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Case report

A case of Gitelman syndrome: our experience with a patient treated in clinical practice on a local island

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Abstract

Background: Gitelman syndrome (GS) is an autosomal recessive salt-losing renal tubulopathy resulting from mutations in the thiazide-sensitive Na-Cl cotransporter (*NCC*) gene. Notably, lack of awareness regarding GS and difficulty with prompt diagnosis are observed in clinical practice, particularly in rural settings.
Case presentation: We report a case of a 48-year-old man with GS who presented to a local clinic on a remote island. Occasional laboratory investigations incidentally revealed a reduced serum potassium level of 2.6 mmol/L. A careful medical interview revealed episodes of intermittent paralysis of the lower extremities and muscular weakness for >30 years. Subsequent laboratory investigations revealed hypomagnesemia, hypocalciuria, and hypokalemic metabolic alkalosis. Based on the patient's history, clinical presentation, and laboratory investigations, we suspected GS. Genetic testing revealed a rare homozygous in-frame 18 base insertion in the *NCC* gene that might have resulted from the founder effect, consequent to his topographically isolated circumstances.
Conclusion: More case studies similar to our study need to be added to the literature to gain a deeper understanding of the functional consequences of this mutation and to establish optimal management strategies for this condition, particularly in rural clinical settings.

Key words: Gitelman syndrome, thiazide-sensitive Na-Cl cotransporter, hypomagnesemia, hypokalemic metabolic alkalosis, proteinuria

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Introduction

Gitelman syndrome (GS) is an autosomal recessive salt-losing renal tubulopathy characterized by fluid and electrolyte disturbances, as well as urinary, and hormonal abnormalities, including hypomagnesemia, hypocalciuria, and secondary hyperreninemic aldosteronism, that causes hypokalemic metabolic alkalosis[1, 2]. Biallelic inactivating mutations in the solute carrier family 12, member 3 gene (*SLC12A3*) encoding the thiazide-sensitive Na-Cl cotransporter (*NCC*) have received increasing attention as etiopathogenetic contributors to the disease[1, 3]. GS can be associated with neuromuscular complaints including intermittent muscle weakness, spasms, cramps, or tetany, although a few subsets of patients with GS may be asymptomatic[2]. Despite the increasing number of reports describing GS that are being added to the literature[3–6], lack of awareness regarding this condition and the consequent delay in accurate diagnosis remain a clinical challenge, particularly in rural clinical settings. We report a case of GS in a man from a local island in Kagoshima Prefecture, Japan.

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Case Report

A 48-year-old man with a history of dyslipidemia that had been treated with oral pravastatin at a dose of 10 mg/day at our clinic on Amami-oshima Island, one of the Amami

Islands, located approximately 250 miles southwest of Kyushu Island, the third largest island of Japan, was incidentally found to have a reduced serum potassium level of 2.6 mmol/L at an occasional laboratory investigation. A careful medical interview revealed that he was born and raised on this island and that he had experienced intermittent paralysis of the lower extremities and muscular weakness for >30 years; however, he did not seek any medical advice owing to the transient nature of symptoms. He was born to non-consanguineous parents, who were also born and raised on this island. No member of his immediate or extended family reported similar complaints. He denied the use of any herbal medicine, diuretics, or laxatives. His medical history included proteinuria (2+), which was diagnosed approximately 2 years earlier at the time of a general health checkup. His renal parameters were not monitored on a regular basis.

Physical examination at the time revealed a well-nourished man who was 170 cm tall and weighed 68.6 kg. His blood pressure was 130/70 mmHg with a regular pulse rate of 86 beats/min. Chest auscultation revealed his lungs were clear and heart sounds were normal. No peripheral edema or rash was observed. Electrocardiography was unremarkable. Computed tomography revealed no structural abnormalities in the right or left kidney or in the abdomen. Laboratory investigations at the time of presentation are summarized in Table 1. As shown, we observed hypokalemic metabolic alkalosis and increased plasma renin activity without hyperaldosteronism. Despite the serum mineral disturbances and acid-base imbalance associated with hyperreninemia, we did not focus on these abnormalities at the time. He was therefore empirically treated with oral potassium supplementation. Not surprisingly, we observed persistent hypomagnesemia (approximately 1.1 to 1.4 mg/dL), while his serum potassium levels remained at approximately 2.4 to 2.8 mmol/L.

