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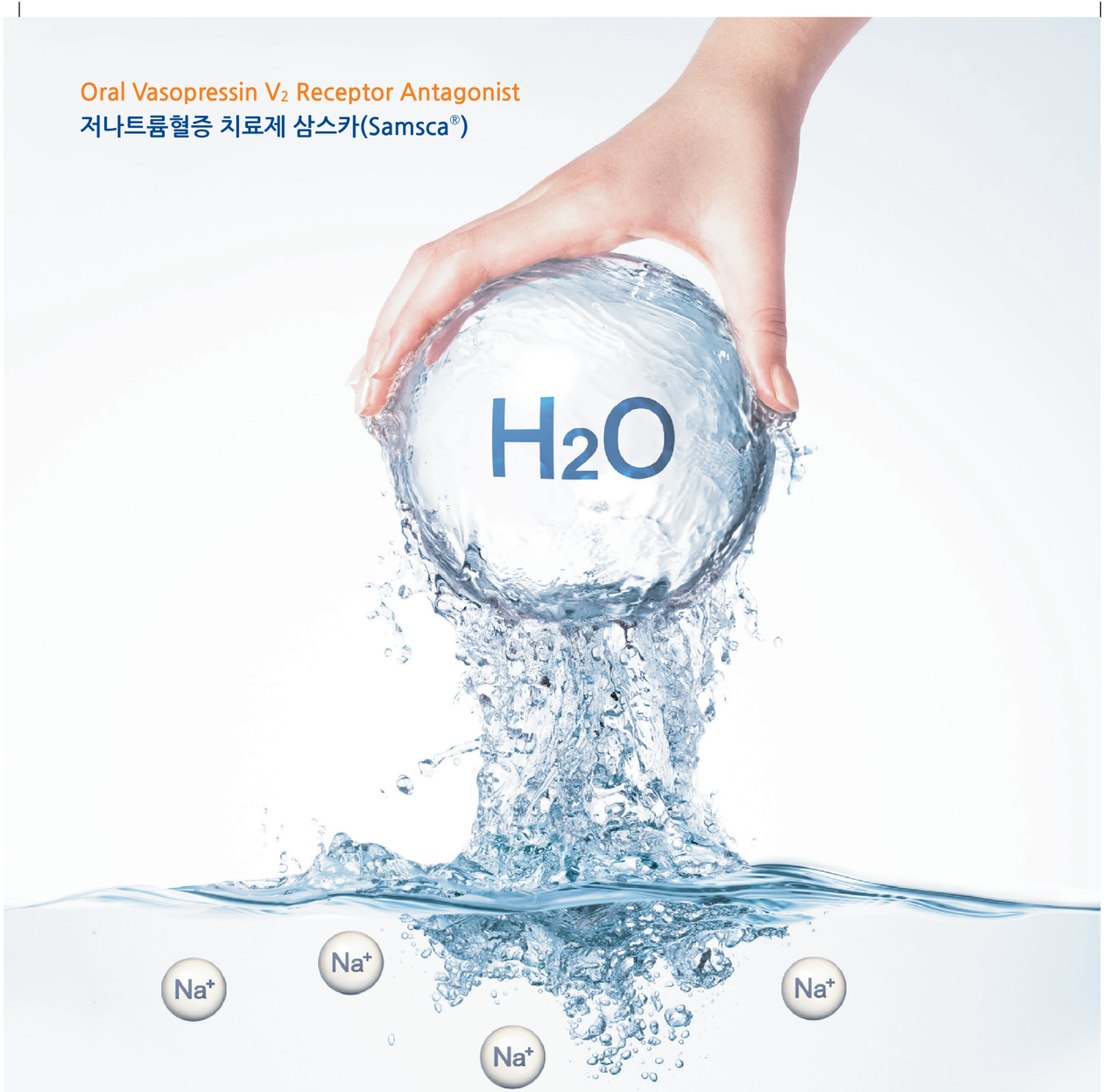

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Case Report

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Pseudo-Gitelman Syndrome Presenting with Hypokalemic Metabolic Alkalosis and Hypocalciuria

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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.

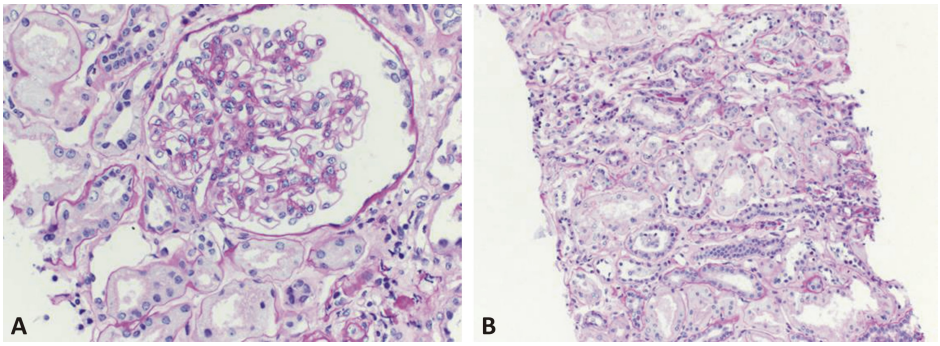

Fig. 1. The kidney biopsy findings in Case 2. The high power image reveals that there were no remarkable morphological changes in the glomeruli (**A**). The image with low power reveals that mild interstitial fibrosis was associated with moderate degrees of tubular atrophy and interstitial inflammation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

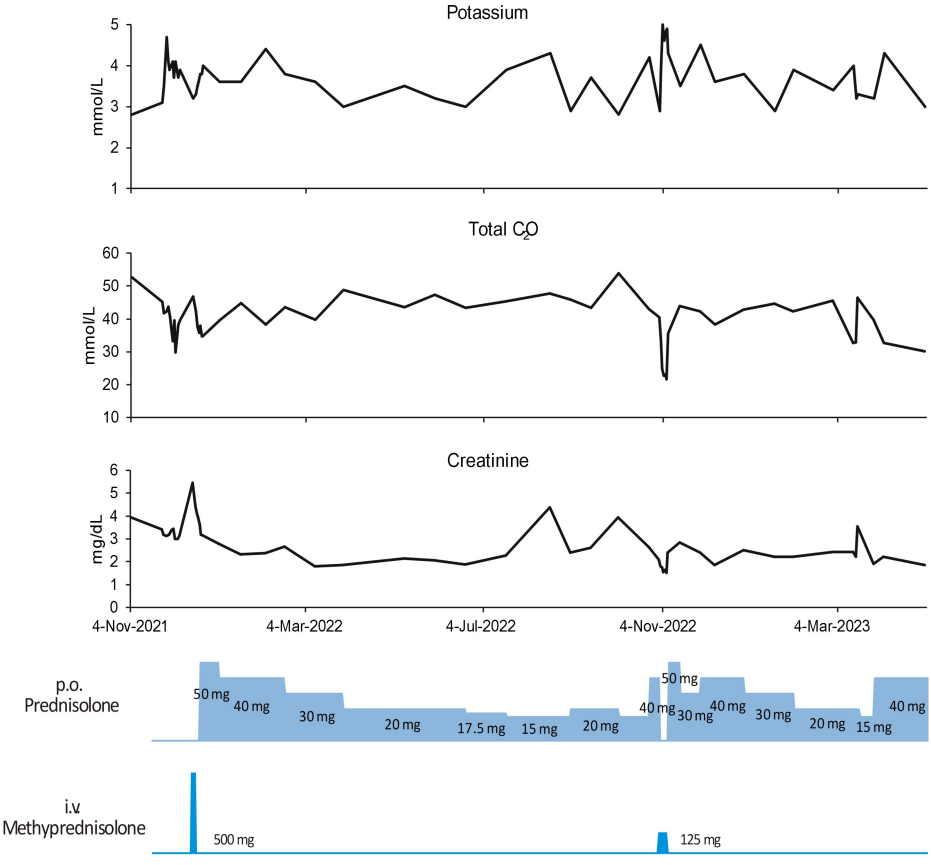

Fig. 2. The course of hypokalemic metabolic alkalosis and azotemia in Case 2. Changes in serum potassium, total CO_2, and creatinine levels in response to glucocorticoid therapy are shown.

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.

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The Efficacy of Single-pill Combination of Olmesartan Medoxomil and Amlodipine Besylate on Office Blood Pressure in Hypertensive Patients who did not Respond to Amlodipine Besylate Monotherapy

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Background: As combination therapy, switching to single-pill combination (SPC) medication after a short period of monotherapy is helpful because reducing pill numbers can improve patients' adherence to medications. This study was aimed to assess the effect of the single-pill combination (SPC) of olmesartan medoxomil 20 mg and amlodipine besylate 5 mg (OLM 20 mg/AML 5 mg) on blood pressure (BP) reduction in hypertensive patients who did not respond to amlodipine besylate 5 mg (AML 5 mg) monotherapy for 4 weeks.

Methods: This study was a prospective, open-label, multi-center, non-comparative study. Patients whose BP was not got the target BP (≥140 mmHg and if diabetic patients ≥130 mmHg) after 4 weeks treatment with AML 5 mg, were enrolled. AML 5 mg was switched to the SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks. The primary effectiveness endpoint was the reduction of seated systolic blood pressure (SeSBP) after SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks. The changes of brachial-ankle pulse wave velocity (baPWV), central BP (CBP), and augmentation index (AIx@75) were evaluated also.

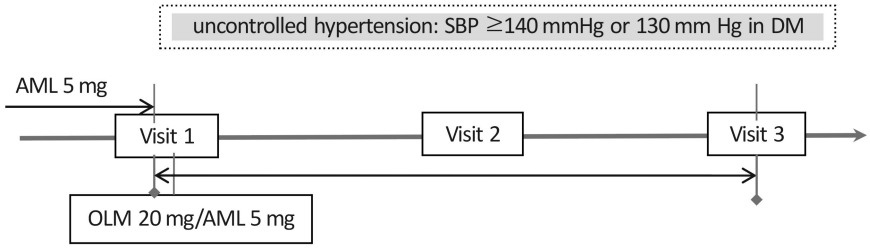
Results: Forty-seven patients were enrolled (mean age = 52±9 years, 36 men). After the SPC treatment for 8 weeks, SeSBP was reduced from 153±9 mmHg to 131±18 mmHg and seated diastolic BP (SeDBP) from 95±8 mmHg to 81±11 mmHg ($p<0.001$ and $p<0.001$, respectively). The reduction of SeSBP/SeDBP were 22 mmHg and 14 mmHg, respectively. The target goal BP achievement rate was 74.5%, and baPWV, CBP, and AIx@75 were improved.

Conclusion: SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks was effective in reducing BP, achieving target BP goal, and also improving arterial stiffness in uncontrolled hypertensive patients with AML 5 mg monotherapy.

Key Words: Hypertension, Antihypertensive agents, Drug combination, Blood pressure

INTRODUCTION

Hypertension is one of the major risk factors for cardiovascular disease (CVD), and a leading cause of death[1,2]. Achieving the target blood pressure (BP) is crucial in reducing the complications and mortality caused by hypertension[3,4]. In many patients, it is difficult to achieve the target blood pressure with monotherapy. Therefore, an increase in the dose or combination of different classes of antihypertensive drugs is required. As combination therapy, switching to single-pill combination (SPC) medication after a short period of monotherapy is helpful because a reduc-



Visit 1 (-2+0 week)	**Visit 2** (4 weeks±1 week)	**Visit 3** (8 weeks±1 week)
Screening and prescribe a test drug	Middle visit	Final visit
SeSBP/SeDBP PWV and CBP Laboratory test	SeSBP/SeDBP	SeSBP/SeDBP PWV and CBP Laboratory test

Fig. 1. Study protocol schedule.
SBP, systolic blood pressure; DM, diabetes mellitus; AML, amlodipine besylate; OLM, olmesartan medoxomil; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; PWV, pulse wave velocity; CBP, central blood pressure.

tion of pill numbers can improve patients' adherence to medications. Recently, many guidelines recommended SPC therapy as an initial treatment to achieve the target BP[3,4]. The purpose of the study was to examine the effects of the SPC of Olmesartan (OLM) 20 mg and amlodipine (AML) 5 mg on BP reduction in hypertensive patients who did not respond to AML 5 mg monotherapy for 4 weeks.

