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CASE REPORT

Gitelman syndrome, a rare cause of refractory hypokalemia. A case report

Síndrome de Gitelman, causa rara de hipopotasemia refractaria. Reporte de caso

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Abstract

Introduction: Gitelman syndrome is a rare hereditary primary renal tubular disorder, with a prevalence of approximately 1 to 10 cases per 40 000 people. It does not have specific symptoms, so its diagnosis depends on high clinical suspicion by the treating physical and a sequential approach to hypokalemia, especially in young patients. Thus, a diagnostic algorithm is proposed at the end of this report.
Case presentation: A 23-year-old woman with a history of hospitalization due to hypokalemia presented to the emergency service with intermittent cramping in her lower limbs, which was exacerbated by gastrointestinal symptoms. Laboratory tests reported the following findings: metabolic alkalosis, elevated levels of potassium, magnesium, chloride and sodium in urine, and reduced levels of calcium in urine. Thus, potassium supplementation and eplerenone administration were started, obtaining the complete resolution of symptoms. At her last follow-up appointment, the patient was asymptomatic, and her serum electrolyte levels were normal. In addition, during her hospital stay and due to the high suspicion of Gitelman syndrome, a genetic study was performed, which reported a mutation of the SCL12A3 gene, confirming the diagnosis.
Conclusion: The sequential approach to a patient with recurrent hypokalemia is very important to reach an accurate diagnosis among a wide range of differential diagnoses.

Resumen

Introducción. El síndrome de Gitelman es un trastorno tubular renal primario hereditario poco frecuente, con una prevalencia aproximada de 1 a 10 casos por cada 40 000 personas; su sintomatología es inespecífica, por lo que su diagnóstico depende de la alta sospecha clínica por parte del médico tratante y de un abordaje secuencial de la hipopotasemia, sobre todo en pacientes jóvenes, para lo cual se propone un algoritmo diagnóstico al final de este reporte.
Presentación de caso. Mujer de 23 años con antecedente de hospitalización por hipopotasemia, quien consultó por calambres musculares intermitentes en miembros inferiores, los cuales se agudizaron debido a síntomas gastrointestinales. En los exámenes de laboratorio se reportaron los siguientes hallazgos: alcalosis metabólica, niveles elevados de potasio, magnesio, cloro y sodio en orina, y niveles reducidos de calcio en orina, por lo que se inició suplementación de potasio y manejo con eplerenona, obteniéndose resolución completa de los síntomas. En su último control, la paciente se encontraba asintomática y sus niveles séricos de electrolitos eran normales. Además, durante la hospitalización, y debido a la alta sospecha de síndrome de Gitelman, se solicitó estudio genético que reportó mutación del gen SCL12A3, confirmándose el diagnóstico.
Conclusión. El abordaje secuencial de un paciente con hipopotasemia recurrente es de gran importancia para realizar un diagnóstico certero ante una amplia gama de diagnósticos diferenciales.

Introduction

Hereditary tubulopathies comprise a large group of diseases involving different segments of the nephron.[1] Gitelman syndrome is one of these diseases and is rarely reported in the related literature.[2] In Colombia, as of the date of this report, there are no studies or records that evaluate the prevalence of this syndrome in the general population, only isolated case reports.[3] However, in 2017, Blanchard *et al.*[4] established that worldwide prevalence is approximately 1 to 10 cases per 40 000 people, with a possible higher rate in Asia.

Gitelman syndrome is classified as an autosomal recessive hereditary tubulopathy caused by a mutation in the *SCL12A3* gene located on the long arm of chromosome 16 (16q13).[5] There are approximately 500 known mutations in this gene, which codes for the thiazide-sensitive sodium/chlorine (Na-Cl) cotransporter located on the apical surface of the distal convoluted tubule. These mutations alter the normal function of this protein and therefore lead to sodium chloride reabsorption and volume depletion that ends up increasing the release of hormones such as renin and aldosterone, which in turn leads to potassium and hydrogen losses.[5,6]

This syndrome is an entity usually detected in adolescents or young adults[4] and has a broad spectrum of manifestations ranging from mild symptoms, such as muscle weakness, fatigue, thirst, nocturia or cramps, to severe conditions, such as rhabdomyolysis, tetanus and even life-threatening arrhythmias.[7] Similarly, Bettinelli *et al.*,[8] in a study of 34 pediatric patients with primary renal tubular hypokalemic metabolic alkalosis divided into two groups, one of 16 participants with Bartter syndrome and one of 16 participants with Gitelman syndrome, found that the manifestations of the latter group were metabolic alkalosis hypokalemia with hypomagnesemia and hypocalciuria.

The following is the case of a patient with Gitelman syndrome, in which the clinical, paraclinical, and molecular diagnostic behavior of this disease is described in order to place it within the broad range of differential diagnoses of recurrent or refractory hypokalemia, as well as to present its therapeutic approach.

