Case Report

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:72-76
https://doi.org/10.5049/EBP.2023.21.2.72

Pseudo-Gitelman Syndrome Presenting with Hypokalemic Metabolic Alkalosis and Hypocalciuria

Seung Heon Lee[1], Sukyung Lee[2], Hyunsung Kim[3], Gheun-Ho Kim[1]

[1]*Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea;*
[2]*Department of Internal Medicine, Pohang St. Mary's Hospital, Pohang, Republic of Korea;*
[3]*Department of Pathology, Hanyang University College of Medicine, Seoul, Republic of Korea*

Received: Agust 4, 2023
Revised: September 4, 2023
Accepted: September 5, 2023
Corresponding Author: Gheun-Ho Kim, MD, PhD
Department of Internal Medicine, Hanyang University College of Medicine, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea
Tel: +82-2-2290-8318; Fax: +82-2-2298-9183
E-mail: kimgh@hanyang.ac.kr

Pseudo-Bartter syndrome is a well-known differential diagnosis that needs to be excluded in cases of normotensive hypokalemic metabolic alkalosis. Pseudo-Bartter syndrome and pseudo-Gitelman syndrome are often collectively referred to as pseudo-Bartter/Gitelman syndrome; however, pseudo-Gitelman syndrome should be considered as a separate entity because Gitelman syndrome is characterized by hypocalciuria and hypomagnesemia, while Bartter syndrome is usually associated with hypercalciuria. Herein, we report the cases of two young adult female patients who presented with severe hypokalemic metabolic alkalosis, hypocalciuria, and hypomagnesemia. Diuretic or laxative abuse and self-induced vomiting were absent, and a chloride deficit and remarkable bicarbonaturia were observed. Initial sequencing studies for *SLC12A3*, *CLCKNB*, and *KCNJ10* revealed no mutations, and whole-exome sequencing revealed no pathogenic variants. The metabolic alkalosis was saline-responsive in one case, and steroid therapy was necessary in the other to relieve chronic tubulointerstitial nephritis, which was diagnosed with kidney biopsy. A new category of pseudo-Gitelman syndrome should be defined, and various etiologies should be investigated.

Key Words: Hypocalciuria, Hypokalemia, Metabolic alkalosis, Pseudo-Gitelman syndrome, Whole exome sequencing

INTRODUCTION

Both Bartter syndrome (BS) and Gitelman syndrome (GS) are characterized by hypokalemic metabolic alkalosis resulting from the renal loss of potassium and sodium chloride. However, their inherited molecular etiologies differ along the thick ascending limb of Henle's loop and distal convoluted tubule. Accordingly, their clinical phenotypes differ. The most significant difference lies in hypercalciuria in BS, and hypocalciuria and hypomagnesemia in GS[1)].

Pseudo-BS is a well-known differential diagnosis from BS in cases of normotensive hypokalemic metabolic alkalosis. It is commonly associated with loop diuretic or laxative abuse and surreptitious vomiting[2)]. Pseudo-BS and pseudo-GS are often collectively referred to as pseudo-BS/GS[3,4)]. However, we believe that pseudo-GS should be considered a distinct entity because it is characterized by thiazide diuretic-induced hypocalciuria. In contrast to pseudo-BS, the scope and etiology of pseudo-GS remain unclear.

Here, we report the cases of two young adult female patients who presented with clinical features similar to those of GS: hypokalemic metabolic alkalosis with renal salt wasting, hypocalciuria, and hypomagnesemia. There were no indications of pseudo-BS, including loop or thiazide diuretic abuse. Initial sequencing studies for *SLC12A3*, *CLCKNB*, and *KCNJ10* revealed no mutations, and subsequently performed whole-exome sequencing revealed no pathogenic variants. The metabolic alkalosis was saline-responsive in

one case as is typical, and steroid therapy was necessary in the other to relieve chronic tubulointerstitial nephritis, which was diagnosed with kidney biopsy.

