Gitelman syndrome (GS; OMIM 263800) is a rare autosomal recessive, inherited renal tubular disorder first described by Gitelman et al in 1966 [1]. The prevalence of GS is unknown, but one study published in 1988 estimated it to be 1.2 cases per million [2]. It is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. All of them were treated with oral potassium and magnesium supplements. They received regular pediatric clinic follow-up to check electrolytes and monitor development. These three cases reminded us that doctors should be alert to unexplained hypokalemia, which is usually the initial presentation of GS.

**Case Presentations**

**Case 1**
This patient was a 17-year-old girl born at term to unrelated parents. While being evaluated for an episode of pneumonia at another hospital, the patient was incidentally found to have hypokalemia (2.6 mmol/L). A review of medical history showed nothing remarkable, including no history of laxative, diuretic abuse or vomiting. Physical examination revealed a well-developed girl without distress. There was no sign of hypertension and cardiovascular examination showed normal rate and rhythm without murmur, rubs, or gallops. No abdominal tenderness, hepatosplenomegaly, or peripheral edema was found. Neurologic examination disclosed no sensory or motor deficit. She did not have Chvostek and Trousseau sign.

Other laboratory values, analyzed at our hospital in March 1999 are shown in Tables 1–3. The abnormal findings included hypokalemia (2.6 mmol/L), metabolic alkalosis (pH 7.51 and bicarbonate 26.3 mmol/L) and hypomagnesemia (1.23 mmol/L). The supine plasma renin was >20 ng/mL/hour (normal range, 2.47 ± 2.23 ng/mL/hour), and supine aldosterone was 63.19 pg/mL (normal range, 1–16 pg/mL), but parathyroid hormone (iPTH) was <9 pg/mL (normal range, 10–65 pg/mL). The daily excretions of potassium and calcium were 88.6 mmol/day and 16.8 mg/day, respectively, and urine calcium/creatinine ratio was 0.015.

She was treated with oral magnesium (450 mg/day) and potassium (24 mmol/day) supplements for...
persistent electrolyte imbalance. While on potassium and magnesium supplements, her plasma potassium and magnesium levels were still low (potassium 2.5 mmol/L and magnesium 1.39 mmol/L). The patient’s 24-hour urine potassium excretion remained at 88.66 mmol. After treatment, her plasma-free calcium concentration was persistently low (ionized calcium, 3.76 mg/dL) and post-treatment plasma level of iPTH was 15.8 pg/mL (normal range, 10–65 pg/mL).

Case 2
This patient was an 18-year-old girl born at term with a normal prenatal history. The patient presented in our clinic with numbness over all extremities for 6 months. Hypokalemia was found at that time (2.5 mmol/L). She had no history of medication usage, including diuretics and laxative. Physical examination in 1999 showed that she had a height of 152 cm (10th to 25th percentile). She had no hypertension. Cardiovascular examination showed a regular heart rate and rhythm without murmur, rubs, or gallops. No abdominal tenderness, hepatosplenomegaly, or peripheral edema was found. Neurologic examination revealed no sensory or motor deficit. There was no Chvostek or Trousseau sign.

The initially abnormal laboratory values at our hospital in November 1999 showed hypokalemia (2.5 mmol/L), metabolic alkalosis (pH 7.46 and bicarbonate 32.7 mmol/L), and hypomagnesemia (1.39 mmol/L). Hormone examinations showed supine plasma renin to be 20 ng/mL/hour (normal range, 2.47–2.23 ng/mL/hour), supine aldosterone to be 7.8 pg/mL (normal range, 1–16 pg/mL) and iPTH to be 17.7 pg/mL (normal range, 10–65 pg/mL). The daily excretions of potassium and calcium were 91.7 mmol/day and 32.8 mg/day, respectively. The urine calcium/creatinine ratio was 0.05 (Tables 1–3).

She was treated with oral magnesium (450 mg/day) and potassium (32 mmol/day) supplements. While on potassium and magnesium supplements, her plasma potassium and magnesium levels were consistently low (potassium around 3.3 mmol/L and magnesium around 1.39 mmol/L). After treatment, her ionized plasma calcium was 4.64 mg/dL. The 24-hour urine potassium and calcium excretion was 58.2 mmol and 21.7 mg, respectively. Further urine examination showed the urine calcium/creatinine ratio to be 0.28, potassium 38.2 mmol/day, and magnesium 66.3 mg/day.

Case 3
This patient was a 13-year-old boy, a brother of case 2, who had complained of numbness of the four extremities for 6 months. Hypokalemia was found at that time (2.5 mmol/L). She had no history of medication usage, including diuretics and laxative. Physical examination showed a regular heart rate and rhythm without murmur, rubs, or gallops. No abdominal tenderness, hepatosplenomegaly, or peripheral edema was found. Neurologic examination revealed no sensory or motor deficit. There was no Chvostek or Trousseau sign.

