

# Gitelman syndrome combined with growth hormone deficiency

## Three cases report

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### Abstract

**Rationale:** Gitelman syndrome (GS) is a rare autosomal recessive hereditary salt-losing tubulopathy caused by loss-of-function mutations in the *SLC12A3* gene. It is usually characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. There are only a few reports on GS combined with growth hormone deficiency (GHD).

**Patient concerns:** Three patients presented with weakness, spasm, and growth retardation, respectively.

**Diagnoses:** GS was diagnosed based on the clinical symptoms, laboratory test results, and genetic analysis. GH stimulation tests were performed when the magnesium level returned to normal under magnesium oxide (MgO) therapy.

**Interventions:** Initially, all patients received oral replacement of MgO and potassium chloride, and 2 of them received simultaneous spironolactone therapy. Recombinant human growth hormone (rhGH) therapy was initiated after they were diagnosed with GHD.

**Outcomes:** All 3 patients exhibited satisfactory growth velocity and normal serum magnesium level, although the potassium level was still slightly lower than normal.

**Lessons:** We suggest that all GS patients should undergo genetic evaluation, especially regarding *SLC12A3* gene mutation. GHD should be considered if these patients have short stature. rhGH therapy is useful for stimulating the patients' growth, and it may increase the serum magnesium level.

**Abbreviations:** BS = Bartter syndrome, ClC-Kb = chloride voltage-gated channel Kb, FGF-23 = fibroblast growth factor-23, GHD = growth hormone deficiency, GHST = growth hormone stimulation test, GS = Gitelman syndrome, IGF-1 = insulin-like growth factor 1, NCCT = thiazide-sensitive sodium chloride cotransporter channel, rhGH = recombinant human growth hormone, SDS = standard deviation score.

**Keywords:** genetic analysis, Gitelman syndrome, growth hormone deficiency, therapy

## 1. Introduction

Gitelman syndrome (GS) is a rare autosomal recessive hereditary salt-losing tubulopathy with a characteristic set of metabolic abnormalities, including hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria.<sup>[1]</sup> The GS phenotype is usually caused by loss-of-function mutations in the *SLC12A3* gene which

encodes the thiazide-sensitive sodium chloride cotransporter channel in the distal convoluted tubule of the kidney. Clinically, these patients may present with fatigue, tetany, cramps, muscle weakness, vomiting, diarrhea, and abdominal pain.<sup>[2]</sup> In addition, growth retardation was noted in some patients with GS.<sup>[3]</sup> Although potassium depletion may have some negative effects on growth, the pathogenesis of growth retardation in GS is

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Written informed consent was obtained from the patients' parents for their blood collection and genetic analysis. Genetic analyses were also approved by the ethics committee of our hospital.

The authors have no conflicts of interests to disclose.

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still unclear. There are few reports on GS combined with growth hormone deficiency (GHD).<sup>[4–7]</sup> Herein, we describe 3 cases of patients with GS combined with GHD.

## 2. Clinical case

### 2.1. Case 1

A 6-year, 2-month-old boy was admitted to our hospital complaining of a 4-day history of weakness. His birth weight was 3.00 kg. No family history of endocrine, renal, celiac, and cardiovascular diseases or history of diuretic use was noted. Blood pressure was normal (91/63 mmHg). Initial biochemical analysis revealed metabolic alkalosis with hypokalemia (Table 1) based on the following values: serum total calcium level was 2.40 mmol/L (normal range: 2.20–2.65 mmol/L), phosphorus was 1.25 mmol/L (normal range: 1.29–2.26 mmol/L), and serum magnesium level was very low compared to the normal range. Further investigations revealed high serum renin and aldosterone levels. The 24-hour urinalysis showed that calcium was 2.5 mg/24 hour, significantly lower than the normal range of 100–300 mg/24 hour. The patient had normal adrenal, hepatic, renal, parathyroid, and thyroid function. Abdominal ultrasound