CASE REPORT

Case 1: A 20-year-old woman visited our emergency room (ER) in August 2012 for severe dizziness. She had two episodes of fainting in the past 3 months. Her blood pressure was 90/60 mmHg, and her hemoglobin level was 10.4 g/dL. Laboratory tests revealed a serum sodium concentration of 136 mmol/L, potassium level of 2.5 mmol/L, chloride level of 79 mmol/L, and total CO_2 of 50.3 mmol/L. Urinalysis revealed a specific gravity of 1.015, pH of 8.5, albumin +, glucose -, 1-4 red blood cells (RBCs)/high-power field (HPF), and 1-4 white blood cells (WBCs)/HPF. Urine electrolyte levels were as follows: sodium, 89 mmol/L; potassium, 95 mmol/L; chloride, 52 mmol/L; and creatinine, 88 mg/dL. Arterial blood gas analysis revealed a pH of 7.62, $PaCO_2$ of 52 mmHg, PaO_2 of 193 mmHg, and HCO_3- of 52 mmol/L. Serum calcium level was 9.3 mg/dL, phosphorus level was 2.6 mg/dL, magnesium level was 2.3 mg/dL, blood urea nitrogen (BUN) was 15.3 mg/dL, and creatinine level was 0.85 mg/dL. The urine calcium-to-creatinine ratio was 0.08 mg/mg, and fractional excretions of sodium, potassium, and chloride were calculated as 0.6%, 36.7%, and 0.6%, respectively. Mutation analysis for *SLC12A3* revealed no abnormalities.

The patient neglected outpatient care and was readmitted 10 times over a decade for paraparesis and/or fainting. Hypomagnesemia was often observed. There was no evidence of diuretic or laxative abuse or surreptitious vomiting. Dental examination revealed no tooth erosion caused by gastric acid. Further sequencing studies for *CLCKNB* and *KCNJ10* revealed no mutations. During each hospital stay, saline was infused with intravenous potassium chloride and oral magnesium oxide to correct the hypokalemic metabolic alkalosis and hypomagnesemia, respectively. Table 1 summarizes the treatment response during her most recent admission in January 2023. Her metabolic alkalosis improved with saline infusion, and azotemia and hyperuricemia were ameliorated. However, hypocalciuria and hypomagnesemia were not saline-responsive. Whole-exome sequencing revealed no pathogenic variants.

Table 1. Laboratory data during saline infusion and KCl supplementation in Case 1

Data	Day 1	Day 2	Day 3	Day4
Serum				
Na (mmol/L)	134	135	138	138
K (mmol/L)	2.2	2.2	3.4	3.8
Cl (mmol/L)	82	89	102	106
tCO_2 (mmol/L)	42.7	34	26.3	23.6
Ca (mg/dL)	9.5	8.8	8.7	8.2
P (mg/dL)	3	3.8	2.7	2.4
Cr (mg/dL)	0.94	0.78	0.59	0.58
BUN (mg/dL)	17.5	13.6	10.4	8.5
UA (mg/dL)	12	11.3	8.9	6.7
Mg (mg/dL)	1.9	2	1.7	1.6
Urine				
Na (mmol/L)	78	109	188	
K (mmol/L)	129	134	72	
Cl (mmol/L)	45	60	57	
Cr (mg/dL)	76	86	99	
Ca (mg/dL)	3	2.1	4.9	
Mg (mg/dL)	23.7	18.8	23.5	
Urine Ca/Cr	0.04	0.02	0.05	
Fractional excretion				
Na (%)	0.72	0.73	0.81	
K (%)	72.5	55.2	12.6	
Cl (%)	0.68	0.61	1	
Mg (%)	22	12.2	11.8	

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; tCO_2, total CO_2; UA, uric acid.

Case 2: A 28-year-old woman was referred from a local hospital for the evaluation of hypokalemic metabolic alkalosis. She was previously healthy throughout 2016 with no abnormal findings during her check-up. However, in 2018, she visited the ER twice due to collapse while traveling in the United States and was diagnosed with hypokalemia and had a serum potassium level of ~2 mmol/L. Upon returning to South Korea, she visited a university hospital in Seoul and was suspected of having GS. Oral potassium and magnesium tablets were prescribed. However, she was admitted to a local hospital in 2020 because of fainting and limb paralysis.

