International Journal of Advances in Medicine
Kusumadewi IGSAJ et al. Int J Adv Med. 2023 Dec;10(12):845-848
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20233569

Case Report

A rare case: evaluation of chronic hypoklemia in patient with Gitelman syndrome

I. Gusti Sri Agung Jaya Kusumadewi[1], Putu Nindya Ayu Ningrum Subadra[1], Ketut Suryana[2]*

[1]Department of Internal Medicine, Wangaya General Hospital, Denpasar, Bali, Indonesia
[2]Department of Internal Medicine, Merpati Clinic, HIV and Allergy – Clinical Immunology Services Unit, Wangaya General Hospital, Denpasar, Bali, Indonesia

Received: 11 October 2023
Accepted: 09 November 2023

***Correspondence:**
Dr. Ketut Suryana,
E-mail: ketutsuryana@gmail.com

ABSTRACT

Gitelman syndrome (GS) is inherited in a recessive manner and is caused by inactivating mutations in the SLC12A3 gene characterized by the loss of salt, leading to hypokalemic metabolic alkalosis with concurrent hypomagnesemia and hypocalciuria. Hypokalemia is defined as a plasma potassium concentration of less than 3.5 mmol/l. A 24-year-old woman came with weakness and numbness in both lower limbs for the past 1 day and later extended to all four extremities. This patient had been admitted to hospital twice in the last 2 months with similar complaints. Laboratory results showed hypokalemia, hypocalcemia, hypomagnesemia, and metabolic alkalosis accompanied by elevated eGFR, anemia and increased potassium secretion in the distal tubules. Gitelman syndrome is the rare case and does not have specific symptoms, so the diagnosis depends on the accuracy of high clinical suspicion, especially those experiencing hypokalemia.

Keywords: Gitelman syndrome, Hypokalemia

INTRODUCTION

Gitelman syndrome (GS) is an autosomal recessive kidney tubular disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria.[1] GS is associated with various symptoms of hypokalemia and hypomagnesemia, such as muscle weakness, tetany, fatigue, nausea, vomiting, and palpitations.[2] The estimated prevalence of Gitelman syndrome is 1-10 in 40,000 individuals, with potentially higher rates in Asia. GS is typically diagnosed during adolescence or adulthood, often incidentally or in conjunction with mild or nonspecific symptoms. The condition exhibits considerable phenotypic variability and significantly impacts the patient's quality of life, sometimes leading to severe manifestations.[3] The diagnosis of GS can pose a challenge due to its rarity, requiring a high index of clinical suspicion, a comprehensive assessment of serum and urine profiles, and genetic testing to establish a definitive diagnosis.[4] Therefore, in cases presenting with biochemical and metabolic abnormalities, particularly hypokalemia, Gitelman syndrome should be considered. Here, we report a case of GS with recurrent hypokalemia.

CASE REPORT

A 24-year-old woman presented to the emergency department with complaints of weakness and numbness for the past 1 day. The weakness was initially felt in both lower limbs and later extended to all four extremities. The patient also complained of nausea, vomiting twice, and had diarrhoea five times, without any blood or mucus. There was no fever. The patient reported feeling weak and debilitated for the past 2 months. She had been admitted to RSUD Wangaya Denpasar twice in the last 2 months with similar complaints. She denied any regular medication use.

On physical examination, the patient was conscious (Glasgow coma scale E4M6V5) with a blood pressure of 98/62 mmHg, heart rate of 80 beats per minute, respiratory

rate of 18 breaths per minute, oxygen saturation of 96%, body temperature of 36.8°C, and a capillary refill time of 2 seconds. She appeared weak, and there were no abnormalities noted on general examination. Motor and sensory function examinations were within normal limits.

Laboratory investigations revealed a complete blood count with white blood cell count of 10.19, hemoglobin level of 6.9, and platelet count of 426. There was evidence of renal dysfunction with a urea level of 22, serum creatinine of 2.2, and an estimated glomerular filtration rate (eGFR) of 31 ml/min/1.73 m^2. Liver function tests were within normal limits, with SGOT at 34 and SGPT at 25. Serum electrolyte levels showed sodium at 141, chloride at 101, potassium at 2.4, and magnesium at 1,4. Thyroid hormone function was within normal limits, with TSH at 1.19 and FT4 at 40.96. Arterial blood gas analysis revealed metabolic alkalosis with a pH of 7.53, PCO_2 of 40, PO_2 of 100, bicarbonate (HCO_3) of 34, anion gap (ABE) of 11, standard bicarbonate (SBC) of 35, and oxygen saturation (SO_2) of 99. A 24-hour urine collection showed sodium at 125 mmol/l/24 hours, potassium at 34 mmol/l/24 hours, chloride at 152 mmol/L/24 hours, calcium at 85.3 mg/24 hours, urine osmolality at 320 mOsmol/kgH_2O, serum osmolality at 300.6 mOsmol/kgH_2O, and a trans tubular potassium gradient (TTKG) of 12.8 (TTKG >4 indicating increased potassium secretion in the distal tubules).