showed that the kidneys and liver were normal. Whole blood DNA sequencing revealed 2 heterozygous mutations in the *SLC12A3* gene (c.473G>A p.R158Q and c.602-16G>A p. splicing) (Table 2). Administration of oral replacement of magnesium oxide (MgO, 1 g/day), potassium chloride (KCl, 2.0 g/day), and spironolactone (2 mg/kg·day<sup>-1</sup>) was done. Serum potassium and magnesium levels increased to 3.0 mmol/L and 0.85 mmol/L, respectively. The frequency of weakness significantly decreased. However, his growth rate was just 4.2 cm/year, slightly higher than that before MgO and KCl therapy, which was only 3.2 cm/year.

His height was 108 cm (−2.78 standard deviation score [SDS]) and his weight was 18.7 kg (−1.58 SDS) at 9.50 years. The pubertal stage was genitalia stage I and pubic hair stage I, and his bone age (BA), according to the Greulich-Pyle method, was 6 years old. Growth hormone stimulation tests (GHSTs) (L-dopa and arginine) for short stature identified GHD, the peak GH level was 6.00 ng/mL (see Table 1). Pituitary MRI revealed no remarkable findings. The patient was treated with 0.277 mg/kg/week of recombinant human growth hormone (rhGH), and he achieved a 10.6-cm height gain over 11 months.

**Table 1**  
Clinical characteristics of the three patients.

	Case 1	Case 2	Case 3
<b>Clinical characteristics</b>			
Age (year)	9.5	9.25	4.67
Gender	M	F	M
Chief complaint	Weakness	Short stature	Spasm
Family history of diabetes	Negative	Negative	Negative
Birth weight (kg)	3.0	3.6	3.45
Blood pressure (mmHg)	91/63	113/71	87/66
Height (cm)	108.0 (−2.78 SDS)	120.0 (−2.27 SDS)	97.0 (−2.57 SDS)
Weight (kg)	18.7 (−1.58 SDS)	19.5 (−2.26 SDS)	11.5 (−3.32 SDS)
Target height (cm)	170.5	155.0	169.0
<b>Laboratory test</b>			
pH	7.479 (normal 7.35–7.45)	7.424	7.459
Standard base excess	4.8 (normal −3–3)	6.9	4.7
Sodium (mmol/L)	146 (normal 135–145)	142	141
Potassium (mmol/L)	2.4 (normal 3.5–5.5)	2.1	2.5
Chloride (mmol/L)	101 (normal 98–106)	102	103
Total calcium (mmol/L)	2.40 (normal 2.20–2.65)	2.37	2.40
Phosphorus (mmol/L)	1.25 (normal 1.29–2.26)	1.40	0.73
Magnesium (mmol/L)	0.55 (normal 0.73–1.06)	0.56	0.65
24 h urine sodium (mmol/24 h)	103.45 (normal 130–260)	216.33	65.76
24 h urine potassium (mmol/24 h)	58.89 (normal 25–100)	40.82	32.12
24 h urine calcium (mg/24 h)	2.5 (normal 100–300)	13.3	17.8
Kidney ultrasonography	Normal	Normal	Normal
GH peak to stimulants (ng/mL)	6.00	6.88	3.30
IGF-1 before therapy (ng/mL)	62.9 (normal 88–452)	71.3 (normal 74–388)	46.3 (normal 50–286)
<b>Therapy</b>			
KCL dosage (g)	2	3	2.0
Aldactone	Yes	Yes	No
Potassium after KCL therapy (mmol/L)	3.0	3.1	3.2
MgO dosage (g)	1	1.5	1
Magnesium after MgO therapy (mmol/L)	0.85	0.83	0.91
rhGH dosage (mg/kg/wk)	0.277	0.280	0.300
Growth velocity before rhGH therapy (cm/y)	4.2	3.6	3.6
Growth velocity after rhGH therapy (cm/y)	11.6	12.8	11.2
IGF-1 after rhGH therapy (ng/mL)	143.1 (normal 88–452)	179.5 (normal 74–388)	145.6 (normal 50–286)

GH=growth hormone, IGF-1=insulin-like growth factors 1, KCL=potassium chloride, MgO=magnesium oxide, rhGH=recombinant human growth hormone.