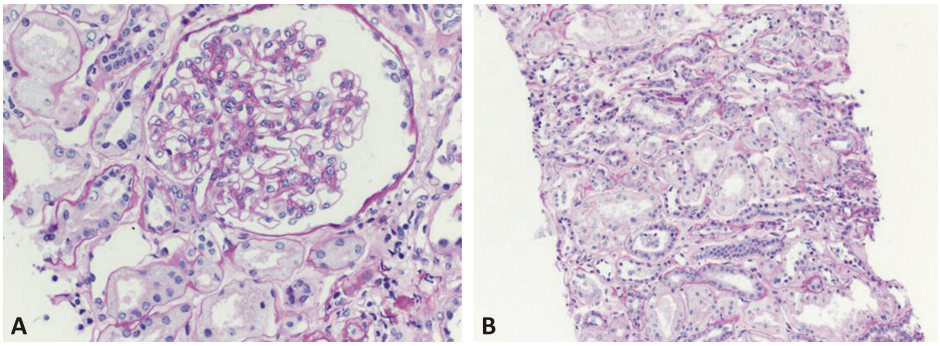

Fig. 1. The kidney biopsy findings in Case 2. The high power image reveals that there were no remarkable morphological changes in the glomeruli (**A**). The image with low power reveals that mild interstitial fibrosis was associated with moderate degrees of tubular atrophy and interstitial inflammation (**B**).

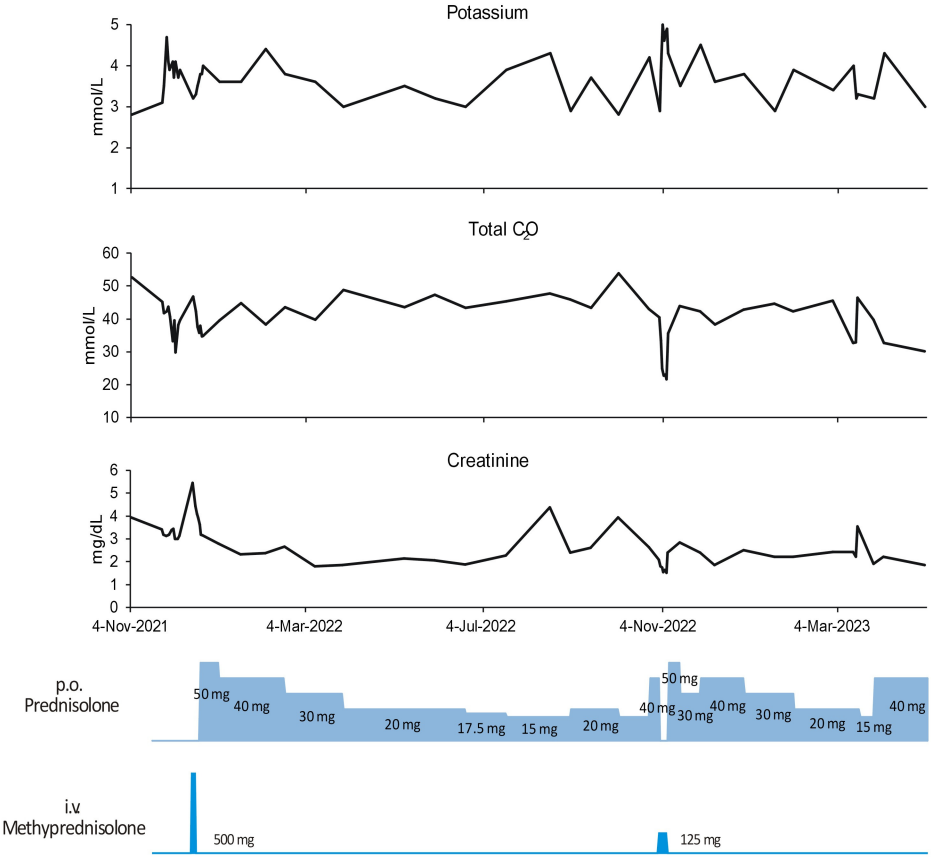

Fig. 2. The course of hypokalemic metabolic alkalosis and azotemia in Case 2. Changes in serum potassium, total CO_2, and creatinine levels in response to glucocorticoid therapy are shown.

The patient's family history was unremarkable. She did not take any self-medication, including diuretics or laxatives. No gastrointestinal problems, including vomiting or diarrhea, were observed. At the first admission to our hospital in March 2021, her blood pressure and body mass index were 90/60 mmHg and 20.3 kg/m^2, respectively.

