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Gitelman's Syndrome with Vomiting Manifested by Severe Metabolic Alkalosis and Progressive Renal Insufficiency

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Gitelman's syndrome is an autosomal recessive salt-losing tubulopathy showing hypokalemic hypomagnesemic hypocalciuria with metabolic alkalosis and hyperreninemic hyperaldosteronism. This syndrome is caused by mutations in the *SLC12A3* gene that encodes sodium-chloride cotransporter expressed at the apical membrane of renal distal convoluted tubule. Symptoms and renal outcomes of Gitelman's syndrome are, in general, mild and benign, and renal insufficiency from Gitelman's syndrome associated with long-standing hypokalemia and volume depletion is extremely rare. Herein, we report a 27-year-old male patient with Gitelman's syndrome who manifested renal failure, hypokalemia, severe metabolic alkalosis and altered mentality. About one year ago, the patient had been transferred to Seoul National University Hospital, because of unsolved hypokalemia, and was diagnosed as Gitelman's syndrome by clinical features and genetic analysis of the *SLC12A3* gene. The patient carries a missense mutation at one allele of *SLC12A3* gene (c.781C>T, p.Arg261Cys). His mother is also heterozygous for the same mutation and she had a history of hypokalemia. On this admission, the patient had recurrent bouts of vomiting induced by psychiatric eating disorder and showed severe volume depletion with hypotension, azotemia and metabolic alkalosis. Intense hydration therapy and emergency hemodialysis transiently improved his fluid-electrolyte imbalance and renal function. However, renal dysfunction progressively deteriorated despite the medical treatment. Our findings suggest that even in Gitelman's syndrome, constant monitoring for volume status and other comorbid conditions should be employed to prevent progressive renal injury.

Keywords: acid-base imbalance; Gitelman's syndrome; hypokalemia; renal insufficiency; vomiting
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Introduction

Gitelman's syndrome is an autosomal recessive salt-losing tubulopathy that is initially reported by Gitelman et al. (1966). This relatively uncommon syndrome is characterized by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria, and hyperreninemic hyperaldosteronism. This syndrome is usually caused by loss-of-function mutations in the *SLC12A3* gene on chromosome 16 that encodes the renal thiazide-sensitive sodium-chloride cotransporter (Simon et al. 1996). This transporter, which is expressed at the apical membrane of renal distal convoluted tubule, reabsorbs sodium and chloride, and is blocked by thiazide diuretics (Knoers and Levtchenko 2008).

The clinical characteristics of Gitelman's syndrome are usually mild compared to Bartter's syndrome that is caused by mutations of genes encoding ion transporters expressed in the thick ascending limb and is characterized by hypokalemic metabolic alkalosis, normal to low blood pressure, polyuria, dehydration, normomagnesemia, and hypercalciuria (Amirlak and Dawson 2000). Patients with Bartter's syndrome present in early childhood with severe clinical course, showing edema, growth retardation, polyuria and hearing loss (Onem et al. 2008; Fremont and Chan 2012). Gitelman's syndrome usually manifests itself in adults, and patients can sustain normal life with excellent long-term prognosis (Cruz et al. 2001; Knoers 2006; Knoers and Levtchenko 2008). A few cases of chronic renal failure were reported in patients with Bartter's syndrome (Birkenhager et al. 2001; Jeck et al. 2001; Brochard et al. 2009), but in case of Gitelman's syndrome the renal function is usually maintained despite long-standing hypokalemia, renin-angiotensin activation, and low blood pressure. There are only two cases of chronic renal failure associated with Gitelman's syndrome reported in international literature (Bonfante et al. 2001; Calo et al. 2003).

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Here, we report a patient with Gitelman's syndrome who manifested severe metabolic alkalosis with progressive renal insufficiency and episode of acute kidney injury.

Clinical Report

On August 2010, a 27-year-old Korean man was admitted via emergency room because of drowsy mentality. The patient vomited repeatedly for two days and showed decreased urine output with progressive drowsy mentality.

About one year ago, this patient was transferred to Seoul National University Hospital because of hypokalemia, nocturia, weight loss, and decreased renal function. He denied taking herbal medicine, diuretics or laxatives. Initially, the patient denied alcohol ingestion or frequent vomiting, but eventually he admitted excessive drinking and vomiting. His mother also had a history of hypokalemia.