METHODS

1. Study population and protocol

This study was a prospective, open-label, multi-center, non-comparative study, and investigator-initiated and sponsored one. Forty-seven patients with uncontrolled BP were enrolled and visited Dongguk University Hospital and Daegu Catholic University Hospital in Korea from June 2015 to August 2016 (26 patients at Dongguk University Hospital, 21 patients at Daegu Catholic University Hospital). The uncontrolled BP was defined as seated systolic BP (SeSBP) ≥ 140 mmHg or SeSBP ≥130 mmHg in diabetic patients after AML 5 mg treatment for 4 weeks. The inclusion and exclusion criteria are described in the supplement.

Primary effectiveness endpoint was reduction of SeSBP after SPC (OLM 20 mg/AML 5 mg) medication for 8 weeks from baseline. And secondary effectiveness endpoint was target SeSBP attaining rate after SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks.

All patients were measured Brachial-ankle pulse wave velocity (baPWV), CBP, and AIx@75 at baseline and after 8 weeks SPC (OLM 20 mg/AML 5 mg) treatment.

All patients took the scheduled dosage of single tablet (OLM 20 mg/AML 5 mg) once a day for 8 weeks, and other antihypertension medications were prohibited during this study. All patients were taken laboratory tests included renal profiles, lipid profiles, hepatic profiles, random serum glucose, glycosylated hemoglobin (HbA1c), uric acid, and high sensitivity C reactive protein (hsCRP), urine dipstick test at baseline and the final visit of the study (8 weeks).

The protocol was approved by the Institutional review board of Dongguk University Gyeongju Hospital in and Daegu Catholic University Hospital (IRB No. 11-10, IRB No. CR-11-033). All of the patients gave written informed consent. Overall protocol was described in Figure 1.

2. Measurement of office blood pressure, brachial-ankle pulse wave velocity, and central blood pressure

After rest for at least 5 minutes, brachial BP was measured two times at 1-2 minutes interval. The arm with higher SBP at the screening visit was designated as the index arm. During the next visit, the BP was measured in the index arm.

The average value was considered as the BP at the visit. The validated oscillometric BP device (WatchBP Home, Microlife, Taiwan) was used for BP measurement at the first visit, 4th week, and 8th week visit. A baPWV was measured in a quiet room controlled at 22±1℃. And all patients asked to visit for test overnight fasted state. All patients asked to stop drinking caffeine-containing beverages, drinking alcohol and smoking at least 12 hours before test. After 15-minute rest, baPWV was measured using an automated device (VP-1000; Colin, Co. Ltd, Komaki, Japan) in the supine position[5]. After 10-minute rest, CBP and augmentation index (AIx) were measured in the sitting using a commercially available radial artery tonometry device (SphygmoCor®; AtCor Medical, Sydney, Australia), Radial artery applanation tonometry was conducted using a hand-held tonometer over the radial artery and applying mild pressure to partially flatten the artery. AIx@75 that was adjusted AIx assuming a heart rate was 75 beats per minute was obtained. Measurements were taken at baseline and after 8 weeks treatment period.

3. Statistical Analysis

Based on the existing literature, the difference between the reference group (AML 5 mg) and after 8 weeks SPC (OLM 20 mg/AML 5 mg) treatment was -0.29 mmHg, and the maximum standard deviation was set to ± 0.7 mmHg. So, this study should need 36 patients at 5% significance level and 80% power[6]. Therefore, the total number of patients required 45 patients assuming the dropout rate of 20%[6].

Continuous variables are presented as the mean ± standard deviation and compared with paired t-test and repeated ANCOVA, and categorical variables are compared by performing the chi-square test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Version 20.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Forty-seven patients were enrolled in this study. The mean age of the patients was 52±9 years (range: 43-61 years). Men were 36 (77%), and women were 11 (23%). On the previous medical history, 1 patient (2.1%) had diabetes mellitus, and 4 patients (8.5%) had dyslipidemia. The mean body mass index (BMI) was 26.1±4.4 kg/m^2 (range: 21.7-30.5) (Table 1).

In the laboratory findings, there were no statistically significant change in creatinine, estimated glomerular filtration rate (eGFR), Total cholesterol, high-density lipoprotein (HDL)-cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), serum glucose, HbA1c, uric acid, and hsCRP, proteinuria after 8-weeks treatment from baseline. However, only low-density lipoprotein (LDL)-cholesterol decreased significantly at 8-weeks of treatment from baseline (Table 2).

After the SPC treatment, SeSBP was reduced from 153±9

Table 1. Baseline clinical characteristics

	Number (%)
Total	47
Age	52±9
Men	36 (77)
DM	1 (2.1)
Dyslipidemia	4 (8.5)
BMI (kg/m^2)	26.1±4.4

DM, diabetes mellitus; BMI, body mass index

Table 2. Laboratory findings of baseline and after 8 weeks SPC (OLM 20 mg/AML 5 mg) medication

	Baseline	At week 8	p value
Creatinine (mg/dl)	0.8±0.1	0.9±0.2	0.906
eGFR	98.3±13.2	99.9±13.9	0.588
Total cholesterol (mg/dl)	200±40	192±26	0.147
TG (mg/dl)	146±81	157±93	0.787
LDL-cholesterol (mg/dl)	138±38	125±31	0.01
HDL-cholesterol (mg/dl)	56±12	54±12	0.395
AST (mg/dl)	31±15	28±12	0.228
ALT (mg/dl)	33±19	29±14	0.138
Serum glucose (mg/dl)	106±38	103±28	0.587
HbA1c (%)	6.0±0.8	6.0±0.7	0.541
Uric acid (mg/dl)	5.3±1.7	5.5±1.7	0.366
hsCRP (mg/dl)	0.21±0.32	0.13±0.14	0.084
Proteinuria			
- 0	39 (84.8%)	37 (90.2%)	0.244
- Trace	2 (4.3%)	4 (9.8%)	
- 1+	2 (4.3%)	0 (0.0%)	
- 2+	2 (4.3%)	0 (0.0%)	
- 3+	0 (0.0%)	0 (0.0%)	
- 4+	1 (2.2%)	0 (0.0%)	

eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate transaminase; ALT. alanine transaminase; HbA1c, hemoglobin A1c; hsCRP, high sensitivity c-reactive protein.

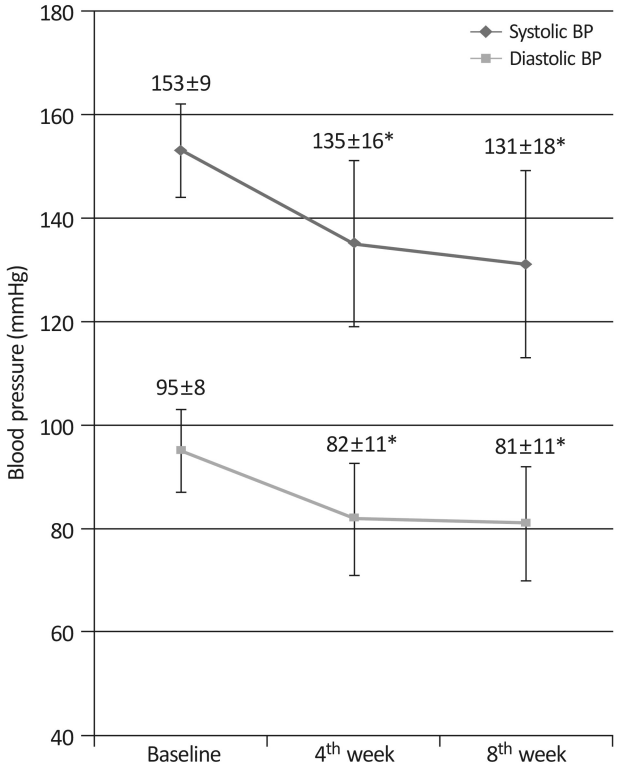


Fig. 2. Mean seated blood pressure over the treatment *p<0.001 baseline vs. 4th and 8th week. BP, Blood pressure.

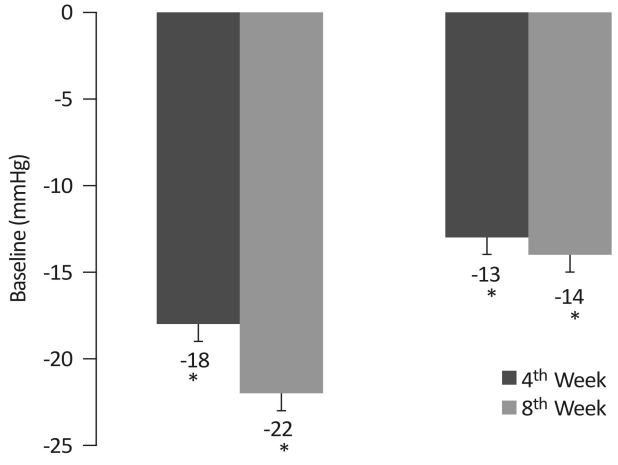


Fig. 3. Change from baseline in seated SBP and DBP (±SE of the mean) over the treatment. *p<0.001. SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure.

mmHg to 135±16 mmHg at 4th week and 131±18 mmHg at 8th week (p<0.001 and p<0.001, respectively). And SeDBP was also reduced from 95±8 mmHg to 82±11 mmHg at 4th week and 81±11 mmHg at 8th week (p < 0.001 and p<0.001, respectively) (Fig. 2). After the SPC treatment, SeSBP reduction was 18 mmHg at 4 week and 22 mmHg at 8 week, respectively (p<0.001). SeDBP reduction was 13 mmHg at 4 week and 14 mmHg at 8 week, respectively (p<0.001) (Fig. 3). After the 8-weeks SPC treatment, the target systolic blood pressure (SBP) goal achievement rate was 74%, and the diastolic blood pressure (DBP) goal achievement rate was 82.9% (Fig. 4).

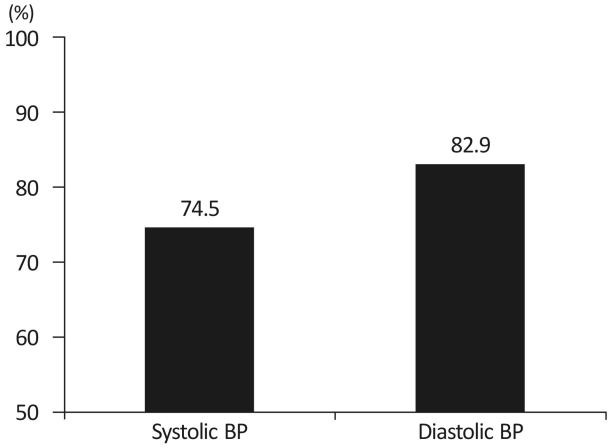


Fig. 4. Target blood pressure achievement rate after 8 weeks treatment with single pill combination drug.

Table 3. The differences of blood pressure and PWV, AIx between baseline and after 8 weeks treatment of single pill combination of olmesartan medoxomil 20 mg and amlodipine besylate 5 mg

Parameters	Baseline	At week 8	p value
SeSBP (mmHg)	153±9	131±18	0.001
SeDBP (mmHg)	95±8	80±11	0.001
baPWV (cm/sec)	1,494±262	1,279±140	<0.001
Central SBP (mmHg)	144±13	120±13	<0.001
Central DBP (mmHg)	98±7	83±10	<0.001
AIx@75 (%)	27±9	21±10	<0.001

SeSBP, sitting systolic blood pressure; SeDBP, sitting diastolic blood pressure; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; AIx, augmentation index; AIx@75, augmentation index adjusted assuming heart rate was 75 beats per minute

The SPC treatment for 8 weeks reduced baPWV from 1,494±262 cm/sec to the 1,279±140 cm/sec, and also reduced CBP and AIx@75 significantly (p<0.001) (Table 3).