Case presentation

A 23-year-old mixed-race woman visited the emergency department of a quaternary care center in Cali, Colombia, due to intermittent muscle cramps in the lower limbs during the night, especially in the calves, lasting between 1 minute and 2 hours. These cramps, which had started three months earlier and were being treated with non-steroidal anti-inflammatory drugs (without complete remission), were accompanied by asthenia, adynamia, and a sensation of palpitations, and worsened shortly before the assessment due to gastrointestinal symptoms (emesis and fluid stools). Her only relevant clinical history included a hospital admission due to severe hypokalemia (1.9 mmol/L) one year earlier; on that occasion, she received intravenous fluids and no further studies were performed.

On admission, physical examination revealed hypotension (90/60 mmHg), signs of dehydration (xerostomia and tachycardia), intermittent muscle fasciculations in the lower limbs, and hyperreflexia. Laboratory tests showed severe hypokalemia with hypomagnesemia, normal renal function, hyperreninemia, and normal aldosterone levels (Table 1). Given the findings, potassium (central potassium chloride at 15 mEq/hour for 6 hours and then at 5 mEq/hour) and magnesium (1.5 g of intravenous magnesium sulfate every 8 hours) replacement therapy was initiated, which resulted in an improvement of her clinical condition after 3 days, when an electrolyte follow-up test showed normal ranges (K: 3.9 mEq/L and Mg: 1.10 mEq/L).

Table 1. Laboratory test results.

Lab test		Result	Normal values
Potassium		1.9	3.5-5.0 mEq/L
Magnesium		0.7	0.85-1.10 mEq/L
Blood urea nitrogen (BUN)		35	6- 20 mg/dL
Creatinine (Cr)		0.9	0.6- 1.1 mg/dL
Arterial gases	pH	7.51	7.35-7.45
	Bicarbonate (HCO_3)	34	22-28 mEq/L
	PCO_2	38	35-45 mmHg
Plasma renin activity		8.91	1.9-3.7 ng/mL/hour
Aldosterone		16.8	0.0- 1.2 mg/dL
Aldosterone-to-renin ratio		0.19	<25

Source: Own elaboration.

Two days after completing the treatment, the patient had an electrolyte disorder again (K: 2.0 mEq/L and Mg: 0.7 mEq/L) and muscle cramps, this time without an apparent cause (absence of gastrointestinal symptoms).

The arterial blood gas test showed metabolic alkalosis. In addition, the urine electrolytes test (Table 2) found elevated levels of potassium, magnesium, chlorine, and sodium, and reduced levels of calcium. It was decided to restart potassium and magnesium replacement (peripheral at 4 mEq/L every 8 hours and 1.5 g intravenously every 8 hours, respectively) and to start additional administration of eplerenone at a dose of 25 mg/day. Normal electrolyte levels were observed in a follow-up test performed 3 days after treatment was restarted (K: 4.1 mEq/L and Mg: 1.2 mEq/L), thus the patient was prescribed a diet, oral potassium replacement with 15 cm^3 of potassium gluconate every 8 hours, and an aldosterone antagonist administered at the same dose. Renal and urinary tract ultrasound was also performed, which allowed to rule out morphological alterations.

Table 2. Electrolytes in urine.

Lab test	Result	Normal values
Potassium in spot urine sample	193.8	20-80 mEq/L
Magnesium in spot urine sample	38.3	2.4-7.4 mEq/L
Calcium in spot urine sample	10	13.4-42 mEq/L
Sodium in spot urine sample	168	20-110 mEq/L
Chlorine in spot urine sample	222	55-125 mEq/L
24-hour urine calcium	≤1	2.5-7.5 mEq/24 hours

Source: Own elaboration.

In a young patient with a history of recurrent hypokalemia of renal origin (elevated urine potassium) associated with hypomagnesemia, normocalcemia with hypocalciuria, contraction alkalosis, secondary hyperaldosteronism and hyperreninemia, and after ruling out other diagnostic possibilities, Gitelman syndrome was suspected. Consequently, genetic studies were requested to identify the causal mutation.

Amplification and sequencing analysis of the *SCL12A3* gene revealed a homozygous intronic mutation within 7+1 G>T (NM_001126108.2(SLC12A3):c.964+1G>T), consisting of a substitution of guanine for thymine at position 964; since this is a donor splice site at intron 7, an absent or altered protein product is expected from this mutation.

Since the patient was stable and her symptoms disappeared, she was discharged with the following indefinite outpatient management: potassium gluconate oral solution 31.2% (15 cm³ every 8 hours), magnesium gluconate (550 mg orally every 8 hours), and eplerenone (50 mg/day orally). At her last follow-up, 1 year after recovery, her serum electrolyte levels were normal (K: 4.0 mEq/L and Mg: 1.26 meq/L) and she reported no recurrence of similar symptoms.