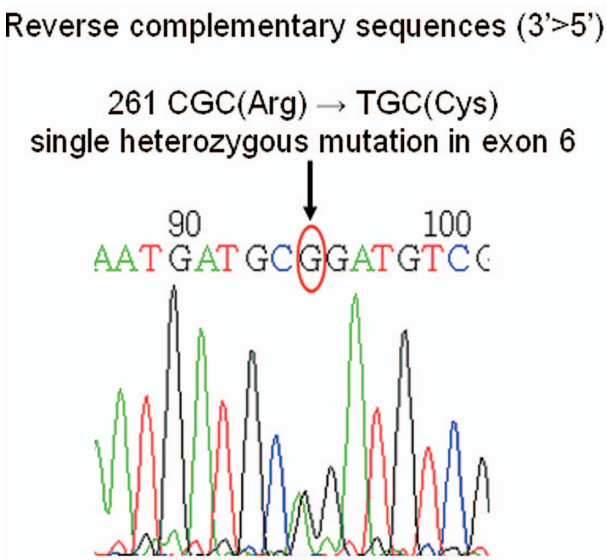

Fig. 1. *SLC12A3* mutation analysis of the patient.
The patient carries a single heterozygous mutation at 261 CGC codon in exon 6, which leads to conversion of arginine to cysteine.

Two months later, he was admitted for further evaluation. On examination, his blood pressure was 100/60 mmHg, serum sodium 139 mmol/L, potassium 3.1 mmol/L, total carbon dioxide 41 mmol/L, magnesium 0.95 mmol/L, and creatinine 4.6 mg/dL. Amount of daily urinary calcium excretion was 59 mg/day. After replacement of normal saline and potassium, his creatinine level improved to 2.3 mg/dL. Genomic analysis was performed by direct DNA sequencing after amplification of all coding 26 exons and flanking introns, and revealed a missense mutation at one allele of *SLC12A3* gene (c.781C>T, p.Arg261Cys) (Fig. 1) (Ji et al. 2008). His mother had also been genotyped for *SLC12A3* and had the same heterozygous mutation. His father and sister had normal serum potassium levels without relevant symptoms of electrolyte disorders. Mutation analysis for *SLC12A3* gene was not performed in them. Kidney biopsy showed focal ischemic glomeruli and focal tubulointerstitial inflammation with fibrosis (Fig. 2). Psychiatric consultation concluded bipolar disorder with eating problem. After discharge, his renal function fluctuated according to his volume status.

On this admission, the patient's height was 184 cm, body weight was 47.5 kg, blood pressure was 96/60 mmHg and heart rate was 58 beats/min. Blood chemistry showed sodium 132 mmol/L, potassium 3.5 mmol/L, chloride 50 mmol/L, magnesium 0.8 mmol/L, blood urea nitrogen 53 mg/dL and creatinine 11.7 mg/dL. Arterial blood gas analysis revealed pH 7.59, pCO_2 72.6 mmHg, pO_2 37.4 mmHg, and bicarbonate 67.6 mmol/L. Spot urine sodium concentration was 61 mmol/L, potassium 73.6 mmol/L, chloride 15 mmol/L, and creatinine 50.8 mg/dL despite severe volume depletion. Patient's laboratory data is summarized in Table 1. He was transferred to intensive care unit, and vigorous volume replacement with normal saline (3-4 L/day) was done with potassium and calcium supplementation. Hemodialysis was performed consecutively for the first two days. Drowsy mentality improved on the next day of admission. On the 4th day of admission, his body weight increased to 56.3 kg and serum creatinine level decreased to 4.9 mg/dL. His serum sodium was 135 mmol/L, potassium