At the 4th week, there were no adverse events two cases of adverse events were but those were not related to study drug. And there was no adverse reaction and adverse event were observed at 8th week. In this study, no severe sympto-

Table 4. The clinical characteristics between the group that achieved the target blood pressure goal and the group that did not achieve.

Target BP Goal achievement	No (N=12)	Yes (N=35)	p value
Sex			0.301
- Women	1 (8.3%)	10 (28.6%)	
- Men	11 (91.7%)	25 (71.4%)	
Age	48.3±13.5	52.9±7.5	0.290
BMI	27.4±5.0	25.7±4.2	0.283
SeSBP (mmHg)	157.3±11.3	151.5±8.0	0.056
SeDBP (mmHg)	97.7±10.3	93.4±7.1	0.120
DM			0.571
- No	11 (91.7%)	35 (100.0%)	
- Yes	1 (8.3%)	0 (0.0%)	
Dyslipidemia			0.532
- No	12 (100.0%)	31 (88.6%)	
- Yes	0 (0.0%)	4 (11.4%)	
Creatinine (mg/dl)	0.9±0.2	0.8±0.2	0.264
eGFR	98.8±17.1	98.2±11.9	0.904
AST (mg/dl)	25.8±5.8	31.9±15.7	0.060
ALT (mg/dl)	25.8±10.5	33.0±19.9	0.123
Total cholesterol (mg/dl)	179.9±18.9	206.7±42.6	0.008
TG (mg/dl)	160.5±114.7	144.4±80.5	0.597
LDL-cholesterol (mg/dl)	116.8±21.7	141.3±40.5	0.015
HDL-cholesterol (mg/dl)	51.1±15.8	57.2±12.4	0.191
Serum glucose (mg/dl)	127.8±66.2	100.9±16.9	0.192
hsCRP (mg/dl)	0.1±0.1	0.2±0.3	0.056
Uric acid (mg/dl)	5.3±1.1	5.3±1.9	0.891
HbA1c (%)	6.2±1.1	5.9±0.6	0.410
Proteinuria			0.297
- 0	9 (75.0%)	30 (88.2%)	
- Trace	1 (8.3%)	1 (2.9%)	
- 1+	0 (0.0%)	2 (5.9%)	
- 2+	1 (8.3%)	1 (2.9%)	
- 3+	0 (0.0%)	0 (0.0%)	
- 4+	1 (8.3%)	0 (0.0%)	

BMI, body mass index; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT. alanine transaminase; TG, triglyceride; LDL, tow density lipoprotein; HDL, high density lipoprotein; hsCRP, high sensitivity c-reactive protein; HbA1c, hemoglobin A1c

matic hypotension or syncope, were observed. Furthermore, there were no cases where participants withdrew from the study due to adverse reactions.

There was significant difference in baseline total cholesterol and LDL-cholesterol between the patients that achieved the target blood pressure goal and the patients that did not (Table 4).

DISCUSSION

The present study demonstrated that the fixed-dose SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks effectively reduced BP, achieved target BP. In addition, central BP was reduced, and arterial stiffness was improved in uncontrolled hypertensive patients with AML 5 mg monotherapy. The 8 weeks SPC treatment reduced SeSBP/SeDBP 22 mmHg and 14 mmHg respectively. The target goal achievement rate was 74.5% for SeSBP and 82.9% for SeDBP. These results support that SPC can be very effective in controlling BP in patients with uncontrolled hypertension with amlodipine 5 mg monotherapy. Poorly controlled hypertension could be related to multiple factors including low antihypertensive efficacy of single drug therapies, reluctance of primary care physicians to modify/titrate initially chosen therapy, and poor compliance with medication[7]. Many hypertension guidelines recommend combination therapy for the treatment of high BP ≥150 mmHg and combination of standard dose of two drugs as the initial management in mild/moderate arterial hypertension[3,4]. They also encourage to use SPC. The clinical guidelines are conveying messages that using fixed dose combination therapies to control hypertension may be more effective than monotherapy with regular dose, leading to better control of BP and reducing cardiovascular/cerebrovascular morbidity and mortality caused by hypertension in the population[3,4,7].

Arterial stiffness has been known to be an important independent risk factor for cardiovascular disease in hypertensive patients[8]. Arterial stiffness can be easily estimated by using measurement of pulse wave velocity (PWV) and augmentation index. In addition, CBP was more closely related to the occurrence of cardiovascular disease than the brachial arterial BP[9-14]. Clinical studies had shown that central SBP and pulse pressure were more useful for prediction of cardiovascular events than brachial artery BP[15].

SPC treatment reduced baPWV, CBP and AIx significantly from baseline at week 8, indicating an improvement of arterial stiffness. It is unclear whether the reduced arterial stiffness and CBP with short-term treatment with SPC may im-

prove cardiovascular outcomes. However, more effective BP control and reduction of arterial stiffness may increase the satisfaction of both physicians and patients. This will lead to improved adherence to treatment and BP control and, eventually reduction of cardiovascular events.

There were no statistically significant differences in creatinine, eGFR, total cholesterol, HDL-cholesterol, AST, ALT, Serum glucose, HbA1c, uric acid, and hsCRP, proteinuria between baseline and at week 8, except significantly reduced LDL-cholesterol. These results suggest SPC (OLM 20 mg/AML 5 mg) was a safe and well-tolerated fixed-dose single pill combination medication.

There were no significant differences in clinical characteristics between the group that achieved the target blood pressure and the group that did not except total cholesterol and LDL-cholesterol. The reason for these results were thought to be as follows, there were a higher number of dyslipidemia patients, and as a result, their total cholesterol and LDL-cholesterol levels were higher compared to those who did not achieve the target BP and small number of study subjects also.

Although statistically insignificant, baseline SeSBP of the group that did not achieve the target goal BP had about 7 mmHg higher than that of group that achieved the target goal BP. Considering the small sample size of the study, 7 mmHg difference could be clinically relevant because the change to SPC (OLM 20 mg/AML 5 mg) can be considered in patients with SeSBP <155 mmHg after 4 weeks AML 5 mg monotherapy, but not in patients with SeSBP ≥155 mmHg. Patients with a SeSBP ≥155 mmHg are more likely to require three of more antihypertensive drugs with higher doses to achieve the target BP goal. This should be evaluated in further studies.

There were limitations to this study. The number of subjects was small. The follow-up period was short. Moreover, the single-arm design of the study did not allow comparing BP lowering effect of SPC treatment to other treatment.

In conclusion, SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks was effective in reducing BP, achieving target BP goal and improving arterial stiffness in uncontrolled hypertensive patients with AML 5 mg monotherapy. SPC treatment for 8 weeks was safe and well tolerated. But further large scaled and comparative design studies are needed to confirm these results and evaluate long-term outcomes.

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Conflict of interest

B.K. Kim has received lecture honorarium from Daewoong Co., Ltd. and Daiichi-Sankyo Korea Ltd.

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SUPPLEMENT

Inclusion criteria are defined as follows.

1. Male and female patients aged 20 to 80
2. Uncontrolled hypertensive patients who meet the following conditions:
   1) Uncontrolled hypertension is Amlodipine (Amlodipine besylate) 5 mg monotherapy for 4 weeks
   2) Average seated systolic blood pressure (SeSBP) of at least 140 mmHg after treatment for at least 4 weeks (diabetic patients' case average SeSBP $\geq$130 mmHg)
   3) Patients who voluntarily consented to participate in this clinical trial

Exclusion criteria are defined as follows.

1. Secondary hypertension patients (renovascular hypertension, aortic coarctation, pheochromocytoma, primary aldosteronism, etc.).
2. Patients with mean SeSBP greater than 180 mmHg or mean sitting diastolic blood pressure (SeDBP) greater than 110 mmHg at the screening.
3. Patients whose SeSBP difference of the selected arm greater than 20 mmHg or SeDBP difference of the selected arm greater than 10 mmHg at the screening.
4. Patients with hypertensive encephalopathy, unstable angina, transient ischemic attack, acute myocardial infarction, severe aortic stenosis, severe congestive heart failure or any type of angioplasty within the last 6 months.
5. Patients with heart failure, 2nd or 3rd degree atrioventricular block, severe arrhythmia or valve heart disease.
6. Patients with severe cardiovascular, cerebrovascular, gastrointestinal or hematologic disease.
7. Severe renal failure, patients with unilateral or bilateral renal artery stenosis, kidney transplanted patients, patients with only one kidney, patients with dialysis
8. Patients with severe liver failure, patients with biliary obstruction, or patients with confirmed liver disease based on past data.
9. Patients with uncorrected sodium or fluid depletion.
10. Patients with hypersensitivity to ingredients contained in this test drug, such as amlodipine besylate or other dihydropyridine drugs and olmesartan medoxomil.
11. Tumor patients.
12. Patients with uncontrolled neurological and psychiatric conditions
13. Pregnant women, lactating mothers, women who have a plan for pregnancy or may become pregnant
14. If patients have participated in another clinical trial within the past month
15. Patients who are judged by investigators to have difficulty performing this clinical trial or have medical findings that do not meet the clinical trial.

Original Article

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The Association Among Post-hemodialysis Blood Pressure, Nocturnal Hypertension, and Cardiovascular Risk Factors

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Background: Most hemodialysis (HD) patients suffer from hypertension and have a heightened cardiovascular risk. While blood pressure (BP) control is essential to end-stage kidney disease (ESKD) patients, overly stringent control can lead to intradialytic hypotension (IDH). This study aimed to examine BP variations during and after HD to determine whether these variations correlate with IDH risk.
Methods: BP measurements during dialysis were taken from 28 ESKD patients, and ambulatory BP monitoring was applied post-dialysis. Laboratory parameters and risk factors, including diabetes, coronary disease, and LV mass index, were compared between IDH and non-IDH groups using an independent t-test.
Results: Of the 28 patients with an average age of 57.4 years, 16 (57.1%) had diabetes, 5 (17.9%) had coronary artery disease, and 1 (3.6%) had cerebrovascular disease. The mean systolic blood pressure (SBP) during and post-HD was 142.26 mmHg and 156.05 mmHg, respectively (p=0.0003). Similarly, the mean diastolic blood pressure (DBP) also demonstrated a significant increase, from 74.59 mmHg during HD to 86.82 mmHg post-HD (p<0.0001). Patients with IDH exhibited a more substantial SBP difference (delta SBP, 36.38 vs. 15.07 mmHg, p=0.0033; age-adjusted OR=1.58, p=0.0168) and a lower post-dialysis BUN level (12.75 vs. 18.77 mg/dL, p=0.0015; age-adjusted OR=0.76, p=0.0242). No significant variations were observed in daytime and nocturnal BP between the IDH and non-IDH groups.
Conclusion: Hemodialysis patients exhibited a marked increase in post-dialysis BP and lacked a nocturnal BP dip, suggesting augmented cardiovascular risks. This highlights the importance of more stringent BP control after hemodialysis.

Key Words: Ambulatory blood pressure, End-stage kidney disease, Hemodialysis, Hypertension, Nocturnal hypertension

INTRODUCTION

Life expectancy has risen due to better control over infectious diseases and acute cardiovascular conditions, leading to an increased number of chronic illnesses such as diabetes and hypertension. Additionally, as patients with diabetes and hypertension age, the incidence of end-stage kidney disease (ESKD) also rises[1)]. Although advancements in dialysis treatment have improved survival rates for ESKD[2)], these patients still have significantly lower survival rates than the general population, primarily due to cardiovascular complications[3)].

Hypertension, following diabetes, is the second most common cause of ESKD, and its severity correlates with a decreased glomerular filtration rate. As renal function deteriorates, patients often become hypertensive, and most of

those undergoing dialysis suffer from hypertension[4]. Factors such as vascular stiffness and autonomic dysfunction also contribute to fluctuations in blood pressure (BP) among dialysis patients[5]. While regulating the BP of hemodialysis patients is crucial, stringent BP control during dialysis treatments can result in intra-dialytic hypotension (IDH), leading to potential vascular access thrombosis[6]. Notably, there's a U-shaped relationship between BP and mortality in dialysis patients, emphasizing the importance of proper BP regulation in dialysis environments[7]. While Ambulatory blood pressure monitoring (ABPM) is an effective diagnostic tool for hypertensive patients[8], its application is limited in hemodialysis patients due to compliance issues and constraints related to the use of the arteriovenous fistula arm.