The patient's hemoglobin level was 10.2 g/dL. Other laboratory findings were serum sodium level of 137 mmol/L, potassium level of 2.5 mmol/L, chloride level of 86 mmol/L, and total CO_2 of 42.9 mmol/L. Urine electrolyte levels were

as follows: sodium, 159 mmol/L; potassium, 49 mmol/L; chloride, 21 mmol/L; and creatinine, 72 mg/dL. Arterial blood gas analysis revealed a pH of 7.57, $PaCO_2$ of 47 mmHg, PaO_2 of 89 mmHg, and HCO_3- of 43 mmol/L. Urinalysis revealed a specific gravity of 1.015, pH of 9.0, albumin +, glucose -, 3-4 RBCs/HPF, and 0-2 WBCs/HPF.

Serum calcium level was 9.7 mg/dL, phosphorus level was 1.7 mg/dL, uric acid level was 11.3 mg/dL, magnesium level was 1.5 mg/dL, BUN was 18.9 mg/dL, and creatinine level was 1.56 mg/dL. Fractional excretions of sodium, potassium, and chloride were 2.5%, 42.5%, and 0.5%, respectively. The urine calcium-to-creatinine ratio was 0.01 mg/mg, urine protein-to-creatinine ratio was 301 mg/g, and urine 2-microglobulin was 2.27 mg/L (reference <0.19 mg/dL).

A kidney biopsy was performed to evaluate azotemia. The glomerular pathology was unremarkable; however, moderate interstitial inflammation, moderate tubular atrophy, and mild interstitial fibrosis were observed, which were consistent with chronic tubulointerstitial nephritis (Fig. 1). Mutation analysis for *SLC12A3*, *CLCKNB*, and *KCNJ10* revealed no abnormalities.

Initially, the patient's metabolic alkalosis appeared to be temporarily responsive to saline infusion. However, the condition persisted until December 2021, when she was readmitted because of progressive azotemia. Intravenous methylprednisolone (500 mg) was administered daily for 3 days, and then switched to oral prednisolone (50 mg) once daily. However, the patient could not tolerate high-dose prednisolone and required reduced steroid therapy. Figure 2 shows the laboratory parameter trends between November 2021 and May 2023, suggesting that the aggravated metabolic alkalosis and azotemia were improved by increasing prednisolone dosage. To reduce the prednisolone dosage, we sequentially administered cyclosporine and mycophenolate mofetil. However, both these agents were ineffective and intolerable. Whole-exome sequencing of her genomic DNA revealed no pathogenic variants.

DISCUSSION

In the differential diagnosis of hypokalemic metabolic alkalosis, whether or not hypertension is present should be first identified. If hypertension is present, mineralocorticoid excess, such as primary aldosteronism, must be considered after excluding the possibility of diuretic use in hypertensive patients.

Our cases had low-normal blood pressure, severe hypokalemia, and remarkable metabolic alkalosis, as evidenced by pH >7.55 and HCO_3- >40 mmol/L. The spot urine potassium-to-creatinine ratio clearly indicated renal potassium loss[5]. Urine chloride is also useful in the differential diagnosis of metabolic alkalosis because a chloride deficit is crucial for the maintenance of metabolic alkalosis[6]. Our patients had urine chloride levels of >20 mmol/L, excluding the possibility of self-induced vomiting and chloride diarrhea[2]. Importantly, they had additional diagnostic features of GS: fractional excretion of chloride >0.5%, hypocalciuria defined as a urine calcium-to-creatinine ratio <0.2, and hypomagnesemia <1.70 mg/dL[1].

The established criteria for the diagnosis of GS include the identification of biallelic inactivating mutations in *SLC12A3*, which encodes the Na^+-Cl^--cotransporter (NCC) expressed in the distal convoluted tubule[1]; however, we found no mutations in *SLC12A3* in our cases. In addition, whole-exome sequencing excluded the possibility of newly identified pathogenic variants in various genes (e.g., *CLCKNB*, *KCNJ10*, *FXYD2*, and *HNF1B*) that may indirectly reduce NCC activity[7]. Diuretic or laxative screening was unavailable in our practice. Nevertheless, we believe that our cases were not related to drug abuse or surreptitious vomiting because of our patient-physician relationships for more than 5-10 years. Therefore, our findings are compatible with a diagnosis of pseudo-GS. Interestingly, Mori et al. reported that approximately 50% of 70 clinically diagnosed patients with GS were mutation-negative based on gene panel sequencing[8].