Table 1 Laboratory data at the time of presentation

White blood cells	5,890/μL	(3,500–9,700)
Neutrophils	68.90%	(42.0–74.0)
Eosinophils	0.80%	(0.0–7.0)
Basophils	0.20%	(0.0–2.0)
Monocytes	4.10%	(1.0–8.0)
Lymphocytes	26.00%	(18.0–50.0)
Serum hemoglobin	15.4 g/dL	(13.6–18.3)
Platelet count	23.9×10^4/μL	(14.0–37.9)
Serum blood urea nitrogen	14.2 mg/dL	(8.0–20.0)
Serum creatinine	0.63 mg/dL	(0.65–1.09)
Serum aspartate aminotransferase	26 U/L	(10–40)
Serum alanine aminotransferase	25 U/L	(5–45)
Serum sodium	140 mmol/L	(135–145)
Serum potassium	2.6 mmol/L	(3.5–5.0)
Serum chloride	93 mmol/L	(98–108)
Serum calcium	9.4 mg/dL	(8.6–10.2)
Serum magnesium	1.2 mg/dL	(1.7–2.6)
Serum triglycerides	106 mg/dL	(50–149)
Total serum cholesterol	230 mg/dL	(150–219)
pH	7.52	(7.32–7.43)
$PaCO_2$	45 mmHg	(36–48)
HCO_3^-	36.0 mmol/L	(23–29)
Plasma renin activity	13 ng/mL/h	(0.3–4)
Plasma aldosterone	157 pg/mL	(36–240)
Urinary sodium	222 mmol/L	NA
Urinary potassium	61 mmol/L	NA
Urinary chloride	222 mmol/L	NA
Fractional excretion of sodium	0.70%	NA
Fractional excretion of potassium	11%	NA
Urinary creatinine	136 mg/dL	NA
Urinary albumin	9.4 mg/dL	NA
Urinary albumin/creatinine ratio	0.069 g/gCr	(0.05–0.15)

Reference ranges for each parameter used at our clinic are indicated in parentheses. HCO_3^-: bicarbonate ion; NA: not available; $PaCO_2$: partial pressure of carbon dioxide.

The patient occasionally developed neuromuscular symptoms over the next 2 years. Urinalyses performed as outpatient assessments at 50 years of age revealed fractional excretion of potassium of 11.1% and a urine potassium-to-creatinine ratio of 44 mmol/gCr despite a reduced serum potassium level of 2.4 mmol/L. Based on these findings, his primary care practitioner confirmed the persistence of a hypokalemic state secondary to renal potassium wasting[7, 8]. Additionally, a reduced urine calcium-to-creatinine (Cr) ratio of 0.008 g/gCr indicated concurrent hypocalciuria[9]. His primary care practitioner therefore strongly suspected GS as a cause of the patient's clinical manifestations and electrolyte disturbances, and referred the patient to a nephrologist who provided a special nephrology service once a month at another regional hospital.

The nephrologist supported the diagnosis and advised conducting a thorough genetic evaluation. Decision-making for this procedure was exclusively done at the clinic, and the patient ultimately decided to undergo the evaluation. After obtaining his written informed consent, we performed comprehensive genetic testing in this patient for dozens of known genes for sodium-losing nephropathy using next-generation sequencing, as reported previously[10]. This genetic testing revealed a homozygous in-frame 18 base insertion in *SLC12A3* (NM_000339.2: c.804_805ins ATTGGCGTGGTCTCGGTC) (Figure 1), thereby confirming the diagnosis of GS.