In this study, we examined BP changes during and post-hemodialysis, including nocturnal BP variations using ABPM, to determine the relationship between BP fluctuations and the cardiovascular risks in ESKD patients.

METHODS

1. Patients

From Sep 1st, 2019, to Aug 31, 2020, we prospectively enrolled ESKD patients at Chungbuk National University Hospital who had undergone hemodialysis for at least 3 months, were >19 years of age, had hypertension (>140/90 mmHg), took anti-hypertensive medication, and agreed to undergo a 24-hour BP measurement. We excluded patients with acute illnesses, those who had been admitted to a hospital within the past 6 months, those with cancer, and those with uncontrolled anemia (Fig. 1). All patients continued taking their anti-hypertensives, and adjustments were made by clinicians based on BP changes. IDH was defined as a required systolic blood pressure (SBP) or diastolic blood pressure (DBP) decline of >20 mmHg during hemodialysis sessions on the day of the ABPM check. Delta SBP and DBP were defined as the differences between the highest and lowest values recorded during dialysis treatment or ABPM. This research was approved by the Institutional Research Board (IRB) of Chungbuk National University Hospital (IRB No: 2020-03-039). We included only participants who provided informed consent.

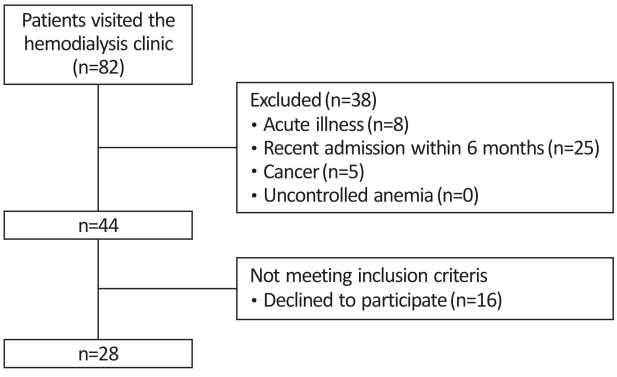

Fig. 1. Flow diagram of the patient selection.

2. Hemodialysis and BP Analysis

Hemodialysis sessions lasted 4 hours each and were conducted thrice a week. The morning sessions were scheduled from 08:30-09:00 to 12:30-13:00, while the afternoon sessions took place from 13:00-13:30 to 17:00-17:30. We utilized the Artis Physio dialysis machine by Baxter (USA) and the 5008S machine from Fresenius Medical Care (Germany). Dialyzers employed included Theranova 400 (Baxter, USA) and FX-100 (Fresenius Medical Care, Germany), matched to their respective manufacturers. Blood pressure was monitored hourly during each session. As per clinical guidelines, the patients' target blood pressure was set at 140/90 mmHg before dialysis and adjusted to 130/80 mmHg post-dialysis.

3. 24-Hour BP Monitoring

Ambulatory BP was measured using the TM-2430 ABPM kit (A&D company, Japan). At the end of the dialysis session, we applied a portable BP cuff and compared BP with those of the dialysis machine. All the patients were educated to keep the ABPM for at least 24 hours post-dialysis. The collected ABPM data were transferred to a desktop in the hemodialysis unit for analysis. Daytime BP readings, which included the dialysis period, spanned from 6:00 a.m. to midnight. Nocturnal BP readings were taken from midnight to 6:00 a.m. using the ABPM kit.

4. Blood Test and Echocardiography

All patients underwent routine laboratory tests in the dialysis unit every month. Chest X-rays were performed every

three months. Additionally, patients received echocardiography at least once every two years, which included assessments of the left ventricle (LV) ejection fraction and LV mass index. Medications for phosphorus, potassium, and anemia were adjusted monthly.

5. Statistical Analysis

All data are presented as mean ranges. The paired t-test was employed to compare BP during dialysis with home BP. Patients with and without intra-dialytic BP changes were compared using a two-sample t-test. To ascertain the relationship between IDH and clinical laboratory tests, we conducted a logistic regression analysis, accounting for age as a covariate. Statistical analyses were performed using SPSS Statistics ver. 25.0 and SAS® Analytics Pro Version 9.4.

RESULTS

1. Characteristics of the patients

We included 28 hemodialysis patients who consented to undergo ABPM, of which 11 were males and 17 were females. The average age of the participants was 57.4 years. Out of these, 16 patients (57.1%) had diabetes, 5 (17.9%) had angiography-confirmed coronary artery disease, and 1 (3.6%) had cerebrovascular disease (Table 1). Every patient was on at least two types of anti-hypertensive medications, which included calcium channel blockers, beta-blockers, and angiotensin receptor blockers.

2. Changes in BP during and after hemodialysis

Ambulatory monitoring showed that patients had elevated BP compared to their resting BP during hemodialysis (Fig. 2). During hemodialysis treatment, the mean SBP was 142.26 (107.20-186.80) mmHg and the mean DBP was 74.59

Table 1. Characteristics of the patients

	N=28 (%)	Range
Age	57.54±11.52	31.00-74.00
Male	11 (39.3)	
Diabetes	16 (27.1)	
Ischemic heart disease	5 (17.9)	
CVA	1 (3.6)	
BUN (mg/dL)	59±12	34.01-78.63
Creatinine (mg/dL)	10.45±2.80	4.39-17.95
Albumin (g/dL)	4.0±0.3	3.44-4.45
iPTH (pg/mL)	319±193	8.10-742.20
URR (%)	72.80±7.62	55.30-84.14
LVMI (g/m^2)	107.60±21.01	77.00-147.30
LV EF (%)	63.33±9.10	36.90-75.80
Anti-HT Pill burden*/d	3.25±3.11	0.5-10.0

CVA, cerebrovascular accident; iPTH, intact parathyroid hormone; URR, urea reduction ratio; LVMI, left ventricular mass index; LV EF, left ventricular ejection fraction; HT, hypertensives. *Fixed dose combination was counted as 2 pills

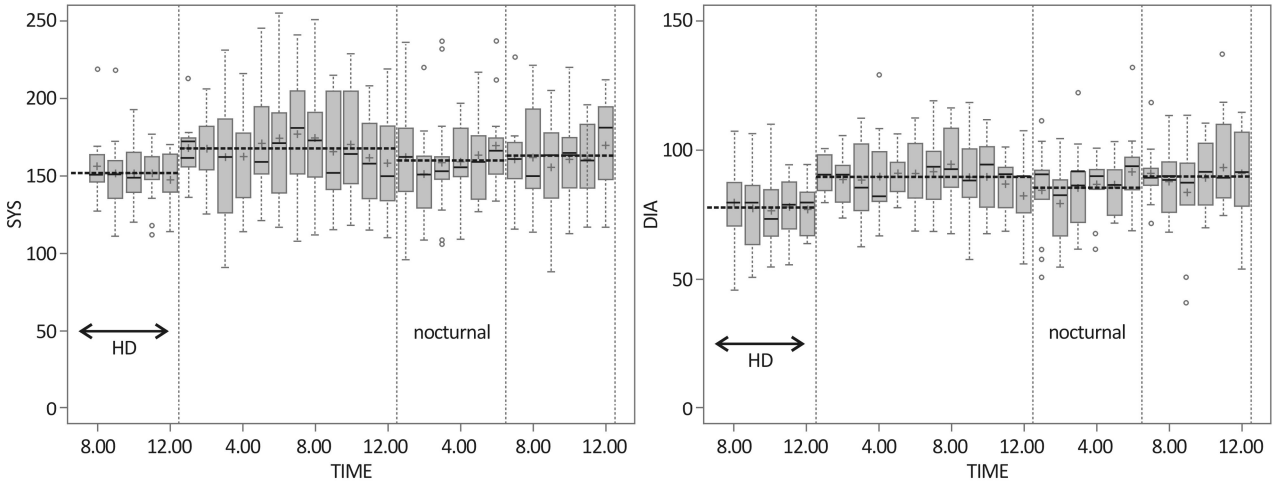

Fig. 2. Changes of BP during and after hemodialysis. The patients' systolic (left) and diastolic (right) BP were monitored by ABPM. Ambulatory BP was significantly higher than the BP recorded during the hemodialysis sessions.

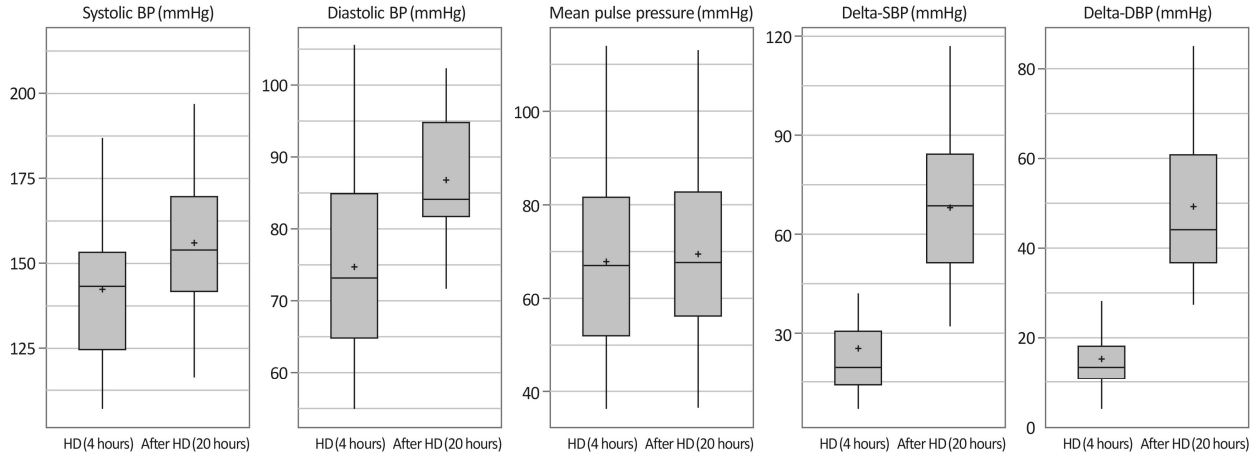

Fig. 3. Boxplot of BP differences during and after hemodialysis: Ambulatory BP monitoring indicated higher SBP, DBP, and greater BP differences post-dialysis.

Table 2. BP difference during and after hemodialysis session

	HD (4 hours)		After HD (20 hours)		p-value
	Mean	Range	Mean	Range	
Systolic BP (mmHg)	142.26	(107.20-186.80)	156.05	(116.17-213.92)	0.0003
Diastolic BP (mmHg)	74.59	(54.80-105.40)	86.82	(71.32-102.38)	<0.0001
Mean PP (mmHg)	67.66	(36.40-113.80)	69.23	(36.36-113.08)	0.5250
Delta-SBP (mmHg)	24.96	(7.00-103.00)	68.07	(32.00-117.00)	<0.0001
Delta-DBP (mmHg)	15.14	(4.00-42.00)	49.21	(27.00-85.00)	<0.0001

PP, pulse pressure; Delta-SBP/DBP, the average difference of SBP and DBP

(54.80-105.40) mmHg. Post-dialysis ambulatory measurements via ABPM revealed mean SBP and DBP values of 156.05 (116.14-213.92) mmHg and 86.32 (71.32-102.38) mmHg, respectively. These post-dialysis measurements demonstrated statistically significant differences when compared to the intra-dialysis mean SBP and DBP ($p=0.0003$ and $p<0.0001$, respectively) (Table 2). Moreover, the difference between SBP and DBP (delta-SBP and delta-DBP) during and after dialysis was also markedly increased after dialysis with statistical significance ($p<0.0001$) (Fig. 3). While the pulse pressure (PP) also showed an increase after dialysis, this change was not statistically significant (67.66±19.13 mmHg vs. 69.23±20.27 mmHg, respectively, $p=0.5250$).