**Table 2**  
**SLC12A3 gene analysis of the 3 patients.**

	Chromosome location	Exon/intron	Nucleotide change	Amino acid change	hom/het/hemi	Pathogenic analysis	Inheritance	Source of variation
Case 1	chr16-56902252	Exon3	c.473G>A	p. R158Q	Het	Pathogenic	AR	Father
	chr16-56903992	Intron4	c.602-16G>A	splicing	Het	Pathogenic	AR	Mother
Case 2	chr16-56914054	Exon12	c.1456G>A	p.D486N	Het	Pathogenic	AR	Father
	chr16-56906567	Exon8	c.965-1G>A	splicing	Het	Pathogenic	AR	Mother
Case 3	chr16-56903640	Exon4	c.506-1G>A	splicing	Het	Pathogenic	AR	Father
	chr16-56906321	Exon7	c.911C>T	p.T304M	Het	Pathogenic	AR	Mother

hemi=hemizygous mutation, het=heterozygous mutations, hom=homozygous mutations.

## 2.2. Case 2

A 9-year, 3-month-old girl came to the clinic with a chief complaint of a 7-year history of growth retardation. No complaints of weakness, nausea, or abdominal distension were observed. At full-term birth, the weight was 3.60 kg. No family history of cardiovascular, endocrine, or renal diseases was noted. Her height and weight were 120 cm (−2.27 SDS) and 19.5 kg (−2.26 SDS), respectively. The patient was Tanner stage 1 for breast and pubic hair, and the BA was 7 years old. Blood pressure was 113/71 mmHg. Moreover, laboratory test results revealed low potassium level with metabolic alkalosis, hypocalciuria, and hypomagnesemia (Table 1). The patient also had normal thyroid, adrenal, hepatic, parathyroid, and renal function. Abdominal ultrasound showed that the kidneys and liver were normal. Furthermore, whole blood DNA sequencing identified 2 heterozygous mutations in the *SLC12A3* gene (c.1456 G>A p.D486N and c.965-1G>A p.splicing) (Table 2). She received oral replacement of 1.5 g/day MgO, 3.0 g/day KCl, and spironolactone (2 mg/kg·day<sup>−1</sup>). Within 3 months of treatment, serum potassium and magnesium levels increased to 3.1 mmol/L and 0.83 mmol/L, respectively. At that time, her growth velocity was 3.6 cm/year. Then, GHST was performed and GHD was identified, the peak GH level was 6.88 ng/mL (see Table 1). No remarkable findings were shown based on pituitary MRI. She was treated with 0.280 mg/kg/week of rhGH and achieved a 3.2-cm height gain over the first 3 months.

## 2.3. Case 3

A 4-year, 8-month-old boy who complained weakness and spasm for 1 week were referred to our hospital. He reported no headache, nausea, vomiting, or abdominal distension. Birth weight was 3.45 kg. No medical history of cardiovascular, endocrine, or renal diseases was noted. His height and weight were 97 cm (−2.57 SDS) and 19.5 kg (−2.26 SDS), respectively. His Tanner stage was genitalia stage I and pubic hair stage I. Heart rate was 110 beats per minute, blood pressure was 87/66 mmHg, respiratory rate was 30 breaths per minute, and oxygen saturation was 98% on ambient air. The sodium level was 141 mmol/L, potassium level was 2.5 mmol/L, chloride level was 103 mmol/L, total calcium level was 2.40 mmol/L, phosphorus level was 0.73 mmol/L, magnesium level was 0.65 mmol/L, and 24-hour urine calcium was 17.8 mg/24 hour (normal range, 100–300 mg/24 hour) (Table 1). The patient also had normal thyroid, adrenal, hepatic, parathyroid, and renal function. No remarkable findings were noted on electroencephalogram and pituitary MRI. Likewise, abdominal ultrasound showed that the kidneys and liver were normal. He was treated with magnesium sulfate and his weakness and spasm diminished. Whole blood DNA sequencing also identified two heterozygous mutations in