Urological ultrasound did not reveal any abnormalities in the kidneys. Peripheral blood smear analysis suggested features of iron-deficiency anemia with inflammatory anemia, possibly chronic disease-related. Chest X-ray and EKG were within normal limits.

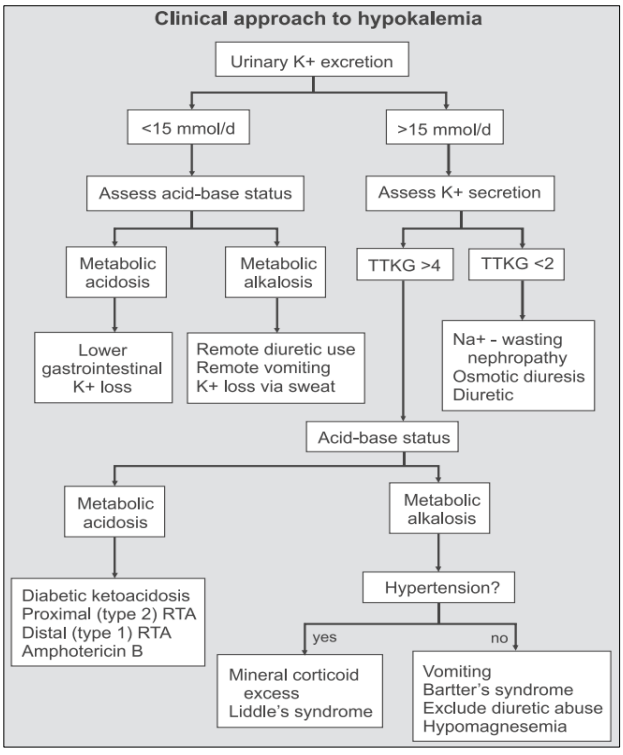

Figure 1: Clinical approach to hypokalemia.

During the course of treatment, the patient received symptomatic therapy for gastrointestinal complaints, including Diagit 3 times daily, Ondancentrone 3 times with 4mg injections, and Esomeprazole 40 mg injection once daily. The patient also received 4 units of packed red blood cell transfusions, resulting in an improvement in her condition and an increase in hemoglobin to 10.8 g/dl. Intravenous potassium supplementation was given at 50 mEq in 500 ml NaCl every 12 hours for a total of 8 doses, correcting hypokalemia to 2.9. This was followed by oral potassium supplementation with KRS 3 times daily.

DISCUSSION

Hypokalemia is defined as a plasma potassium concentration of less than 3.5 mmol/l. The causes of hypokalemia can be categorized into four main groups: inadequate intake (e.g., anorexia nervosa, prolonged malnutrition), gastrointestinal losses (e.g., vomiting, diarrhea), potassium shifting from extracellular fluid to intracellular fluid, and excessive renal losses.[5] Patients with hypokalemia need to undergo an evaluation to determine its underlying cause. Hypokalemia is a condition that requires prompt treatment. Warning signs for immediate attention include severe hypokalemia (potassium level <2.5 mEq/l), hypokalemia with a sudden onset, palpitations, muscle weakness, changes in electrocardiogram (ECG) patterns, or if the patient has a history of heart disease or underlying hepatic cirrhosis.[6]

In this case, a 24-year-old woman presented with complaints of severe weakness in all extremities that had been progressively worsening over the past day. There was no history of regular medication use. Laboratory tests revealed hypokalemia (potassium level of 2.4 mEq/l), hypomagnesemia (magnesium level of 1.4 mEq/l), and metabolic alkalosis. The possibility of potassium loss due to gastrointestinal factors could not be ruled out. Thyroid hormone levels in the patient were within normal limits, eliminating the possibility of potassium shifting from the extracellular to intracellular space as seen in thyrotoxic periodic paralysis.

To identify the underlying problem, we followed the algorithm outlined in Figure 1. This algorithm reveals that, after excluding reduced intake and intracellular shifts as potential causes of hypokalemia, an examination of the renal response can help clarify the source of potassium loss.[7] Factors such as extracellular fluid (ECF) volume status, blood pressure, and associated acid-base disorders can assist in distinguishing the causes of excessive renal potassium loss. One rapid and straightforward test designed to assess the driving force for net potassium secretion is the trans tubular potassium concentration gradient (TTKG). TTKG is calculated as the ratio of potassium concentration in the lumen of the cortical collecting duct ([K+]CCD) to that in peritubular capillaries or plasma ([K+]P). The validity of this measurement relies on three assumptions: minimal solute reabsorption in the medullary collecting duct (MCD), potassium neither

secreted nor reabsorbed in the MCD, and knowledge of the fluid osmolality in the terminal CCD. The TTKG can be calculated using the formula provided.[8,9] Additional 24-hour urine collection tests were conducted to establish the diagnosis.