3. Nocturnal BP changes in dialysis patients

We examined the nocturnal BP of dialysis patients in comparison to their daytime BP. The average daytime SBP and DBP were 153.88±22.55 mmHg and 84.12±10.37 mmHg respectively. In contrast, nocturnal SBP and DBP were 152.07 ±25.98 mmHg and 85.11±10.60 mmHg. Notably, we observed no significant nocturnal BP dipping during sleeping hours, with readings of 153.88/84.12 mmHg during the day compared to 152.07/85.11 mmHg at night (Fig. 2). Patients with diabetes showed higher SBP and pulse pressure during the night, though the difference was not statistically significant (155.98/83.77 mmHg versus 146.85/86.90 mmHg, $p=0.367$ for SBP, 0.449 for DBP).

4. Intradialytic hypotension and cardiovascular risk factors

We differentiated between two patient groups based on their SBP changes during dialysis: those with changes greater than 20 mmHg and those with changes less than 20 mmHg. Out of the 28 patients, 13 (46.4%) experienced IDH. The IDH group exhibited a more pronounced delta-SBP (148.48 vs. 136.87 mmHg, $p=0.0033$) and PP (76.02 vs. 60.43 mmHg,

Table 3. Difference between IDH group and non-IDH group

	IDH		Non-IDH		p-value
	Mean	Range	Mean	Range	
Age	62.54	(46.00-74.00)	53.13	(31.00-69.00)	0.0274
Systolic BP (mmHg)	148.48	(109.60-186.80)	136.87	(107.20-172.00)	0.1405
Diastolic BP (mmHg)	72.46	(54.80-99.00)	76.44	(55.40-105.40)	0.4272
Delta-SBP (mmHg)	36.38	(20.00-103.00)	15.07	(7.00-26.00)	0.0033
Delta-DBP (mmHg)	15.85	(6.00-30.00)	14.53	(4.00-42.00)	0.6752
Pulse pressure (mmHg)	76.02	(46.20-113.80)	60.43	(36.40-93.80)	0.0286
Nocturnal Systolic BP (mmHg)	156.15	(121.00-203.14)	148.53	(104.57-221.14)	0.4416
Nocturnal Diastolic BP (mmHg)	82.88	(66.57-101.00)	87.05	(67.86-109.14)	0.3027
LVMI (g/m^2)	106.44	(85.00-147.30)	108.60	(77.00-141.00)	0.7917
LV EF (%)	63.33	(36.90-75.80)	63.32	(44.50-75.60)	0.9976
Hemoglobin (g/dL)	10.33	(9.80-11.92)	10.48	(9.04-13.19)	0.6428
Pre-BUN (mg/dL)	53.03	(34.01-70.99)	64.14	(43.07-78.63)	0.0145
Post-BUN (mg/dL)	12.75	(7.93-23.91)	18.77	(11.29-27.13)	0.0015
Cholesterol (mg/dL)	136.00	(102.92-187.61)	134.39	(93.67-179.17)	0.8523
Albumin (g/dL)	3.87	(3.44-4.18)	4.14	(3.70-4.45)	0.0041

IDH, Intradialytic hypotension; LVMI, Left Ventricular Mass Index

Table 4. Logistic regression analysis to evaluate risk factors for IDH adjusted by age

	Estimate	Standard Error	Ward	p-value	Odds Ratio	95% CI
Delta-SBP (mmHg)	0.4554	0.1904	5.7207	0.0168	1.5768	1.0857-2.2902
Delta-DBP (mmHg)	0.0346	0.0507	0.4670	0.4944	1.0352	0.9374-1.1433
Pulse pressure (mmHg)	0.0446	0.0285	2.4477	0.1177	1.0457	0.9888-1.1058
LVMI (g/m^2)	0.0058	0.0213	0.0732	0.7867	1.0058	0.9647-1.0485
LV EF (%)	-0.0088	0.0451	0.0382	0.8449	0.9912	0.9073-1.0829
Hemoglobin (g/dL)	-0.1165	0.5375	0.0469	0.8285	0.8901	0.3104-2.5526
Pre-BUN (mg/dL)	-0.0745	0.0465	2.5682	0.1090	0.9282	0.8474-1.0168
Post-BUN (mg/dL)	-0.2738	0.1215	5.0802	0.0242	0.7605	0.5994-0.9649
Cholesterol (mg/dL)	0.0146	0.0200	0.5305	0.4664	1.0147	0.9757-1.0553
Albumin (g/dL)	-4.3480	2.3350	3.4680	0.0630	0.0130	0.0000-1.2560

Table 5. Comparison of post-dialysis blood pressure between IDH group and non-IDH group

	IDH (n=7)		Non-IDH (n=6)		p-value
	Mean	Range	Mean	Range	
Systolic BP MD to MN (mmHg)	164.18	(135.64-198.64)	169.52	(117.20-222.38)	0.7677
Diastolic BP MD to MN (mmHg)	86.58	(75.62-98.69)	92.78	(76.10-101.23)	0.2487

Only 13 patients on morning-session dialysis could be compared. MD, midday (noon); MN, midnight

p=0.0286) during hemodialysis compared to their counterparts. Furthermore, the IDH group had lower pre-dialysis BUN (53.03 vs. 64.14 mg/dL, p=0.0145), post-dialysis BUN (12.75 vs. 18.77 mg/dL, p=0.0015), and serum albumin levels (3.87 vs. 4.14 g/dL, p<0.005) (Table 3).

To evaluate the risk factors associated with IDH, we performed a logistic regression analysis, adjusting for age as a covariate due to its independent correlation with hypotension and cardiovascular risk factors. Notably, the important risk factors of IDH were delta-SBP during dialysis (OR=1.5768, 95% CI: 1.0857-2.2902, p=0.0168) and post-dialysis BUN (OR=0.7605, 95% CI: 0.5994-0.9649, p=0.0242).

Nonetheless, we found no clinical significance linking IDH with delta-DBP, PP, LV mass index, cholesterol, or albumin levels (Table 4).

To assess if there was a disparity in post-dialysis BP between the IDH and non-IDH groups, we examined the BP of morning dialysis patients from noon to midnight post-dialysis. However, there was no significant statistical difference between the two groups (Table 5).

DISCUSSION

This study provides pivotal data regarding real-world post-dialysis BP in Korean hemodialysis patients. Despite the acknowledged significance of BP regulation during dialysis, managing BP in ESKD patients remains challenging, particularly as many exhibit resistant hypertension. Medical practitioners often express concerns that strategies aimed at maintaining appropriate BP during dialysis might elevate the risk of IDH. Indeed, IDH emerges frequently as a hemodialysis complication, attributable to the external circulation and fluid removal fundamental to the dialysis process[5,9]. Studies indicate that approximately 20-30% of hemodialysis patients experience IDH, a condition closely associated with cardiovascular mortality[10], and potential triggers for myocardial ischemia and cerebrovascular insufficiency[10,11]. Nevertheless, Takeda et al. posited that even elevated pre-dialysis BP might not avert IDH[12], suggesting that there's no requisite for an augmented pre-dialysis BP to avoid IDH. Intriguingly, in our research, while the mean BP during hemodialysis aligned with the recommended BP guideline of 140/90 mmHg for hemodialysis, post-dialysis BP in clinical practice was markedly higher than anticipated. Our findings underscore the need for more rigorous BP management in dialysis clinics to mitigate cardiovascular morbidity.

Compared to the general population, hemodialysis patients typically exhibit higher rates of hypertension and a more frequent occurrence of mild to moderate LV hypertrophy[13], and a greater incidence of ischemic heart disease, all of which contribute to increased cardiovascular morbidity and mortality[13] Beyond these, hemodialysis patients have many other co-morbidities than the general population[14,15]. While Miskulin et al. observed no changes in LV mass despite intensive BP regulation[16], numerous studies have underscored the detrimental consequences of prolonged hypertension, linking it to both cardiovascular and cerebrovascular fatalities. Furthermore, IDH has been shown to not only elevate the rate of cardiovascular hospital admissions but also adversely impact the cognitive abilities of dialysis patients[11].

Dialysis patients often have elevated nocturnal BP, and it's common for them to lack the usual physiological drop in BP during sleep[17]. Nocturnal hypertension is closely associated with mortality. Wang et al. reported that nocturnal hypertension significantly increases the risk of kidney failure and cardiovascular mortality in patients with chronic kidney disease[18]. In ESKD patients, both hypertension and sympathetic tones are elevated. Due to increased vascular resistance, these patients often exhibit markedly higher nocturnal hypertension. Additionally, a higher incidence of depression in these patients can lead to sleep disturbances, further contributing to nocturnal hypertension[19]. Li et al. found that nocturnal BP is associated with pulse wave velocity in dialysis patients[20]. In our study, there was no statistically significant difference in daytime and nighttime BP between the IDH and non-IDH groups.

This study's strength lies in its presentation of BP readings for hemodialysis patients' post-dialysis sessions and its documentation of the prevalence of nocturnal hypertension in Korean ESKD patients. Surprisingly, the real-world post-dialysis BP was higher than anticipated, even when regulated during the dialysis session. Additionally, these patients did not exhibit a BP drop during sleep. While it remains uncertain if rigorous BP management during dialysis can enhance nocturnal BP regulation, the resting BP in dialysis clinics should be adjusted to be below the current BP guideline. Yet, concerns about IDH might persist as a challenge when enforcing intensive BP control. In our research, IDH correlated with lower BUN levels both before and after dialysis. A significant finding was the reduced serum albumin concentrations, known to be intricately linked to malnutrition[21]. Thus, there's an imperative to concentrate on elevating the nutritional status of patients to prevent IDH.

There are several limitations to this study. Firstly, we couldn't definitively determine the relationship between IDH, nocturnal BP, and cardiovascular complications, including LVH, morbidity, and ischemic heart disease, in the patients.

This uncertainty may arise because only a limited number of patients consented to undergo ABPM post-dialysis. Many patients on dialysis fear arm pain, dislike frequent BP measurements[22], and technically cannot continue ABPM the day following hemodialysis. Future studies with larger numbers of patients could reveal further precise data on ABPM. Secondly, based on our review of patients' sleep during the ABPM analysis, most patients complained of sleeping disturbance during nocturnal BP measurements. Although the general population also feels a disturbance in nocturnal BP monitoring, as large numbers of dialysis patients have sleeping disturbances, nocturnal BP of ESKD might be higher than expected. Buren et al. observed that an elevated intra-dialytic BP correlated with increased post-dialysis BP using a 44-hour ABPM[23]. If we had designed two days of ABPM which were technically difficult and hard to get informed consent, we would have found the difference between HD day and the next day and could have discovered more reliable sleeping BP. Thirdly, we found that the IDH group had higher delta-SBP, and controlling dialysis SBP is important for decreasing intra-dialytic BP changes. However, as delta-SBP itself includes intra-dialytic hypotension, delta-SBP might be a correlation, not a risk of IDH. Lastly, we couldn't compare the differences and effects among the classes of anti-hypertensive medication and BP changes based on their action time. Patients on dialysis often require higher doses of anti-hypertensives, complicating the task of solving the details of hypertension treatment. Future comprehensive, controlled trials might better elucidate the variances in dialysis BP resulting from different medications.

CONCLUSIONS

In conclusion, our research revealed significant elevations in post-dialysis BP among Korean hemodialysis patients, despite adhering to existing clinical guidelines during dialysis sessions. Additionally, the lack of a nocturnal BP dip indicates heightened cardiovascular risks for these individuals. This emphasizes the importance of more rigorous BP management after HD, while also considering the complexities of IDH.

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Disclosure

The authors have no potential conflicts of interest to disclosure.