the *SLC12A3* gene (c.911C>T p.T304M and c.506-1G>A p.splicing) (Table 2). His medications included MgO (1.0 g/day) and KCl (2.0 g/day). Serum potassium and magnesium level back to 3.2 mmol/L and 0.93 mmol/L, respectively, after three months of treatment. At that time, his growth velocity was still 3.6 cm/year. Then, GHSTs were performed and GHD was identified, the peak GH level was 3.30 ng/mL (see Table 1). Hence, he was treated with 0.300 mg/kg/week of rhGH and achieved a 2.8-cm height gain over the first 3 months.

## 3. Discussion

GS is an autosomal recessive salt-losing renal tubulopathy with a characteristic set of hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. Epidemiologic studies showed that the prevalence of GS was approximately 1 per 40,000 among Europeans.<sup>[8]</sup> Patients were diagnosed with GS based on their clinical features and biochemical parameters. Symptoms of GS include spasm, weakness, and numbness. However, these symptoms are usually nonspecific and variable. Thus, the typical laboratory findings which include hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria are much more important. However, hypomagnesemia and hypocalciuria are not always present in patients with GS. Therefore, genetic testing is the optimal standard for the diagnosis of GS. It was reported that GS is usually caused by loss-of-function mutations in the *SLC12A3* (solute carrier family 12 member 3) gene, encoding the thiazide-sensitive sodium chloride (NaCl) cotransporter protein. Inactivation of *SLC12A3* gene mutation reduces NaCl reabsorption in the distal convoluted tubule and causes the symptoms of GS. To date, more than 400 mutations throughout the *SLC12A3* gene have been identified in different ethnic groups. Recently, 2 studies on GS gene mutations among Chinese patients were reported. These results showed that the D486N mutation of the *SLC12A3* gene appeared to be more frequent than the other mutations in Chinese patients with GS.<sup>[9,10]</sup> This study also found that 1 of the 3 patients had the same mutation. Although mutations have also been identified in the chloride voltage-gated channel Kb (*CLCNKB*) gene in a minority of patients with atypical GS phenotypes, we did not find any mutation of *CLCNKB* gene in our 3 patients. One research from China showed that nearly 30% of Chinese patients with GS carried 0 or just 1 mutant allele; they failed to have a genetic diagnosis of GS based on autosomal recessive inheritance. This might be attributed to undetected large genomic rearrangements and deep intronic mutations, which account for a considerable proportion of GS patients, by direct sequencing.<sup>[9]</sup> Although the gene analysis results are not the only criteria for GS diagnosis, genetic analysis is still recommended for all suspected patients.

**Table 3**  
**Classical Gitelman syndrome with growth hormone deficiency: cases from the literature.**

Reference	Age (years)	Sex	Proven Mutation of <i>SLC12A3</i> gene	GH peak in GHST (ng/ml)	IGF-1 (ng/ml)	rhGH dosage	GV (cm/y)
Min, S. R. <sup>[4]</sup>	12.9	Female	c.494A>T (p.Gln165Leu) c.1868T>C (p.Leu623Pro)	3.6 (L-dopa, clonidine)	161.33 (normal range: 191–462)	0.7 IU/kg/wk	9.6
Slyper, A. H. <sup>[7]</sup>	10.75	Female	N/A	7.5 (L-dopa, clonidine)	Normal (no numerical value)	0.25–0.3 mg/kg/wk	10.2
Bettinelli, A. <sup>[6]</sup>	9.5	Female	p.Gly186Asp	6.0 (clonidine)	89 (normal range: 89–626)	0.8 IU/kg/wk	10.9
	0.58	Male	c.2614fr/unknown	8.0 (insulin, arginine, clonidine)	N/A	0.7 IU/kg/wk	10.0
Ko, C. W. <sup>[5]</sup>	9.82	Male	N/A	3.2 (insulin, arginine, clonidine)	55 (normal range was not given)	0.7 IU/kg/wk	12.0
YAN, J. <sup>[18]</sup>	13.67	Male	N/A	9.8 (no detail about GHRT)	44.6 (normal range was not given)	N/A	12.0
	N/A	N/A	N/A	6.2 (no detail about GHRT)	43.2 (normal range was not given)	N/A	N/A

