Knees, symphysis pubis, shoulders, wrists, left hip	PG-CC	2.6	0.57
	10	79	F	Tetany, recurrent presyncope, weakness, arthritis	50	35	Knees, symphysis pubis, wrists, achilles tendons	PG-CC	2.7	0.45
	11	63	F	Tetany, recurrent presyncope, arthralgia, arthritis	48	52	Knees, symphysis pubis, shoulders, wrists	PG-CC	2.8	0.61
Gutierrez, 2010	12	44	F	Arthritis, carpo-pedal spasm	27	33	Knees, wrists	PG-CC	ND	ND
Gutierrez 2010	13	49	F	Weakness, arthritis	39	49	Knees, wrists, elbows	PG-CC	2.9	0.5
R V Poussou, 2011	14	25	F	Weakness	ND	ND	ND	CC	2.3	0.34
	15	32	F	ND	ND	ND	ND	CC	2.5	0.54
Rim PC, 2011	16	26	F	Arthritis	26	26	Knees	PG-CC	2.9	0.45
A S Balavoine, 2011	17	ND	ND	Arthritis	ND	ND	ND	PG-CC	ND	ND
	18	ND	ND	Arthritis	ND	ND	ND	PG-CC	ND	ND
	19	ND	ND	ND	ND	ND	ND	CC	ND	ND
Koçkara AŞ, 2013	20	56	M	Arthritis	56	ND	Knees	PG-CC	3.1	0.45
Brambilla G, 2013	21	79	M	Weakness, polyarthralgia	ND	75	Elbows, shoulders	PG-CC	3.1	0.61
Ohkubo K, 2014	22	45	F	Wea. kness, arthritis	45	36	Symphysis pubis	PG-CC	2.3	0.61
Iqbal Z, 2016	23	37	F	Weakness, arthritis	37	37	Knee	PG-CC	2.8	0.46
Iqbal Z, 2016	24	60	F	Weakness, arthritis	55	60	Cervical spine	PG-CC	2.5	0.3
Zabotti A, 2016	25	43	M	Arthritis	43	43	Knee	PG-CC	3.05	0.64

ND, not determined; PG, pseudogout; CC, Chondrocalcinosis; K, Potassium; Mg, Magnesium; CPPD, calcium pyrophosphate deposition disease.

Table 4. Demographic and clinic information of patients with Gitelman syndrome presenting with hypertension

Research author	Enrolled Patients	Age (years)	Sex (F/M)	Age of GS Onset (years)	Age of HY Onset (years)	Familiar history of HY	BMI (kg/m^2)
A S Balavoine, 2011	4	54±15.5	ND	48.5±15.8	54±15.6	NO	27.6±0.7
Saban Elitok, 2012	1	45	0/1	ND	44	NO	28
Miriam R, 2013	16	49.8±14.6	3/13	39.8±18.3	ND	ND	ND

ND, not determined; HY, hypertension; F, female; M, male.

cient despite adherence or when side effects are unacceptable or both, the use of potassium-sparing diuretics, renin angiotensin system blockers, or nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, or a combination of the proposed NSAIDs is recommended [1]. A reasonable target for potassium and magnesium may be 3.0 mmol/L and 0.6 mmol/L, respectively [1]. The restoration of normal Mg^{2+} blood levels can prevent occurrence or reduce the frequency and intensity of acute attacks of CPPD [10]. According to the European League Against Rheumatism (EULAR) recommendations for CPPD management, both oral NSAID and low-dose oral colchicine were effective systemic treatments for acute CPPD crystal arthritis. In the therapy of CPPD disease, intra-articular corticosteroids may be considered in patients in whom other drugs may be contraindicated or not tolerated, or in whom few joints are involved [8, 9]. In the present case, potassium chloride, spironolactone, and potassium magnesium aspartate were administered to correct electrolyte disturbances, with perindopril being used to control hypertension. Magnesium supplementation has been shown to significantly improve arthralgia despite failure to normalize hypomagnesemia.

In summary, physicians should raise the awareness of the two rare clinical manifestations of GS: CPPD and hypertension. The presence of arterial hypertension does not exclude the diagnosis of GS in adults. Magnesium supplementation has been shown to significantly improve arthralgia despite failure to normalize hypomagnesemia and improve radiologic findings of involved joints.

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Disclosure of conflict of interest

None.

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