Oral supplementation of potassium and magnesium was then initiated, and although hypomagnesemia (approximately 1.4 mg/dL) persisted, his serum potassium levels returned to 3.6 to 3.7 mmol/L, and the patient became asymptomatic after spironolactone was added to his therapeutic regimen. During the observation period, his serum Cr levels remained at approximately 0.67 mg/dL with steady-state urinary protein levels ranging from 0.27 to 0.41 g/gCr. We are now considering the need for further genetic evaluation in other family members.

Written informed consent was obtained from the patient for the publication of this case report, as well as for performing genetic analysis, which was performed in accordance with the ethical standards of the Tokyo Medical and Dental University.

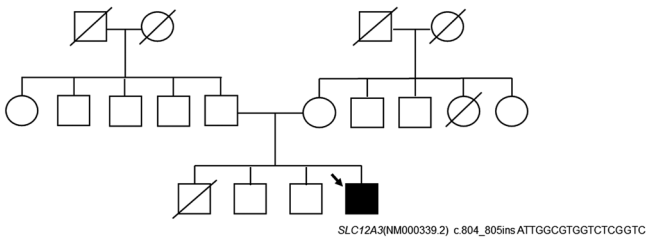

Figure 1 Extended family tree showing over 3 generations of the present patient's family and the results of sequencing analysis of the *SLC12A3* gene in this patient. A homozygous in-frame 18 base insertion was identified in the *SLC12A3* gene (NM000339.2). Males and females are indicated by squares and circles, respectively. The patient (indicated by an arrow) is represented by a closed symbol.

Discussion

To date, >150 scattered mutations have been identified in *SLC12A3* among patients with GS[5, 11]. The in-frame insertion confirmed in the present patient has already been reported in both, the heterozygous and homozygous states[3, 12, 13]. Therefore, the characteristic presentation of our patient may not be surprising; however, the findings in the current case require close attention. In our view, this case report provides valuable clinical information to physicians working in rural areas and emphasizes that accurate diagnosis based on genetic testing is possible even in rural clinical settings through effective coordination with other medical facilities. Furthermore, this is the first report that describes geographical and/or topographical information in a patient with GS showing an 18-base insertion in a homozygous state. This can result from a de novo mutation. Alternatively, our patient may be a homozygous proband derived from heterozygous parents who might have had a common ancestor. We did not investigate in detail whether the patient's family had a similar genetic and/or geographical background; however, it would be reasonable to conclude that the founder effect associated with the topographically isolated circumstances of the patient could be an etiopathogenetic contributor among certain subsets of patients with GS[12, 14, 15] and may be implicated as a putative etiological mechanism in our case.

An interdisciplinary approach is important to establish the genetic diagnosis in this rare condition. Coordination between attending physicians with clinical experience in treating GS and experts in genetic counseling is necessary to function as a medical team to educate patients regarding the risks and benefits of undergoing genetic testing. Additionally, providing social and/or psychological support constitutes an important component of shared decision-making for prompt management[16]. The pre-evaluation strategy adopted in the current case might have been inadequate because the decision-making process was limited to the patient and the attending primary care practitioner at the local clinic on the island. However, the patient was satisfied with the care provided during the diagnostic process, as well as with the results of the genetic testing, and we are currently considering the need for further evaluation in his relatives. Obviously, a high index of clinical suspicion for the disease and timely consultation with a nephrologist led to a prompt diagnosis of GS in our patient. However, this may not be always the case, given the geographic disparity in the distribution of nephrologists, which may preclude equitable accessibility[17]. In this regard, our experience may not necessarily allow us

to thoroughly discuss medical concerns associated with rural areas, which lack reasonable and sufficient distribution of health resources. Nevertheless, systemic studies on these topics are quite lacking, so we strongly recommend the accumulation of more cases similar to our own not only to clarify the overall functional consequence of this mutation, which should add six new amino acids[3], but also to understand the nature of the disease more precisely, thereby delineating specific management strategies relating to rural medical practices, such as how to communicate with a cooperative facility or an expert for further examinations and how to care for a patient and their family members with a specific genetic disposition, which remains to be delineated in the ordinary clinical settings as well[18], in a relatively closed community.