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Case Report

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Osmotic Demyelination Syndrome in a High-Risk Patient Despite Cautious Correction of Hyponatremia

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Hyponatremia is a common electrolyte disorder requiring careful management to prevent severe complications. Osmotic demyelination syndrome (ODS) is a serious neurological disorder that can develop from rapid correction of hyponatremia. Herein, is a description of the case of a 61-year-old man with multiple risk factors, including alcoholism, hypokalemia, malnutrition, and alcoholic liver cirrhosis, who developed ODS despite adherence to the recommended correction rate for hyponatremia. The patient presented to the emergency department with generalized weakness, gait disturbance, and decreased muscle strength. Initial laboratory investigations revealed severe hyponatremia, hypokalemia, and dehydration. The patient was treated with cautious correction of the hyponatremia below 8 mmol/L per day. However, on the seventh hospital day, he developed tremors, rigidity, and decreased consciousness and was diagnosed with osmotic demyelination syndrome. Despite receiving general supportive care, desmopressin, and dextrose 5% in water to reduce the serum sodium levels, the patient did not show significant improvement and was transferred to a nursing home for long-term conservative care on day 35 of hospitalization. This case report highlights the challenges associated with the diagnosis and management of osmotic demyelination syndrome and the importance of identifying patients at high risk of developing this neurological disorder.

Key Words: Alcoholism, Hypokalemia, Hyponatremia, Malnutrition, Osmotic demyelination syndrome

INTRODUCTION

Hyponatremia is a common electrolyte disorder requiring careful management to prevent severe complications. Osmotic demyelination syndrome (ODS) is a serious neurological disorder that can occur because of rapid correction of hyponatremia. This condition was first described in 1959[1]. Since then, significant advances have been made in our understanding of its pathophysiology, diagnosis, and treatment. The diagnosis and management of ODS are challenging, and there is a lack of consensus regarding optimal management strategies. However, both American and European guidelines on hyponatremia emphasize the importance of cautious correction of hyponatremia to prevent ODS. The American Expert Panel recommends that the rate of correction should not exceed 8 mmol/L in any 24-hour period for individuals at high risk of ODS[2], while the European Clinical Practice Guidelines recommend a maximum correction rate of 10 mmol/L within the first 24 hours, followed by a maximum of 8 mmol/L every 24-hour period thereafter[3]. The recently published Korean Society of Nephrology recommendation for hyponatremia similarly suggests that serum sodium concentrations should not be corrected above 10 mmol/L per day, with a stricter limit of 8 mmol/L per day for patients at high risk of ODS[4]. As aforementioned, rapid correction of hyponatremia is the primary mechanism underlying the development of ODS. However, certain patient conditions can increase the risk of developing this neurological disorder, in-

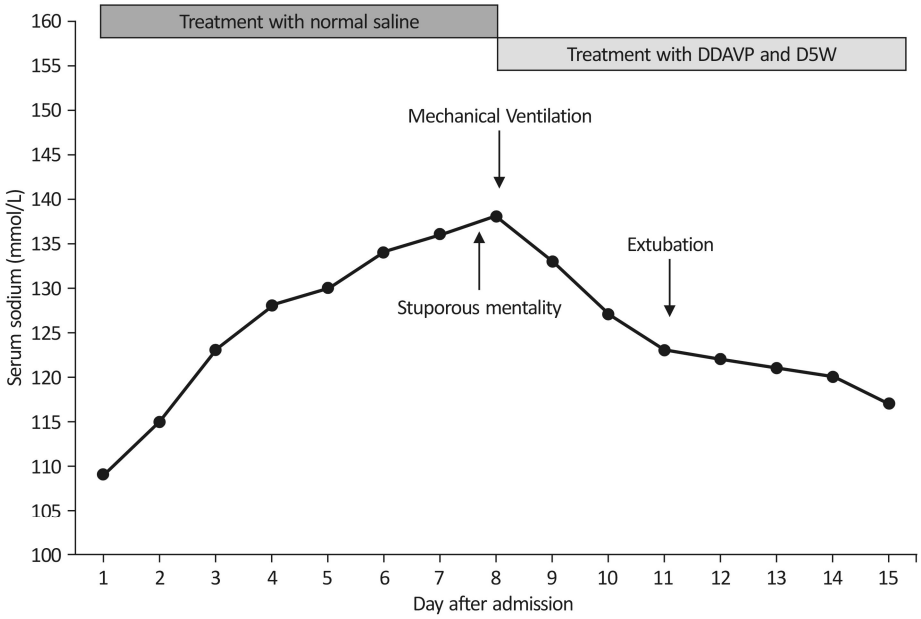

Fig. 1. Clinical course of high-risk patient treated for hyponatremia that later developed Osmotic Demyelination Syndrome.

cluding serum sodium levels <105 mmol/L, hypokalemia, alcoholism, malnutrition, and advanced liver disease[5,6]. In this case report, we present the case of a patient with multiple risk factors who developed ODS despite adherence to the guidelines mentioned above during the correction of hyponatremia.

CASE REPORT

A 61-year-old man presented to the emergency department with symptoms of generalized weakness and gait disturbance that began several days prior to his admittance. He had a medical history of alcoholic liver cirrhosis and hypertension and was taking hydrochlorothiazide 12.5 mg/day. A week prior to admission, he was consuming alcohol daily, without eating any food and only drinking water.

On examination, he appeared systemically malnourished and dehydrated, with a blood pressure of 90/60 mmHg. He was drowsy and confused. The patient had decreased muscle strength in the extremities; however, no other neurological abnormalities were observed.

Initial laboratory investigations revealed a serum sodium level of 109 mmol/L (normal range, 136-145 mmol/L), serum osmolality level of 223 mosm/kg (normal range, 275-300 mosm/kg), serum potassium level of 2.2 mmol/L (normal range, 3.5-5.1 mmol/L), blood urea nitrogen level of 9.1 mg/dL (range, 6-24 mg/dL), serum creatinine level of 0.58 mg/dL (range, 0.74-1.35 mg/dL), urine sodium level of 10 mmol/L (normal range, 40-220 mmol/L), and urine osmolality level of 153 mosm/kg (normal range, 300-800 mosm/kg) (Fig. 1). Based on physical examination findings and abnormally low serum creatinine and urinary sodium levels, it was concluded that his overall nutritional status was poor.

The patient was admitted to the intensive care unit (ICU). Hyponatremia was corrected by discontinuing the hydrochlorothiazide and administering isotonic saline intravenously. The infusion rate was adjusted to correct the sodium levels by no more than 8 mmol/L within the first 24 hours, with a final correction of 6 mmol/L. Subsequently, the correction rate did not exceed 8 mmol/L per day.

On the fifth day of admission, he regained lucidity and mobility and was transferred to the general ward. However, on the seventh day after admission, the patient developed generalized tremors and rigidity. His level of consciousness decreased to a stuporous state and he began to hyperventilate. Upon examination, the patient showed bilateral hyperreflexia, but no Babinski sign or clonus was observed. The patient was transferred to the ICU and required intubation and

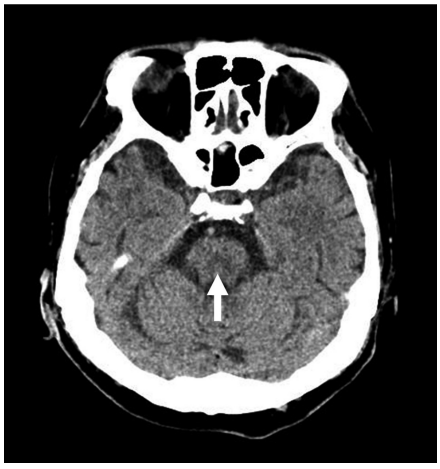

Fig. 2. Initial brain computed tomography of patient being treated for hyponatremia shows ill-defined patch hypodense lesion (arrow) at the pons.

mechanical ventilation.

Further imaging tests revealed hypodense shading of the pontine on computed tomography of the brain (Fig. 2). T2 hyperintense signal in the central pons on brain MRI was indicative of central pontine myelinolysis (Fig. 3). OSD was diagnosed based on the evaluation of clinical and radiological findings.

After diagnosis, he received general supportive care and was treated with desmopressin and dextrose 5% in water to reduce his serum sodium levels. Over the next three days, his serum sodium level decreased by 15 mmol/L, and his breathing stabilized, allowing for the removal of mechanical ventilation and intubation. His level of consciousness improved enough to allow him to follow simple commands; however, the rigidity and tremors remained unchanged. His serum sodium level decreased for three more days, but his condition did not improve. Therefore, relowering therapy was discontinued and he was initiated on rehabilitation and supportive care. The patient was eventually transferred to a nursing home for long-term conservative care on day 35 of hospitalization.

DISCUSSION

During the acute phase of hyponatremia, the brain undergoes a two-step adaptation to hypovolemia. Initially, extracellular fluid moves into brain cells, primarily astrocytes,

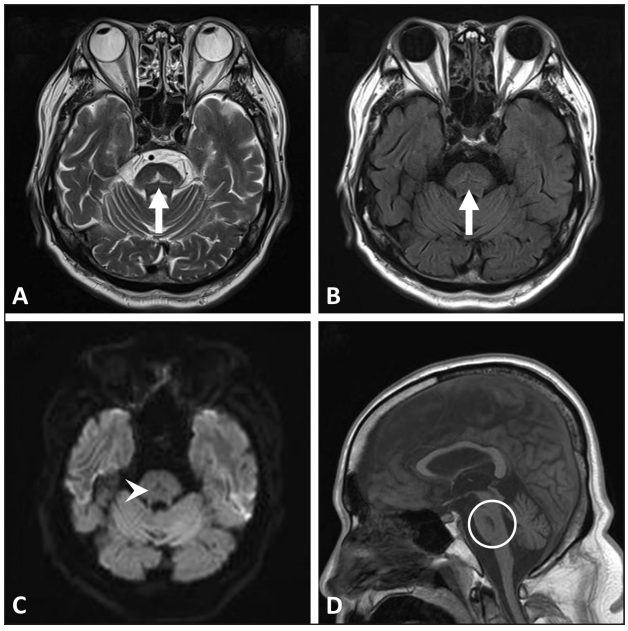

Fig. 3. Brain MRI of the patient being treated for hyponatremia shows triangular high SI lesion that looks like a small lambda symbol (arrow) in the central pons on the T2-weighted image (**A**) and FLAIR image (**B**), and there is diffusion restriction (arrowhead) (**C**). T1-wighted sagittal image reveals low SI lesion (circle) in the pons (**D**). FLAIR: fluid attenuated inversion recovery, MRI: magnetic resonance image, SI: signal intensity.

which raises the hydrostatic pressure in the interstitium and causes the extracellular fluid to move through the cerebrospinal fluid into the systemic bloodstream[7]. If hyponatremia persists for more than three hours, brain cells release intracellular substances such as potassium and organic solutes. If hyponatremia lasts longer, astrocytes release other organic substances (osmolytes), such as phosphocreatine, myoinositol, glutamine/glutamate, and taurine, and the adaptation is completed in approximately 2 days[8]. Through this process, brain cells can eliminate excess water and attain the same tonicity as plasma, preventing a significant increase in cell water, thereby protecting against cerebral edema.

However, once the brain has adapted to hypotonicity, the rate of correction of hyponatremia becomes important, and a rapid correction can lead to ODS. The mechanism underlying ODS is uncertain; however, it has been hypothesized to be related to the downregulation of sodium-coupled amino acid transporters in astrocytes exposed to hypotonicity[9]. This delays the reuptake of osmolytes into as-

trocytes and renders them unable to keep up with changes in the tonicity o the extracellular fluid. This temporal imbalance can lead to brain dehydration, astrocyte and oligodendrocyte death, and subsequent disruption of the blood-brain barrier.

Astrocytes experience hyperosmotic stress during the correction of chronic hyponatremia, as they strive to compensate for increased extracellular osmolality to prevent excessive cell shrinkage, damage, and cell death by transporting myo-inositol and glutamine/glutamate back into the cell. Patients with a history of alcoholism or malnutrition may have chronic deficiencies in substrates, such as phosphate, amino acids, glucose, potassium, and magnesium, which can hinder their ability to mount an adequate compensatory response. Furthermore, these patients are unable to maintain the activity of the Na^+/K^+-ATPase pump because of a decrease in energy supply[10]. Patients with cirrhosis, hepatic encephalopathy, and chronic hyponatremia experience a significant depletion of brain myoinositol stores[11]. This suggests that patients with cirrhosis may be more vulnerable to ODS. Other risk factors related to ODS are serum sodium at presentation below 105 mmol/L and a longer duration of hyponatremia over 2 days.