The results of the 24-hour urine collection test revealed a urinary sodium level of 125 mmol/l/24 hours, urinary potassium level of 34 mmol/l/24 hours, urinary chloride level of 152 mmol/l/24 hours, and urinary calcium level of 85.3 mg/24 hours. Additionally, the TTKG was calculated at 12.8 (TTKG >4 indicating increased potassium secretion in the distal tubules). The primary cause of hypokalemia in this patient is potassium loss through the renal tubules. Based on the patient's medical history, physical examination findings, and the diagnostic tests performed, the diagnosis of Gitelman syndrome has been established.

Gitelman syndrome (GS) is a rare tubulopathy characterized by the loss of salt, leading to hypokalemic metabolic alkalosis with concurrent hypomagnesemia and hypocalciuria. This condition is inherited in a recessive manner and is caused by inactivating mutations in the SLC12A3 gene, which encodes the thiazide-sensitive sodium-chloride cotransporter (NCC).[3,10] In this case, genetic testing was not performed. Genetic analysis is not routinely conducted due to limitations in facilities and cost constraints.

The pathogenesis of Gitelman's syndrome can explain the clinical and laboratory findings we found on this patient. As mentioned above, the primary defect in this disorder is an impairment in sodium reabsorption in distal tubule. The tubular defect in sodium chloride transport is thought to initiate the following sequence. Initial salt loss leads to mild volume depletion, resulting in activation of the renin angiotensin-aldosterone system. The combination of hyperaldosteronism and increased distal flow (due to the re-absorptive defect) enhances potassium and hydrogen secretion at the secretory sites in the collecting tubules, leading to hypokalemia and metabolic alkalosis. The renal release of vasodilator prostaglandins (prostaglandin E2 and prostacyclin) is also increased in this condition and may partially explain why the blood pressure remains normal. Consequently, this patient presented with hipokalemia with metabolic alkalosis and normal blood pressure.[11]

GS has long been considered a benign tubulopathy, usually detected during adolescence or adulthood. The key clinical complaints and manifestations suggesting a diagnosis of GS include the following: salt craving (preference for salty food or a salted treat during childhood); muscle weakness, fatigue, limited sport performance or endurance; episodes of fainting, cramps, tetany, paresthesia, carpopedal spasms; growth retardation, pubertal delay, short stature; thirst or abnormal drinking behaviour; episodes of abdominal pain. Dizziness, vertigo, polyuria, nocturia, palpitations, joint pain, and visual problems may be reported in adults. Severe fatigue may also be observed in some patients and a lower-than-average blood pressure may be seen, consistent with the tendency to salt wasting. In the patient, complaints of weakness in the extremities were observed, which can be attributed to the condition of hypokalemia.[12,13]

Biochemical findings are crucial to the diagnosis of GS, and this patient showed classical abnormalities related to this syndrome, such as hypokalemia with inappropriate renal potassium wasting, metabolic alkalosis, hypomagnesemia. Although the 24-hour urine sample may be more accurate, spot urine samples are usually adequate to evaluate the renal excretion of potassium, magnesium, calcium, sodium, and chloride. Hypocalciuria and concurrent hypomagnesemia are strong predictors of the presence of GS, but the presence of hypocalciuria is variable, and hypomagnesemia is not always present.[14]

Chronic hypokalemia of Gitelman syndrome may induce tubulointertitial injury although direct causal relationship between the degree of hypokalemia and GFR is not established in Gitelman syndrome. Ongoing sodium loss with hyperaldosteronism as the risk factor for the renal pathologic change. This patient has decrease of renal function which shown on increased creatinine serum and decrease GFR 31 ml/min/1.73m^2. In this case we postulate that the cause of chronic progressive renal impairment is most probably due to recurrent episode of acute kidney injury associated with volume depletion.[15]

The tubular defect in Gitelman's syndrome cannot be corrected. As a result, treatment (which must be life-long) is aimed at minimizing the effects of the secondary increases in prostaglandin and aldosterone production.[11] The combination of a nonsteroidal anti-inflammatory drug (NSAID) and a potassium-sparing diuretic (such as spironolactone or amiloride, often in higher than usual doses of up to 300 and 40 mg/day, respectively, to more completely block distal potassium secretion) can raise the plasma potassium concentration toward normal, largely reverse the metabolic alkalosis, and partially correct the hypomagnesemia. Most patients require oral potassium and magnesium supplementation, since drug therapy is usually incompletely effective. However, the restoration of normal magnesium and potassium balance is often difficult to achieve.[16,17]