This disease entity was first described as a separate condition by Gitelman *et al.* in 1966[19]. Since then, a steady growth has been observed in the body of knowledge describing the epidemiology and/or pathophysiology of this condition[6, 9]. The estimated prevalence of GS is approximately 1 in 40,000 individuals, and the prevalence of heterozygotes for GS is approximately 1% of the white population[20, 21]. However, Tago *et al.* reported a much higher prevalence of heterozygous *SLC12A3* mutations (3.21%) among 1,852 subjects representing the general Japanese population[22]. No distinct ethnic predilection has been identified, and both sexes are at equal risk of GS[6, 23]. The serum aldosterone level may not be significantly increased in all patients with GS, as was observed in the patient described in this report. This finding could be attributed to the fact that hypokalemia in these patients suppresses adrenal aldosterone synthesis[2]. It is unclear whether dyslipidemia identified in the present patient would be attributable to GS, although the association between high-dose thiazide diuretics and abnormal lipid metabolism remains debatable[24].

The mainstay of treatment for GS includes the individualized lifelong administration of magnesium and potassium supplements combined with aldosterone antagonists and/or potassium-sparing agents, such as spironolactone, eplerenone, and amiloride (a strategy implemented in the present patient)[9]. No specific association has been observed between the degree of reduction in serum mineral levels and the magnitude of symptoms. However, several clinical manifestations of GS show improvement following potassium and/or magnesium supplementation, and magnesium repletion may be a useful therapeutic option in a few subsets of patients with GS because it inhibits renal potassium excretion and reduces the risk of various neuromuscular complications[9, 25]. Correcting hypomagnesemia may otherwise be challenging because of diarrhea secondary to the use of oral magnesium (administered as sulfate, oxide, or chloride salts)[6, 9]. Therefore, a reasonable target range for serum potassium and magnesium levels may be approximately 3.0 mmol/L and 1.46 mg/dL, respectively, although practical target values may be lower in some patients and may also change with time[9]. To date, an optimal follow-up interval to monitor these serum mineral disturbances remains unknown; however, monitoring these levels once or twice a year in a nephrology clinic is recommended[9, 26].

Progression to renal insufficiency is extremely rare in patients with GS[27, 28]. Several recent studies have reported that some subsets of patients tend to show overt proteinuria[29, 30], which has received attention as an independent risk factor for cardiovascular and chronic kidney disease[31]. Empirical evidence available in the literature shows several glomerulopathies and concomitant proteinuria in patients with GS[32–34]. A few reports have even anecdotally described patients with severe progressive renal failure requiring renal replacement therapy[35, 36]. In the present patient, we could not perform histopathological evaluation or characterize urinary protein. To date, the optimal diagnostic strategy in patients with GS presenting with various abnormalities in renal parameters has not been standardized. In our opinion, it is essential to thoroughly weigh all options and risks of potential complications, as well as disease severity on a case-by-case basis. Establishing patient selection criteria for a renal biopsy in this population is an important concern that needs to be carefully addressed. Furthermore, it is important to establish a strategy for adequate longitudinal surveillance and flexible follow-up for GS, although this appears to be challenging in the present clinical settings.

In conclusion, this case report describes a patient diagnosed with GS at a regional clinic on a small island. He presented with a rare homozygous mutation in the *NCC* gene. Based on his topographically isolated circumstances, it would be reasonable to conclude that the mutation might have resulted from the founder effect. Prompt diagnosis of GS is challenging and more case studies similar to our study need to be added to the literature to gain a deeper understanding of the functional consequences of this mutation and also to establish optimal management strategies for GS in patients diagnosed in rural clinical settings.