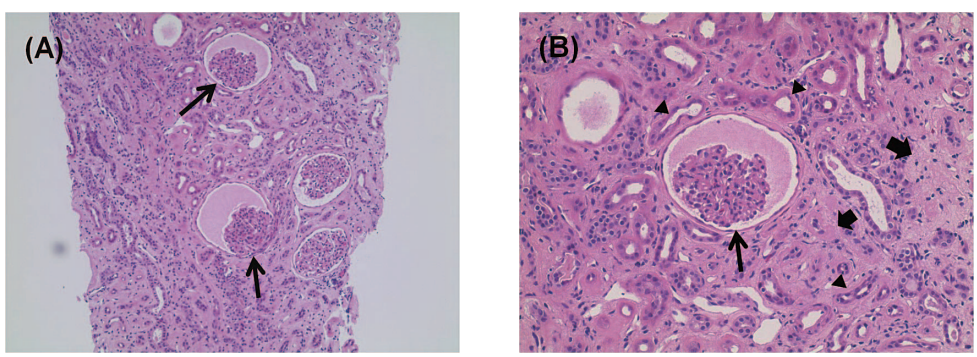

Fig. 2. Light microscopic findings of kidney biopsy.
(A) Glomeruli were normal-sized and focally hypercellular involving mesangial cells. Characteristic lesions of ischemic collapse (depicted with arrows) were observed in 7 glomeruli (26.9%). (B) Mild tubular atrophy (depicted with wedges) and focal moderate interstitial fibrosis (areas depicted with broad arrows) were observed.

Table 1. Summary of the patient's laboratory data.

Variables	Reference range	2 months before admission	On admission	At discharge
Biochemistry				
Sodium (mmol/L)	135-145	141	132	140
Potassium (mmol/L)	3.5-5.5	2.7	3.5	4.4
Chloride (mmol/L)	98-110	84	50	97
Total carbon dioxide (mmol/L)	21-29	44	58	40
Magnesium (mmol/L)	0.75-1.25	1.05	0.80	1.30
Blood urea nitrogen (mg/dL)	10-26	16	53	20
Creatinine (mg/dL)	0.70-1.40	3.70	11.66	3.99
Calcium (mg/dL)	8.8-10.5	9.1	8.7	10.4
Phosphorus (mg/dL)	2.5-4.5	2.4	11.4	3.0
Uric acid (mg/dL)	3.0-7.0	13.3	14.5	7.6
Calcium, ionized (mmol/L)	1.05-1.35	1.02	0.75	N/A
Glucose (mg/dL)	70-110	84	108	98
Arterial blood gas analysis				
pH			7.585	
pCO_2			72.6	
pO_2			37.4	
HCO_3^-			67.6	
Urine chemistry				
Sodium (mmol/L)			61	
Potassium (mmol/L)			73.6	
Chloride (mmol/L)			15	
Creatinine (mg/dL)			50.75	

was 3.1 mmol/L, and chloride was 99 mmol/L with total carbon dioxide 23 mmol/L. Thereafter the patient was treated with continuous intravenous saline (1-2 L/day) and oral potassium chloride (24-121 mmol/day). Total amount of potassium chloride required to maintain normal serum potassium level during 16 days of admission was 1,159 mmol. During the admission, oral intake was encouraged, but he continued habitual vomiting. On the 16th day of admission, he was discharged with body weight of 51.2 kg, serum sodium 140 mmol/L, potassium 4.4 mmol/L, chloride 97 mmol/L, total carbon dioxide 40 mmol/L, and creatinine 4.0 mg/dL.

Discussion

Gitelman's syndrome is a tubulopathy that is characterized by hypokalemic metabolic alkalosis, low blood pressure, hypomagnesemia, and hypocalciuria. Most of these features can be explained by a loss-of-function mutation of thiazide-sensitive sodium-chloride cotransporter of distal tubule of nephron. Patients with Gitelman's syndrome are often asymptomatic (Cruz et al. 2001), or patients may suffer from nocturia and mild neuromuscular symptoms such as paresthesia, cramps, fatigue, and tetany, although severe manifestations such as paralysis, rhabdomyolysis or ventricular arrhythmia are reported (Cruz et al. 2001, Knoers and Levtchenko 2008, Nakamura et al. 2010).

This patient showed some of typical features of Gitelman's syndrome, such as hypokalemic metabolic alkalosis and low blood pressure, and the diagnosis was confirmed by mutation analysis of *SLC12A3* gene. Mutation (c.781C>T, p.Arg261Cys) identified in this study was proved to be associated with low blood pressure phenotype (Ji et al. 2008). However, the present patient also showed peculiar features such as severe metabolic alkalosis with altered mentality and progressive renal insufficiency. On this admission, the patient showed markedly elevated serum bicarbonate concentration (67.6 mmol/L) along with high partial pressure of carbon dioxide (72.6 mmHg) and hypoxemia, all of which could explain this patient's neurologic symptoms. His respiratory compensation seemed adequate for his extremely high serum bicarbonate concentration (Huber and Gennari 2011).