GH=growth hormone, GHST=growth hormone stimulation test, GV=growth velocity, IGF-1=insulin-like growth factor 1, rhGH=recombinant human growth hormone.

A majority of GS patients may present with weakness, muscle cramps, paresthesias, and episodes of tetany or paralysis. Meanwhile, other symptoms, such as nocturia, polydipsia, diarrhea, dizziness, and salt craving are included. These symptoms are all related to electrolyte and acid-base abnormalities. GS is associated with less severe growth retardation, compared with Bartter syndrome (BS). There are some factors that may contribute to growth retardation in BS or GS. Significant salt loss in the antenatal–neonatal period, hypokalemia, or metabolic alkalosis may have some effect on growth. However, the precise causes of growth retardation remain unclear. Some cases investigating GS combined with GHD have been reported in the last 2 decades,<sup>[4–7]</sup> as shown in Table 3. Moreover, because classic BS and GS shared the laboratory finding of hypokalemic alkalosis, Adachi et al<sup>[11]</sup> conjectured that some of the older cases reported in the literature do not comply with the current definition and concept of BS and thus, should be recognized as GS.

Experimental studies suggested that potassium depletion could have a negative effect on growth by reducing the circulating levels of growth hormone and insulin-like growth factor 1 (IGF-1), which may blunt the GH response and lead to false-negative results in GHST.<sup>[12,13]</sup> However, another study showed there was abnormal chondrocyte maturation in rats which fed a potassium-free diet, and it was not normalized by a high dose of exogenous GH. This observation can easily explain why there is resistance to GH in hypokalemic rats.<sup>[13]</sup> The excellent response to GH therapy made us believe that GHD should be regarded as a complication in classic BS or GS, which is similar with the other study.<sup>[5,11,14]</sup> It has also been reported that higher urine magnesium excretion alters the GH/IGF-1 axis in a type 1 diabetes mellitus cohort.<sup>[15]</sup> Matsuzaki et al<sup>[16]</sup> reported that magnesium deficiency increases serum fibroblast growth factor 23 (FGF-23) levels in rats. Another research showed that FGF-23 altered the GH/IGF-1 axis, delayed puberty, malnutrition, and metabolic acidosis.<sup>[17]</sup> Additionally, these researches demonstrated that hypomagnesemia may play an important role in the GH/IGF-1 axis. However, our patients underwent GHST when the serum magnesium concentration return to normal range after therapy. Our result showed that there might be no direct relationship between hypomagnesemia and GHD. In summary, GHD should be regarded as a complication of GS in these three patients, although the exact cause of GS combined with GHD remains unclear.

In our study, all three patients received rhGH therapy and exhibited a growth velocity of 10.3–12.8 cm/year, significantly higher than before. No impaired glucose metabolism or other side

effects were found in our three patients during the treatment. Our result was similar with some other researches which also reported that rhGH therapy markedly improved GS patients' growth rate. Interestingly, rhGH treatment also seemed to be helpful for the correction of hypomagnesemia,<sup>[5]</sup> we suggest that rhGH therapy might be considered in short children with GS, even though they do not suffer from GHD.

In summary, we reported three cases of GS combined with GHD. GS should be diagnosed based on the clinical manifestations and laboratory results. We propose that all patients with GS should undergo genetic test. When these patients suffer from growth retardation, GHD should be considered and GHST should be performed. rhGH therapy is helpful for stimulating the patients' growth and increasing the serum magnesium level.

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