Conflicts of interest: TA is affiliated with an endowed department (Department of Chronic Kidney Disease Pathophysiology) supported by Terumo Co., Chugai Pharmaceutical Co., Ltd., and Kyowa Hakko Kirin Co., Ltd. The authors report no other conflicts of interest relevant to this work.

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References

1. Monkawa T, Kurihara I, Kobayashi K, *et al*. Novel mutations in thiazide-sensitive Na-Cl cotransporter gene of patients with Gitelman's syndrome. J Am Soc Nephrol 2000; 11: 65–70. [Medline]
2. Kurtz I. Molecular pathogenesis of Bartter's and Gitelman's syndromes. Kidney Int 1998; 54: 1396–1410. [Medline] [CrossRef]
3. Tajima T, Kobayashi Y, Abe S, *et al*. Two novel mutations of thiazide-sensitive Na-Cl cotrans porter (TSC) gene in two sporadic Japanese patients with Gitelman syndrome. Endocr J 2002; 49: 91–96. [Medline] [CrossRef]
4. Kumagai H, Matsumoto S, Nozu K. Hypokalemic rhabdomyolysis in a child with Gitelman's syndrome. Pediatr Nephrol 2010; 25: 953–955. [Medline] [CrossRef]
5. Vargas-Poussou R, Dahan K, Kahila D, *et al*. Spectrum of mutations in Gitelman syndrome. J Am Soc Nephrol 2011; 22: 693–703. [Medline] [CrossRef]
6. Nakhoul F, Nakhoul N, Dorman E, *et al*. Gitelman's syndrome: a pathophysiological and clinical update. Endocrine 2012; 41: 53–57. [Medline] [CrossRef]
7. Elisaf M, Siamopoulos KC. Fractional excretion of potassium in normal subjects and in patients with hypokalaemia. Postgrad Med J 1995; 71: 211–212. [Medline] [CrossRef]
8. Wolyniec W, Jakubowska SK, Nagel M, *et al*. A case report of Gitelman syndrome resulting from two novel mutations in SLC12A3 gene. Nefrologia 2016; 36: 304–309. [Medline] [CrossRef]
9. Blanchard A, Bockenhauer D, Bolignano D, *et al*. Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2017; 91: 24–33. [Medline] [CrossRef]
10. Mori T, Hosomichi K, Chiga M, *et al*. Comprehensive genetic testing approach for major inherited kidney diseases, using next-generation sequencing with a custom panel. Clin Exp Nephrol 2017; 21: 63–75. [Medline] [CrossRef]
11. Takeuchi Y, Mishima E, Shima H, *et al*. Exonic mutations in the SLC12A3 gene cause exon skipping and premature termination in Gitelman syndrome. J Am Soc Nephrol 2015; 26: 271–279. [Medline] [CrossRef]
12. Fukuyama S, Okudaira S, Yamazato S, *et al*. Analysis of renal tubular electrolyte transporter genes in seven patients with hypokalemic metabolic alkalosis. Kidney Int 2003; 64: 808–816. [Medline] [CrossRef]
13. Ogihara T, Katsuya T, Ishikawa K, *et al*. Hypertension in a patient with Gitelman's syndrome. J Hum Hypertens 2004; 18: 677–679. [Medline] [CrossRef]
14. Mishima E, Mori T, Sohara E, *et al*. Inherited, not acquired, Gitelman syndrome in a patient with Sjögren's syndrome: importance of genetic testing to distinguish the two forms. CEN Case Rep 2017; 6: 180–184. [Medline] [CrossRef]
15. Coto E, Rodriguez J, Jeck N, *et al*. A new mutation (intron 9 +1 G>T) in the SLC12A3 gene is linked to Gitelman syndrome in Gypsies. Kidney Int 2004; 65: 25–29. [Medline] [CrossRef]
16. Guidelines for Genetic Tests and Diagnoses in Medical Practice. The Japanese Association of Medical Sciences. http://jams.med.or.jp/guideline/genetics-diagnosis_e.pdf.