The patient in this case report had four risk factors for ODS: alcoholism, malnutrition, alcoholic liver cirrhosis, and hypokalemia. Despite following the US and European guidelines, the patient developed ODS and suffered irreversible brain damage. This highlights the importance of not only an appropriate correction rate for hyponatremic patients with multiple risk factors but also a close observation of clinical signs suggestive of ODS. There have been reports of ODS in patients with normonatremia or hypernatremia [12-15], all of whom had at least one of the above risk factors, suggesting that the primary cause of the patient's ODS is related to the underlying conditions rather than the correction rate of hyponatremia.

ODS symptoms can vary widely, ranging from asymptomatic to severe, and include lethargy, dysarthria, ophthalmoplegia, ataxia, confusion, and coma depending on the location of demyelination. Distinguishing these symptoms from those associated with alcohol withdrawal syndrome can be challenging, so close monitoring of patients for the development of neurological symptoms is essential, even if hyponatremia is being corrected at an adequate correction rate.

Although ODS has no known effective treatment and has a high mortality rate, recent research has shown that aggressive supportive care can improve outcomes. A study followed 36 cases of ODS in the ICU for one year and reported that 25 (69%) survived, with 14 (56%) experiencing only minimal neurological deficits[16]. Therefore, aggressive supportive care should be provided during the diagnosis. Several case reports have described the effectiveness of relowering therapy with desmopressin and dextrose 5% in water early after ODS diagnosis[17]. In this case, relowering therapy was attempted, and although the patient did not fully recover, he was successfully weaned off the mechanical ventilation.

In conclusion, although ODS is typically associated with rapid correction of hyponatremia, this case illustrates that it can occur even with slow correction, particularly in patients with multiple risk factors. Healthcare providers should be aware of this possibility and maintain a high index of suspicion of ODS, as prompt diagnosis and aggressive supportive care can improve outcomes. It is important to remember that ODS has a high mortality rate and can cause long-term neurological deficits. Prevention through careful monitoring and management of serum sodium levels is crucial in high-risk patients.

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Fatal Hypermagnesemia in Patients Taking Magnesium Hydroxide

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Hypermagnesemia is a rare but potentially fatal electrolyte disorder often overlooked because of its unfamiliarity. Magnesium is regulated through a balance of bone, intestinal absorption, and renal excretion. Hypermagnesemia typically arises from excessive magnesium intake or reduced renal excretion; however, it also occurs in patients with normal kidney function. Herein, we report two cases of hypermagnesemia in patients taking magnesium hydroxide for constipation. The first case involved an 82-year-old woman with end-stage renal disease who developed metabolic encephalopathy due to hypermagnesemia, after taking 3,000 mg of magnesium hydroxide daily for constipation. Her magnesium level was 9.9 mg/dL. Her treatment involved discontinuing magnesium hydroxide and continuing hemodialysis, which led to her recovery. In the second case, a 50-year-old woman with a history of cerebral hemorrhage and mental retardation developed hypermagnesemia despite having normal renal function. She was also taking magnesium hydroxide for constipation, and her magnesium level was 11.0 mg/dL. She experienced cardiac arrest while preparing for continuous renal replacement therapy (CRRT). After achieving return of spontaneous circulation, CRRT was initiated, and her magnesium level showed a decreasing trend. However, vital signs and lactate levels did not recover, leading to death. These cases highlight the importance of prompt diagnosis and intervention for hypermagnesemia and the need to regularly monitor magnesium levels in individuals receiving magnesium-containing preparations, especially those with impaired kidney function.

Key Words: Hypermagnesemia, Magnesium hydroxide, Chronic kidney disease, End stage renal disease

INTRODUCTION

Hypermagnesemia is a rare electrolyte disorder that has received little attention recently. This condition arises when the balance between bone and intestinal absorption and renal excretion of magnesium, similar to that of calcium and phosphorus, is disrupted[1]. Hypermagnesemia typically occurs iatrogenically due to excessive oral or intravenous magnesium intake, especially when renal function is compromised, thereby reducing magnesium excretion[2,3].

The symptoms of hypermagnesemia may vary widely, from nausea and vomiting to altered mental status, hypotension, and hypoventilation. In some cases, it may be fatal[4]. Diagnosis is usually based on laboratory findings during the evaluation process rather than on suspected symptoms.

Treatment strategies include hydration, loop diuretics, hemodialysis, and calcium administration[5]. This paper presents the cases of two patients who were admitted to the hospital with altered mental status and subsequently diagnosed with hypermagnesemia. Both patients had a history

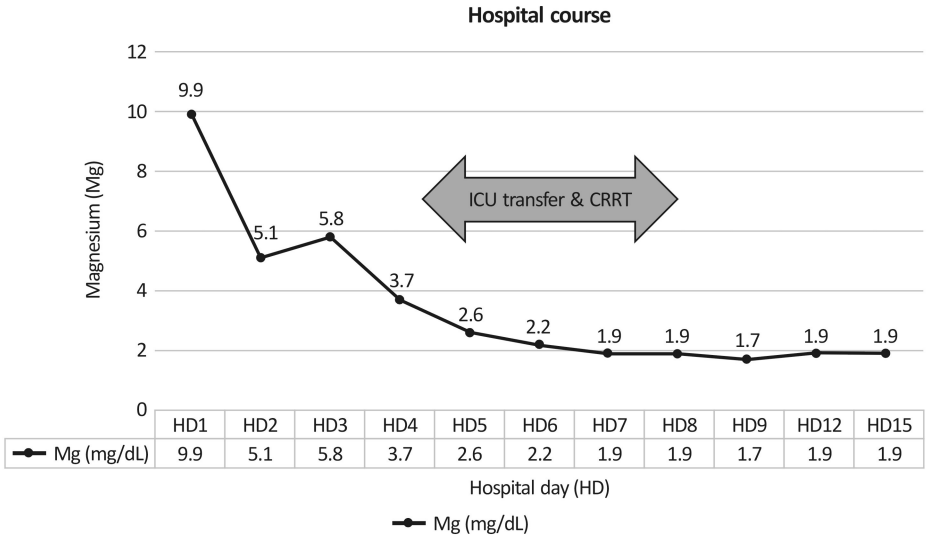

Fig. 1. Changes in magnesium levels during the hospitalization period.

of magnesium-containing laxative use.

CASE REPORT

Case 1.

An 82-year-old woman was transferred to our hospital due to an altered mental status that occurred 4 hours previously. She had undergone hemodialysis for end-stage renal disease and had a medical history of hypertension, diabetes mellitus, and percutaneous coronary intervention. She had constipation and was taking 3,000 mg of magnesium hydroxide daily for 2 weeks. Her vital signs were stable; however, she presented with stuporous mental status, and we conducted a neurological evaluation. Brain computed tomography (CT), electroencephalography, and cerebrospinal fluid examination showed no specific findings; brain magnetic resonance imaging (MRI) showed small chronic infarctions in the right frontal lobe, thalamus, occipital lobes, and cerebellar hemispheres but these were not associated with decreased consciousness. The laboratory test results were as follows: white blood cell count, 11,200/mm^3; hemoglobin, 14.8 g/dL; platelet count, 145,000/mm^3; blood urea nitrogen, 51.8 mg/dL; serum creatinine, 4.24 mg/dL; sodium, 147 mEq/L; potassium, 4.8 mEq/L; calcium, 9.9 mg/dL; and magnesium, 9.9 mg/dL. Based on these results, we concluded that the metabolic encephalopathy was due to hypermag- nesemia.

We immediately discontinued magnesium hydroxide, performed hemodialysis daily, and monitored magnesium levels. By the 4th day of hospitalization, the magnesium level had decreased to 3.5 mg/dL, and mental status had improved to drowsy. However, the blood pressure decreased to 72/44 mmHg due to septic shock. Consequently, she was promptly transferred to the intensive care unit (ICU), and continuous renal replacement therapy (CRRT) was initiated. The patient's blood pressure was restored through antibiotic treatment for pneumonia and Clostridium difficile infection. Her magnesium level improved to 1.9 mg/dL (Fig. 1), leading to a significant improvement in her consciousness, reaching an alert state. The patient was discharged from the hospital on the 16th day after admission.

Case 2.

A 50-year-old woman was admitted to the hospital with complaints of continuous vomiting and loss of consciousness that occurred 2 hours previously. She had a history of cerebral hemorrhage 2 years before presentation and mental retardation. She resided in a nursing home for care.

The patient was taking magnesium hydroxide for constipation; however, the exact dose was unknown. The initial blood pressure was 80/40 mmHg; heart rate was 124 beats/min; respiratory rate was 24 breaths/min; and oxygen satu-

ration was 74%. The patient was in a stuporous mental state, and intubation was immediately performed. The laboratory test results were as follows: white blood cell count, 8,800/mm^3; hemoglobin, 14.3 g/dL; platelet count, 128,000/mm^3; blood urea nitrogen, 19.9 mg/dL; serum creatinine, 1.07 mg/dL; sodium, 136 mEq/L; potassium, 3.9 mEq/L; total calcium, 9.5 mg/dL; magnesium, 11.0 mg/dL; lactate, 8.49 mmol/L; pH 7.201; and HCO_3- 15.9 mmol/L. Brain CT and brain MRI were performed to evaluate the patient's level of consciousness, and no significant findings were revealed. Abdominal CT revealed fecal impaction and diffuse colorectal dilatation (Fig. 2). Despite a normal renal function, the findings indicated impaired magnesium excretion and enhanced magnesium absorption, raising the possibility of hypermagnesemia. The patient was admitted to the ICU scheduled to undergo CRRT. However, a cardiac arrest occurred during the initiation of CRRT, requiring cardiopulmonary resuscitation (CPR). Return of spontaneous circulation was achieved, and CRRT was subsequently initiated. While the magnesium levels showed improvement, reaching 3.3 mg/dL (Fig. 3), blood pressure did not recover, lactate levels continued to increase, and the patient eventually died.

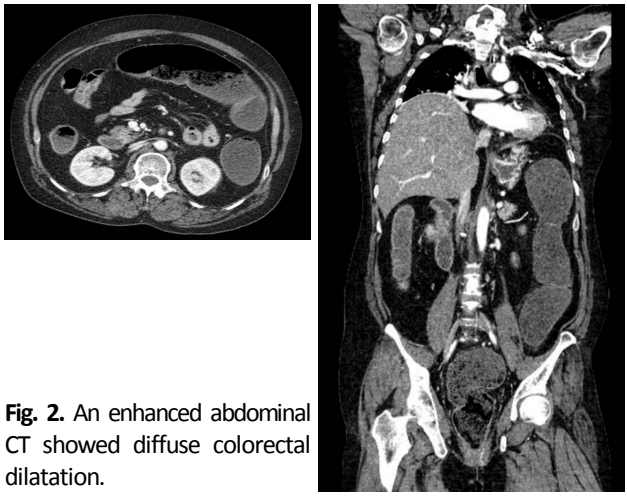

Fig. 2. An enhanced abdominal CT showed diffuse colorectal dilatation.