The initially abnormal laboratory values at our hospital in November 1999 showed hypokalemia (2.5 mmol/L), metabolic alkalosis (pH 7.46 and bicarbonate 32.7 mmol/L), and hypomagnesemia (1.39 mmol/L). Hormone examinations showed supine plasma renin to be 20 ng/mL/hour (normal range, 2.47–2.23 ng/mL/hour), supine aldosterone to be 7.8 pg/mL (normal range, 1–16 pg/mL) and iPTH to be 17.7 pg/mL (normal range, 10–65 pg/mL). The daily excretions of potassium and calcium were 91.7 mmol/day and 32.8 mg/day, respectively. The urine calcium/creatinine ratio was 0.05 (Tables 1–3).

She was treated with oral magnesium (450 mg/day) and potassium (32 mmol/day) supplements. While on potassium and magnesium supplements, her plasma potassium and magnesium levels were consistently low (potassium around 3.3 mmol/L and magnesium around 1.39 mmol/L). After treatment, her ionized plasma calcium was 4.64 mg/dL. The 24-hour urine potassium and calcium excretion was 58.2 mmol and 21.7 mg, respectively. Further urine examination showed the urine calcium/creatinine ratio to be 0.28, potassium 38.2 mmol/day, and magnesium 66.3 mg/day.
extremities for 1 week. Like his sister, he was found to be a well-developed boy without distress. He also did not have hypertension. His cardiovascular examination also showed a regular heart rate and rhythm without murmur, rubs, or gallops. He was also found to have no abdominal tenderness, hepatosplenomegaly, or peripheral edema. Like his sister, he showed no signs of sensory or motor deficit and had no Chvostek or Trousseau sign.

The initial abnormal laboratory values at our hospital in November 1999 were hypokalemia (2.7 mmol/L), metabolic alkalosis (pH 7.46 and bicarbonate 32.6 mmol/L), and hypomagnesemia (1.39 mmol/L). Hormone analysis showed supine plasma renin, 11.8 ng/mL/hour (normal range, 2.47 ± 2.23 ng/mL/hour), supine aldosterone, 3.3 pg/mL (normal range, 1–16 pg/mL) and iPTH, 17.8 pg/mL (normal range, 10–65 pg/mL). The daily excretions of calcium and magnesium were 17 and 77 mg/day, respectively, and urine calcium/creatinine ratio was 0.03 (Tables 1–3).

Like his sister, he was treated with oral magnesium (450 mg/day) and potassium (32 mmol/day) supplements. While on potassium and magnesium supplements, his plasma potassium and magnesium levels were consistently low (potassium around 2.5 mmol/L and magnesium around 1.39 mmol/L). The serum-free calcium concentration was persistently low (ionized calcium, 3.76 mg/dL). His 24-hour urine potassium excretion was 34.1 mmol.

**DISCUSSION**

GS, a rare autosomal recessive inherited disorder first described by Gitelman et al in 1966, is primarily a renal tubular disorder characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria [1]. Epidemiologic studies have demonstrated that there is no ethnic predilection for GS and both sexes are equally affected. The prevalence of GS is unknown, but one study published in 1988 estimated it to be 1.2 cases per million in Sweden [2]. Although many cases appear to be sporadic, the syndrome has often been reported in siblings [1,3].

The marked similarity between the clinical features of patients with GS and those of electrolyte abnormalities induced by thiazide diuretics has led investigators to study whether patients with GS might have mutations that cause loss of function in the thiazide-sensitive cotransporter (TSC), also called the Na–Cl cotransporter (NCCT), which is located on the apical membrane in the distal convoluted tubule [3–6]. Simon et al first demonstrated complete linkage of GS to the NCCT gene (human gene mapping workshop approved symbol SLC12A3) on chromosome 16q13, and specified GS as an autosomal recessive disorder with 99% penetrance [3]. This linkage to chromosome 16q13 has been confirmed by others [7–9]. The defect in TSC leads to sodium chloride (NaCl) wasting and hypovolemia, which stimulates the renin–angiotensin–aldosterone system, and causes an increase in apical Na⁺ reabsorption and stimulation of the basolateral Na⁺–K⁺-ATPase. The elevated aldosterone levels also stimulate H⁺-ATPase pumps in the cortical and medullary collecting ducts, leading to increased apical H⁺ secretion. K⁺ and H⁺ excretion increases as K⁺ enters from the basolateral membrane via the Na⁺–K⁺-ATPase pumps, resulting in hypokalemic metabolic alkalosis. Sodium reabsorption via sodium channels is accompanied by potassium and hydrogen ion excretion, resulting in hypokalemia and further metabolic alkalosis. NaCl uptake through the apical membrane decreases, whereas intracellular Na⁺ continuously leaves the cells through the Na⁺–K⁺-ATPase at the basolateral membrane. This extrusion of Na⁺ reduces intracellular Na⁺ concentration, thereby hyperpolarizing distal convoluted tubular cells and causing Ca²⁺ to enter the apical membrane through Ca²⁺ channels [10]. Similarly, loss of TSC function can inhibit reabsorption of Mg via an apical Na/Mg exchanger. Since distal convoluted tubules reabsorb approximately 5% of filtered magnesium and the reabsorption is load-dependent [11], impairment in magnesium reabsorption in this segment would be expected to result in magnesium wasting and hypomagnesemia, due to a lack of a detectable magnesium transport system in the collecting duct.