The patient received intravenous therapy with KCl (potassium chloride) at a dose of 50 mEq in 500 ml of NaCl 0.9% every 12 hours, totalling 8 administrations. Intravenous potassium therapy was administered due to severe hypokalemia. This resulted in an increase in serum potassium levels from 2.4 to 2.9. The treatment was then continued with oral potassium tablets, taken three times daily at a dose of 1 tablet per dose. Additional symptomatic therapy was provided for gastrointestinal complaints. It's important to note that individuals with Gitelman syndrome must adhere to a consistent medication regimen as prescribed by their healthcare provider throughout their

lifetime. They should also take care to maintain an appropriate fluid and electrolyte balance.[18]

CONCLUSION

Chronic hypokalemia warrants a thorough evaluation of its etiology using an appropriate diagnostic pathway. Potassium loss through the renal tubules in cases of Gitelman syndrome is a rare condition. Hypokalemia can have severe consequences, including fatal outcomes when it reaches a severe state with complications such as paralysis, muscle weakness in the extremities, respiratory muscle weakness, and cardiac rhythm disturbances. Treatment for patients with Gitelman syndrome primarily involves replacing lost potassium and magnesium.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Merwe PD, Rensburg MA, haylett WL, Bardien S, davids MR. Gitelman syndrome in a South African family presenting with hypokalaemia andunusual food cravings. BMC Nephrol. 2017;18:38:1-8.
2. Urwin S, Willows J, Sayer JA. The challenges of diagnosis and management of Gitelman syndrome. Clin Endocrinol (Oxf). 2020;92(1):3-10.
3. Blanchard A, Bockenhauer D, Bolignano D, Calo LA, Cosyns E, devuyst O, et al. Gitelman syndrome: consensus and guidance froma Kidney Disease: Improving Global Outcomes(KDIGO) Controversies Conference. Kidney Int. 2017;91(1):24-33.
4. Nessa L, Singh A, Sharif MW, Enabi J, Bashir M. Diagnostic Challenge of Gitelman Syndrome: A Rare but Significant Cause of Electrolyte Imbalance. J Clini Nephrol. 2023;7:53-6.
5. Kokko JP. Cecil Textbook of Medicine. In: Goldman L, Ausiello D, editors. Fluids and Electrolytes. 22nd ed. Philadelphia: Saunders. 2004;683-5.
6. Anthony J, Niah W, Potassium Disorder: Hypokalemia and Hyperkalemia. Am Fam Phys. 2015;92(6):487-91.
7. Umami V, Oktavia D, Kunmartini S, Wibisana D, Siregar P. Diagnosis and Clinical Approach in Gitelman Syndrome. Acta Med Indones. 2011;43(1):53-8.
8. Lin SH. Laboratory test to determine the cause of hypokalemia and paralysis. Arch Intern Med. 2004;164:1561-6.
9. Groeneveld J, Sijpkens Y, Lin S. An approach to the patient with severe hypokalemia: the potassium quiz. Q J Med. 2005;98:305.
10. Unwin RJ, Luft CF, Shirley DG. Pathophysiology and Management of Hypokalemia: a clinical perspective. J Nat Rev Nephrol. 2011;7(2):75-84.
11. Kurtz I. Molecular pathogenesis of Bartter's and Gitelman's syndromes. Kidney Int. 2018;54:1396.
12. Cruz DN, Shaer AJ, Bia MJ. Gitelman's syndrome revisited: An evaluation of symptoms and health-related quality of life. Kidney Int. 2021;59:710.
13. Cruz DN, Simon DB, Nelson-Williams C. Mutations in the Na-Cl cotransporter reduce blood pressure in humans. Hypertension. 2011;37:1458.
14. Urwin S, Willows J, Sayer JA. The challenges of diagnosis and management of Gitelman syndrome. Clin Endocrinol (Oxf). 2020;92:3-10.
15. Graziani G, Fedeli C, Moroni L, Cosmai L, Badalamenti S, Ponticelli C. Gitelman syndrome: pathophysiological and clinical aspects. QJM. 2010;103(10):741-8.
16. Colussi G, Rombola G, De Ferrari ME. Correction of hypokalemia with antialdosterone therapy in Gitelman's syndrome. Am J Nephrol. 2004;14:127.
17. Griffing GT, Komanicky P, Aurecchia SA. Amiloride in Bartter's syndrome. Clin Pharmacol Ther. 2012;31:713.
18. Bockenhauer D. Bartters Syndrome. National Organization for Rare Disorder (NORD). 2016. Available at: http://raredisease.org/rare-disease/bartters-syndrome/. Accessed on 09 September 2023.

Cite this article as: Kusumadewi IGSAJ, Subadra PNAN, Suryana K. A rare case: evaluation of chronic hypoklemia in patient with Gitelman syndrome. Int J Adv Med 2023;10:845-8.