DISCUSSION

Magnesium is the fourth most abundant cation in the body[6] and is vital for numerous biological processes. Its balance is maintained through bone storage, intestinal absorption, and renal excretion. Disruption of magnesium balance may lead to hypermagnesemia, a rare but potentially fatal condition. Magnesium predominantly exists intracellularly within the bone, muscle, and soft tissue[1]. Approximately 50-60% of magnesium is sequestered in the bone as hydroxyapatite crystal[7]. Only a small fraction of magnesium is stored in the extracellular compartment, approximately 60% of which exists in the biologically active, free form[8]. The normal serum magnesium concentration is 1.7-2.4 mg/dL[6]. Magnesium plays a crucial role in preserving the normal

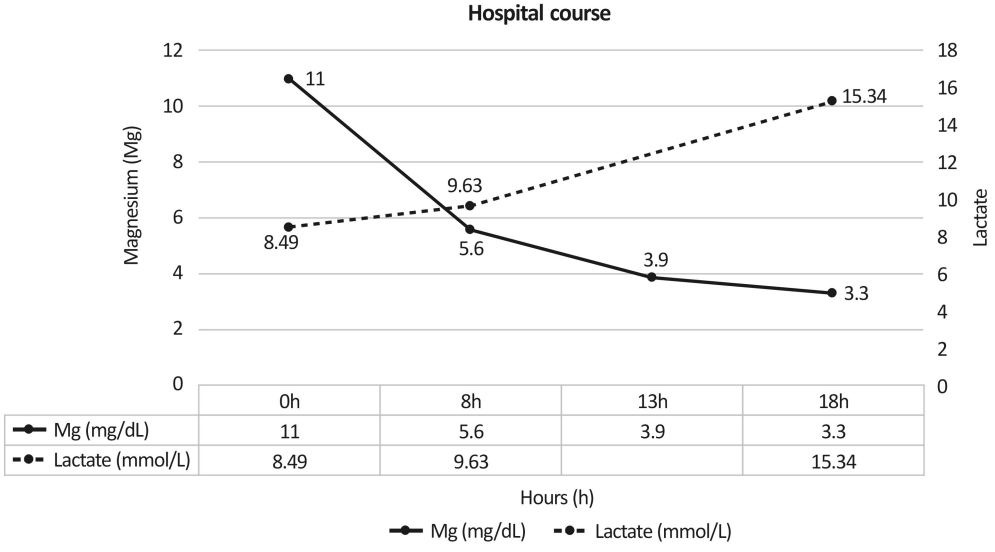

Fig. 3. Changes in magnesium and lactate levels during the hospitalization period.

Table 1. Case reports of hypermagnesemia

	Patient information	Symptoms & Signs	Peak Mg level (mg/dL)	Cause	Treatment	Outcome
Yamaguchi et al.[2]	88-year-old female	Appetite loss, progressive general weakness	6.9	Magnesium oxide in a patient with chronic kidney disease	Hydration, IV loop diuretics, IV Ca gluconate	Survived
	95-year-old female	Altered mental state	6.1	Magnesium oxide in a patient with chronic kidney disease	Hydration, IV loop diuretics	Survived
	87-year-old female	Appetite loss, lethargy	7.6	Magnesium oxide in a patient with chronic kidney disease	Hydration	Survived
	66-year-old female	Altered mental state, hypotension	11.9	Magnesium oxide in a patient with acute colonic ischemia and intestinal perforation	Hydration (Refuse invasive therapy, hemodialysis)	Died
Ishida et al.[14]	56-year-old female	Vomiting, abdomen distension → Altered mental state, hypotension	13.5	Magnesium oxide intake in a patient with intestinal obstruction	Hydration, IV loop diuretics, IV calcium	Survived
Bokhari et al.[15]	53-year-old female	Altered mental state, hypotension, respiratory distress	10.8	Magnesium oxide and magnesium citrate intake in a patient with prolonged colonic retention	Hemodialysis	Died
Weng et al.[16]	72-year-old female	Altered mental state, general weakness → cardiac, respiratory arrest	6.2	Magnesium oxide intake in a patient with chronic constipation and prolonged colonic retention	Hemodialysis, IV calcium, GI decontamination (lactulose, Fleet enema)	Died
Sawalha et al.[17]	73-year-old male	Flaccid paralysis, respiratory distress	9.2	Magnesium citrate and Maalox intake in a patient with pyloric perforation which allowed for increased uptake of magnesium through the inflamed peritoneum	Hydration, IV loop diuretics, Hemodialysis	Survived
Premkumar et al.[18]	42-year-old male	Respiratory distress	8.9 (3.66 mmol/L)	Post-bypass ventricular tachyarrhythmia treated with 1 g IV magnesium sulphate, following earlier 2 g dose post-cross clamp release	Hydration IV loop diuretics IV Ca gluconate Hemodialysis	Survived
Case 1	82-year-old female	Altered mental state	9.9	Excessive magnesium hydroxide intake in ESRD patient	Hemodialysis	Survived
Case 2	50-year-old female	Altered mental state, vomiting, hypotension, respiratory distress → cardiac, respiratory arrest	11.0	Magnesium hydroxide intake in a patient with prolonged gastrointestinal transit time	Hemodialysis	Died

Abbreviations: Mg, magnesium; GI, gastrointestinal; Ca, calcium; ESRD, end stage renal disease

functioning of various biological processes, including protein synthesis, DNA and RNA synthesis, energy production, cardiovascular, and neuromuscular system functioning, and bone formation[9].

Magnesium is predominantly absorbed in the small intestine, particularly in the distal parts of the jejunum and ileum, whereas a portion is absorbed through the large intestine[7]. In general, magnesium is absorbed via the passive paracellular pathway, and the amount absorbed increases with increasing intake concentrations. The transcellular active pathway for magnesium absorption occurs through the transient receptor potential melastatin (TRPM) channels, TRPM6 and TRPM7. However, even with increased magnesium intake, absorption does not occur beyond a certain threshold concentration[9,10].

While the reabsorption of calcium and phosphorus primarily occurs in the proximal convoluted tubule, magnesium reabsorption occurs significantly (40-70%) in the thick

ascending limb of Henle[7,11]. Reabsorption generally occurs via the paracellular pathway, facilitated by tight junctions composed mainly of claudins 16 and 19[12]. Approximately 10-30% of magnesium is reabsorbed through the paracellular pathway in the proximal tubule. The remaining 5-10% is reabsorbed in the distal convoluted tubule predominantly through active transport mediated by TRPM6/7[13]. Hypermagnesemia may occur when this balance is disrupted, such as during increased intake or impaired intestinal elimination, leading to increased absorption or reduced excretion from the kidneys.

In the present cases, both patients developed hypermagnesemia owing to the intake of magnesium-containing laxatives. The first patient was undergoing dialysis and the administration of magnesium hydroxide was initiated for the first time. Typically, magnesium hydroxide is used up to a maximum of 2,000 mg daily. However, this patient consumed 3,000 mg daily for 2 weeks. Given the compromised renal excretion in dialysis patients, it is believed that the extended and excessive use of magnesium hydroxide led to the development of hypermagnesemia. In the second case, the patient was presumed to have been on continuous magnesium hydroxide therapy, but hypermagnesemia occurred despite a relatively preserved renal function, possibly due to a prolonged gastrointestinal transit time, leading to increased absorption. Table 1 summarizes other case reports of hypermagnesemia.

When magnesium levels increase above 5 mg/dL, symptoms such as nausea, vomiting, and dizziness may occur. When magnesium levels exceed 9 mg/dL, deep tendon reflexes diminish, and manifestations may progress to bradycardia, hypotension, hypoventilation, mental changes, respiratory arrest, and even cardiac arrest[14,15]. In the first case, although the other vital signs were stable, there was a change in consciousness. In the second case, the patient experienced hypotension, respiratory failure, and altered consciousness, leading to cardiac arrest during the planned CRRT procedure. Eventually, the magnesium levels showed a downward trend, but the patient succumbed to lactic acidosis and deceased. This highlights the potentially fatal nature of hypermagnesemia and emphasizes the importance of prompt diagnosis and intervention.

The treatment of hypermagnesemia depends on kidney dysfunction and symptom severity. It includes discontinuing causative medications, promoting magnesium excretion through hydration and loop diuretics, or dialysis in severe cases[14]. Calcium administration is necessary to address symptoms, such as hypotension, respiratory depression, and arrhythmias. Caution must be exercised during intermittent hemodialysis to prevent rebound hypermagnesemia. In these situations, CRRT may be beneficial[15]. In the present cases, as both patients had impaired kidney function and severe symptoms, dialysis was performed for both.

In conclusion, although uncommon, hypermagnesemia may be fatal, emphasizing the importance of an early diagnosis and prompt intervention. Regular monitoring of magnesium levels is crucial in patients receiving magnesium-containing preparations, especially in those with impaired kidney function.

Disclosure

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Pseudo-Gitelman Syndrome Presenting with Hypokalemic Metabolic Alkalosis and Hypocalciuria

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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.

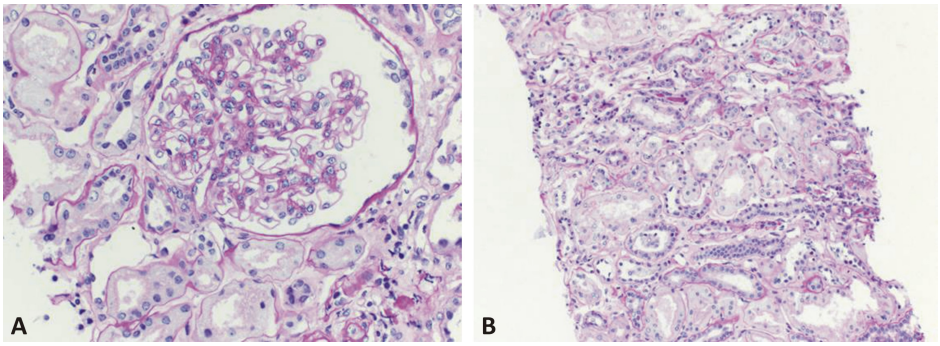

Fig. 1. The kidney biopsy findings in Case 2. The high power image reveals that there were no remarkable morphological changes in the glomeruli (**A**). The image with low power reveals that mild interstitial fibrosis was associated with moderate degrees of tubular atrophy and interstitial inflammation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

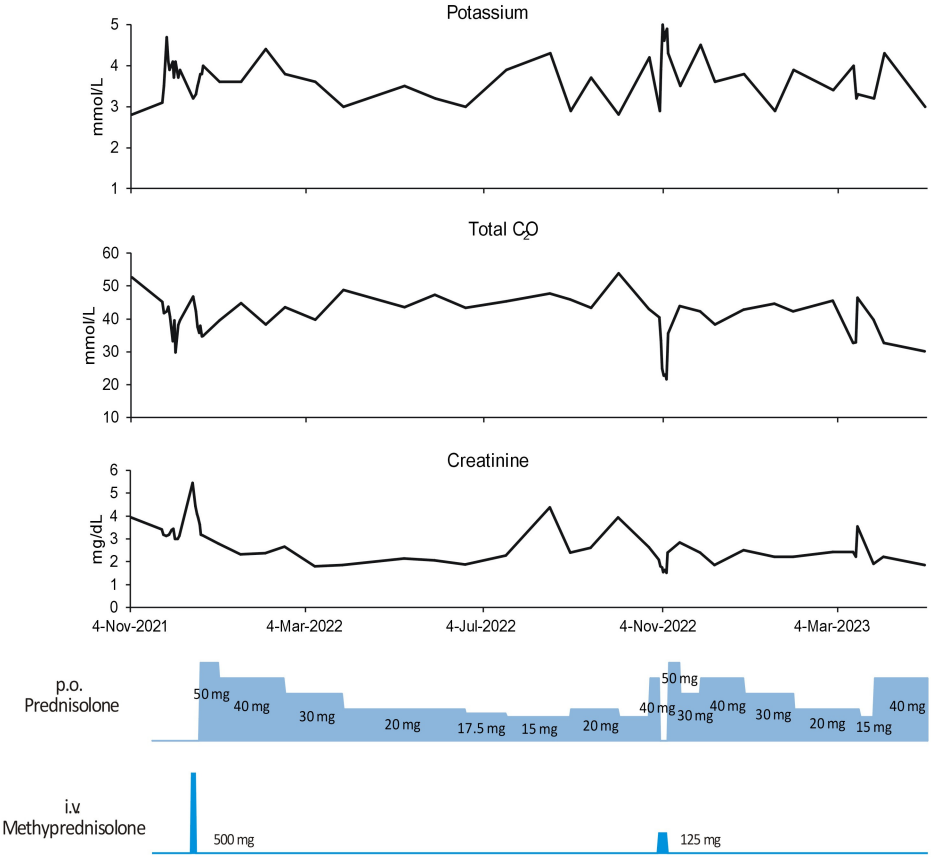

Fig. 2. The course of hypokalemic metabolic alkalosis and azotemia in Case 2. Changes in serum potassium, total CO_2, and creatinine levels in response to glucocorticoid therapy are shown.

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

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