Patients with GS are born at term with normal amniotic fluid volume and do not have symptoms throughout infancy and the preschool years. They are often diagnosed in adolescence or early adulthood. This disorder may be found during an occasional laboratory investigation in asymptomatic patients or patients with intermittent mild symptoms of muscle weakness, fatigue, cramps, and carpopedal spasms. However, severe symptoms such as tetany, rhabdomyolysis, and paralysis have been reported [12–14]. There is no prematurity, polyhydramnios, or polyuria.
Sexual and mental maturation are normal, although there has been a report of growth failure [15]. Chondrocalcinosis, possibly due to hypomagnesemia, has also been reported [16,17].

One study on the symptoms and health-related quality of life (QOL) involved 50 adult GS patients with confirmed mutation in NCCT [18]. Their most common symptoms were salt craving (95%), musculoskeletal symptoms such as cramps (84%), muscle weakness and aches (70%), and constitutional symptoms such as fatigue (82%), dizziness (80%), nocturia (80%), and polydipsia (65%). Health-related QOL was significantly lower in GS patients than in controls, particularly with regard to role limitations caused by physical health, emotion, energy levels, and general health. Furthermore, the symptoms of GS did not correlate with the degree of laboratory abnormalities.

Almost all GS patients have hypokalemia, hypomagnesemia, metabolic alkalosis, and markedly reduced urinary calcium excretion. The molar ratio of urinary calcium to urinary creatinine is <0.1 [19,20]. Chloride clearance increases after furosemide but not after thiazides. Normal urinary excretion of prostaglandin E2 (PGE2), and normal serum PTH, 25-hydroxyvitamin D3, and 1,25-dihydroxyvitamin D3 levels have been reported.

GS should be differentiated from Bartter syndrome [14]. Clinically, the two have been distinguished based on serum magnesium and urinary calcium findings, with GS denoting the subset with hypomagnesemia and hypocalciuria. An additional subset, patients with Bartter syndrome who present neonatally and typically have nephrocalcinosis, has been recognized. Patients with Bartter syndrome typically present before the age of 6 years with severe symptoms such as dehydration and growth retardation. In contrast, patients with GS typically present in early adulthood and with predominantly neuromuscular symptoms. In addition, genetic analysis may further differentiate the two syndromes with complete linkage of GS to the locus encoding NCCT on chromosome 16q13.

The mainstay treatment for GS is oral potassium chloride supplementation. However, treating hypokalemia is generally very difficult. Large amounts of oral potassium (up to 10 mmol/kg/day in children or 500 mmol/day in adults) may be required [14]. Large amounts of exogenous potassium may exacerbate the renal potassium loss by further increasing aldosterone synthesis [21,22]. The addition of potassium-sparing diuretics may lessen the hypokalemia and its associated symptoms. Concurrent oral magnesium supplementation is also used in the treatment of GS. Magnesium must be administered 4 or 5 times daily and the doses required often induce diarrhea. Magnesium chloride also helps replace urinary chloride losses, though many other magnesium salts have been used. Magnesium therapy not only corrects the hypomagnesemia and other mineral disorders, but also improves hypokalemia [23,24]. Long-term prognosis is dependent on growth maintenance and preservation of renal function. Life expectancy is excellent.

Our three patients included one sporadic case and two siblings. The sporadic case was incidentally found to have hypokalemia without significant predisposing factors. The two siblings presented with symptoms of extremity numbness and had hypokalemia and hypomagnesemia. According to the previous report in Taiwanese patients, gender may play an important role in explaining the different clinical presentations in familiar GS [25]. However, our case 2 and 3, sister and brother in a family, had similar clinical presentations and laboratory data. Whether the difference is due to the age of the patients studied is unknown. In addition, lack of genetic study may limit our further discussion to differentiate the difference between two studies.

In conclusion, these three cases reminded us that unexplained hypokalemia may be caused by renal tubular diseases, such as GS. Detailed electrolyte analysis and hormone evaluations are mandatory for differential diagnosis. GS is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Though genetic analysis will further confirm the diagnosis, their clinical presentations were compatible with GS. These three cases remind us that doctors should be alert to unexplained hypokalemia, which is usually the initial presentation of GS.

REFERENCES


吉特曼症候群：三個病例報告與文獻回顧

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吉特曼症候群是一少見的自體隱性，遺傳性的腎小管疾病，最早是在 1966 年由吉
特曼等人提出。在此篇文章中，我們將報告三個病例：一是偶發性個案，另兩位是姐
弟。他們實驗室數據均呈現典型低血鉀，代謝性鹼中毒，低血鎂，及低尿鈣。三個病
人均接受口服方式補充鎂及鉀且規律門診追蹤。我們將於此篇中分析此三個病例，並
做一文獻回顧。

關鍵詞：吉特曼症候群，低血鉀，代謝性鹼中毒
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