His severe metabolic alkalosis may be explained by three factors. First of all, Gitelman's syndrome itself can induce metabolic alkalosis due to increased delivery of tubular sodium load to collecting tubule with renin-angiotensin-aldosterone system activation which leads to increased hydrogen ion excretion (Gennari 2011). However, serum bicarbonate level rarely exceeds 40 mmol/L in Gitelman's syndrome, so this patient's alkalosis cannot be explained solely by Gitelman's syndrome. Secondly, frequent vomiting episodes associated with psychiatric disor-

der may have aggravated alkalosis by loss of significant amount of acid and chloride. Low urine chloride concentration is characteristic finding of vomiting (Gennari and Weise 2008), but in this patient, spot urine chloride concentration was not low. This may be explained by underlying Gitelman's syndrome which can be associated with urinary wasting of sodium, chloride, and potassium ions (Graziani et al. 2010; Fremont and Chan 2012). Frequent vomiting can induce severe alkalosis usually by chloride depletion, where serum bicarbonate level may rise as high as 80 mmol/L (Gennari and Weise 2008; Gennari et al. 2010; Huber and Gennari 2011). However, vomiting associated with psychiatric disorders can be missed unless clinician makes careful history taking and physical examination. Thirdly, depressed glomerular filtration rate (GFR) can aggravate alkalosis by preventing adequate excretion of accumulated bicarbonate ion (Huber and Gennari 2011). This patient's serum creatinine level fluctuated during follow-up period before admission, but was never in the normal range. Furthermore, at the time of admission, serum creatinine level increased to 11.6 mg/dL. Such a low GFR with accompanying volume depletion might have prevented bicarbonate excretion through the kidney. To correct severe metabolic alkalosis and to manage renal insufficiency, emergency hemodialysis was performed as an initial therapy.

In contrast to Bartter's syndrome, progressive renal insufficiency is extremely rare in Giteman's syndrome (Bonfante et al. 2001; Knoers and Levtchenko 2008). There are only two case reports which described patients with Gitelman's syndrome progressed to end-stage renal disease (Bonfante et al. 2001; Calo et al. 2003). They suggested volume depletion and recurrent episodes of prerenal acute renal failure as the contributing factors of progressive renal insufficiency. Our patient showed markedly elevated serum creatinine level on admission, which was recovered to pre-admission level, but not to normal range after hemodialysis and fluid supplementation. These findings suggest that the patient had suffered from an episode of acute renal insufficiency associated with vomiting-induced volume depletion superimposed on underlying chronic kidney disease.

Eating disorder itself can result in acute kidney injury and chronic renal insufficiency (Bouquegneau et al. 2012). In patients with anorexia nervosa, the prevalence of hypokalemic nephropathy is known to be 15-20% (Riemenschneider and Bohle 1983), and the prevalence of end-stage renal disease can be as high as 5.2% (Zipfel et al. 2000). Binge-eating/purging subtype disorder is frequently associates with episodes of acute kidney injury due to volume depletion (Bouquegneau et al. 2012). Gitelman's syndrome is basically salt-losing tubulopathy. Therefore, volume depletion from recurrent vomiting superimposed on this syndrome might have rapidly exacerbated patient's renal function.

Chronic hypokalemia of Gitelman's syndrome may induce tubulointerstitial injury (Graziani et al. 2010), although direct causal relationship between the degree of hypokalemia and GFR is not established in Gitelman's syndrome (Bonfante et al. 2001; Walsh et al. 2011). Rather, Walsh and colleagues suggested ongoing sodium loss with hyperaldosteronism as the risk factor for renal pathologic change (Walsh et al. 2011). Our patient underwent renal biopsy that showed focal areas of tubular atrophy, interstitial inflammation, and fibrosis. These changes may be compatible with chronic hypokalemia, but relatively nonspecific, so in this case we postulate that the cause of chronic progressive renal impairment is most probably due to recurrent episodes of acute kidney injury associated with volume depletion.

We report a patient with Gitelman's syndrome, who presented with progressive renal insufficiency and very severe metabolic alkalosis which was induced and maintained by recurrent bouts of vomiting episodes superimposed on Gitelman's syndrome. Continuous monitoring of volume status and surveillance of other comorbid conditions should be employed to preserve renal function and acid-base status in Gitelman's syndrome patient, even when the patient does not complain subjective symptoms.

Conflict of Interest

The authors declare no conflict of interest.

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