Our two patients shared other clinical features. Both patients were young women with mild anemia, and the dizziness they experienced was so severe that fainting or collapse occurred. Thus, we believe that the chief complaints were due to severe metabolic alkalosis rather than hypokalemia. Remarkable bicarbonaturia was evidenced by a urine pH of >8.5 in most circumstances, and urine chloride level was slightly lower than urine sodium level. Hypomagnesemia was caused by renal magnesium wasting and hyperuricemia was ameliorated by fluid repletion (Table 1). Hyperuricemia has been proposed as a characteristic feature of pseudo-BS

[9], supporting the idea that volume contraction underlies the pathophysiology of metabolic alkalosis induced by pseudo-BS and pseudo-GS. Interestingly, an association between tophaceous gout and GS has rarely been reported in young men[10].

In contrast to case 1, case 2 appears to have a poor long-term prognosis. Renal tubulointerstitial injury was evident, as predicted by persistent azotemia and tubular proteinuria. Autoimmune pathogenesis, including anti-Ro and anti-La antibodies, was investigated, but no systemic causes were found. In patients with Sjögren's syndrome, the presence of circulating autoantibodies against NCC may cause GS[11].

In summary, we report the cases of two young female patients with pseudo-GS who presented with hypokalemic metabolic alkalosis, hypocalciuria, and hypomagnesemia; however, no pathogenic variants were detected on whole-exome sequencing. Volume contraction appears to have caused metabolic alkalosis, but the cause of the chloride deficit remains unidentified. An uncertain immunopathogenesis that produces tubulointerstitial nephritis may also present as a Gitelman-like syndrome.

Acknowledgment

We thank Prof. Hae Il Cheong at Seoul National University for the genetic investigations in our cases.

REFERENCES

1. Blanchard A, Bockenhauer D, Bolignano D, et al.: Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017;91:24-33.
2. Jdiaa SS, Walsh SB, Bockenhauer D, Fakhredine SW, Koubar SH. The hypokalemia mystery: distinguishing Gitelman and Bartter syndromes from 'pseudo-Bartter syndrome'. Nephrol Dial Transplant. 2021;37:29-30.
3. Matsunoshita N, Nozu K, Shono A, et al.: Differential diagnosis of Bartter syndrome, Gitelman syndrome, and pseudo-Bartter/Gitelman syndrome based on clinical characteristics. Genet Med. 2016;18:180-188.
4. Nozu K, Yamamura T, Horinouchi T, et al.: Inherited salt-losing tubulopathy: An old condition but a new category of tubulopathy. Pediatr Int. 2020;62:428-437.
5. Lin SH, Halperin ML. Hypokalemia: a practical approach to diagnosis and its genetic basis. Curr Med Chem. 2007;14: 1551-1565.
6. Do C, Vasquez PC, Soleimani M. Metabolic Alkalosis Pathogenesis, Diagnosis, and Treatment: Core Curriculum 2022. Am J Kidney Dis. 2022;80:536-551.
7. Schlingmann KP, de Baaij JHF. The genetic spectrum of Gitelman(-like) syndromes. Curr Opin Nephrol Hypertens. 2022;31:508-515.
8. Mori T, Chiga M, Fujimaru T, et al.: Phenotypic differences of mutation-negative cases in Gitelman syndrome clinically diagnosed in adulthood. Hum Mutat. 2021;42:300-309.
9. Jiménez ML, Mateos FA, Puig JG, et al.: Hyperuricemia as possible diagnostic aid to factitious-Bartter's syndrome. Adv Exp Med Biol. 1986;195 Pt A:351-356.
10. Rouached L, Hannech E, Jeribi R, et al.: Tophaceous gout in a young man with Gitelman syndrome: a case report with an overview. Clin Rheumatol. 2023;42:285-291.
11. Kim YK, Song HC, Kim YS, Choi EJ. Acquired Gitelman syndrome. Electrolyte Blood Press. 2009;7:5-8.