17. Imasawa T, Nakazato T. [Status of board-certified nephrologists of the Japanese Society of Nephrology among 47 prefectures]. Nippon Jinzo Gakkai Shi 2010; 52: 1015–1021 (in Japanese). [Medline]
18. Gaff CL, Clarke AJ, Atkinson P, *et al*. Process and outcome in communication of genetic information within families: a systematic review. Eur J Hum Genet 2007; 15: 999–1011. [Medline] [CrossRef]
19. Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. Trans Assoc Am Physicians 1966; 79: 221–235. [Medline]
20. Ji W, Foo JN, O'Roak BJ, *et al*. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet 2008; 40: 592–599. [Medline] [CrossRef]
21. Glaudemans B, Yntema HG, San-Cristobal P, *et al*. Novel NCC mutants and functional analysis in a new cohort of patients with Gitelman syndrome. Eur J Hum Genet 2012; 20: 263–270. [Medline] [CrossRef]
22. Tago N, Kokubo Y, Inamoto N, *et al*. A high prevalence of Gitelman's syndrome mutations in Japanese. Hypertens Res 2004; 27: 327–331. [Medline] [CrossRef]
23. Lee YT, Wang IF, Lin TH, *et al*. Gitelman syndrome: report of three cases and literature review. Kaohsiung J Med Sci 2006; 22: 357–362. [Medline] [CrossRef]
24. Weir MR, Moser M. Diuretics and beta-blockers: is there a risk for dyslipidemia? Am Heart J 2000; 139: 174–183. [Medline] [CrossRef]
25. Agus ZS. Hypomagnesemia. J Am Soc Nephrol 1999; 10: 1616–1622. [Medline]
26. Cruz AJ, Castro A. Gitelman or Bartter type 3 syndrome? A case of distal convoluted tubulopathy caused by CLCNKB gene mutation. BMJ Case Rep 2013; 2013: bcr2012007929. [Medline] [CrossRef]
27. Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndromes. Am J Med Sci 2001; 322: 316–332. [Medline] [CrossRef]
28. Knoers NV, Levtchenko EN. Gitelman syndrome. Orphanet J Rare Dis 2008; 3: 22. [Medline] [CrossRef]
29. Berry MR, Robinson C, Karet Frankl FE. Unexpected clinical sequelae of Gitelman syndrome: hypertension in adulthood is common and females have higher potassium requirements. Nephrol Dial Transplant 2013; 28: 1533–1542. [Medline] [CrossRef]
30. Walsh PR, Tse Y, Ashton E, *et al*. Clinical and diagnostic features of Bartter and Gitelman syndromes. Clin Kidney J 2018; 11: 302–309. [Medline] [CrossRef]
31. Cravedi P, Remuzzi G. Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease. Br J Clin Pharmacol 2013; 76: 516–523. [Medline]
32. Bulucu F, Vural A, Yenicesu M, *et al*. Association of Gitelman's syndrome and focal glomerulosclerosis. Nephron 1998; 79: 244. [Medline] [CrossRef]
33. Hanevold C, Mian A, Dalton R. C1q nephropathy in association with Gitelman syndrome: a case report. Pediatr Nephrol 2006; 21: 1904–1908. [Medline] [CrossRef]
34. Demoulin N, Aydin S, Cosyns JP, *et al*. Gitelman syndrome and glomerular proteinuria: a link between loss of sodium-chloride cotransporter and podocyte dysfunction? Nephrol Dial Transplant 2014; 29(Suppl 4): iv117–iv120. [Medline] [CrossRef]
35. Bonfante L, Davis PA, Spinello M, *et al*. Chronic renal failure, end-stage renal disease, and peritoneal dialysis in Gitelman's syndrome. Am J Kidney Dis 2001; 38: 165–168. [Medline] [CrossRef]
36. Lee JH, Lee J, Han JS. Gitelman's syndrome with vomiting manifested by severe metabolic alkalosis and progressive renal insufficiency. Tohoku J Exp Med 2013; 231: 165–169. [Medline] [CrossRef]