Discussion

Gitelman syndrome (entry #263800, according to the Online Mendelian Inheritance in Man® phenotype and genotype registry)[9] is a rare renal tubular salt-wasting disorder that affects adolescents and young adults. It is caused by a dysfunction of the thiazide-sensitive Na/Cl cotransporter that results in a mutation of the *SCL12A3* gene.[5,10-13] This syndrome is characterized by biochemical abnormalities such as hypomagnesemia, hypocalciuria and secondary hyperaldosteronism, which induce hypokalemia and metabolic alkalosis, the latter two being recurrent when the appropriate treatment is not administered.[10]

Symptoms of Gitelman syndrome include cramps, paresthesia, fatigue, and recurrent episodes of emesis, diarrhea, or fever accompanied by carpopedal spasms and hypotension.[11] In this sense, its diagnosis is based on the clinical symptoms associated with biochemical abnormalities and is confirmed by molecular biology techniques.[10]

The patient presented in this case report had a history of hospitalization for hypokalemia for which potassium replacement therapy was prescribed. She consulted due to intermittent cramps in her lower limbs over the past three months, which became severe due to gastrointestinal symptoms, as described in the medical literature.[10-13]

Laboratory tests performed on admission detected hypokalemia once again; since this is a condition associated with biochemical alterations characteristic of Gitelman syndrome,[10,11] systemic diseases such as congestive heart failure or cirrhosis were ruled out.[12] As a result, two genetic disorders were considered as differential diagnoses: Gitelman syndrome and Bartter syndrome.[3,5] The latter was considered improbable since it usually manifests at a younger age and with a more severe phenotype, and because urine calcium excretion is often increased and magnesemia is normal or slightly reduced[11,13] (Table 3).

Table 3. Differences between Bartter and Gitelman syndromes.

Disease	Inheritance	Age of onset	Hypotension	Clinical symptoms	Laboratory tests
Gitelman syndrome	AR, AD **Co-carrier Na/Cl DCT**	**Young adults**	Present (may be normal)	Paresthesias Cramps Muscle fatigue **No kidney failure** Polyuria/**polydipsia** **No dehydration** No growth retardation	Hypomagnesemia **Decreased urine calcium excretion** Normal urinary prostaglandins (PGE 2)
Bartter syndrome	AR, AD **Na/K/2Cl cotransporter LH**	**Children (90%)**	Normal or rarely low	**Sensorineural deafness** Facial weakness **Renal failure** (nephrocalcinosis) Polyuria/nocturia (80%) **Dehydration** **Growth retardation**	Normal magnesium (rarely low) **Increased urine calcium excretion** **Increased urinary prostaglandins**

AR: autosomal recessive; AD: autosomal dominant; DCT: distal convoluted tubule; LH: loop of Henle.
Note: Major differences are highlighted in bold.
Source: Own elaboration based.

According to the literature, the patient's symptoms are explained by the loss of sodium chloride caused by dysfunction of the thiazide-sensitive Na/Cl cotransporter secondary to a mutation of the *SCL12A3* gene. This dysfunction is accompanied by decreased magnesium absorption and increased calcium reabsorption in the first part of the distal convoluted tubule, resulting in hyperreninemia and secondary hyperaldosteronism due to an increase in urinary sodium concentration, as well as increased sodium and water reabsorption by the principal cells and increased potassium secretion in the nephron. Likewise, the intercalated cells located in the collecting ducts secrete a greater amount of hydrogen ions due to a predominantly negative intratubular charge (by chlorine ions).

As mentioned above, the diagnosis of Gitelman syndrome is confirmed by DNA mutation analysis of the *SCL12A3* gene, in which more than 500 mutations have been detected.[6] The mutation detected in the patient of the case described here (homozygous intronic mutation in 7+1 G>T [NM_001126108.2(SLC12A3):c.964+1G>T], consisting of a substitution of guanine by thymine at position 964, is very rare, with few descriptions in the literature.[12,14]

The recommended treatment for Gitelman syndrome is magnesium supplementation combined with a diet high in sodium and potassium, as well as potassium replacement (40-100 mEq potassium chloride/day). If there is no improvement in potassium levels, it is necessary to administer potassium-sparing drugs such as aldosterone antagonists (up to 100mg of spironolactone orally per day or 25mg of eplerenone orally every 12 hours) or sodium channel blockers (5mg of amiloride orally every 12 hours).[15] In accordance with this, the patient reported here received management with diet, potassium replacement and eplerenone, which led to a favorable course.

Figure 1 presents the algorithm used to reach the patient's definitive diagnosis. According to this algorithm, the young woman presented hypokalemia (Figure 1a), increased urinary potassium values (>40 mmol/L) (Figure 1b), low blood pressure (Figure 1c), and metabolic alkalosis (Figure 1d). In contrast, she did not present comorbidities such as heart failure or cirrhosis (without clinical manifestations) (Figure 1e). Based on the findings, two tubulopathies were suspected: Bartter syndrome and Gitelman syndrome; however, the former was ruled out because the symptoms were more associated with the latter. In this regard, it was decided to request a genetic analysis that documented mutations in the *SCL12A3* gene and confirmed the diagnostic suspicion. All of the above confirmed that the sequential approach to a young patient with hypokalemia is useful to establish a timely diagnosis and provide adequate treatment.

Conclusion

Gitelman syndrome is a rare disease with nonspecific symptoms, so an adequate sequential approach to a patient with recurrent hypokalemia is of great importance for making an accurate diagnosis. Likewise, it allows for effective and timely management that favors long-term prognosis and reduces hospital readmission rates.

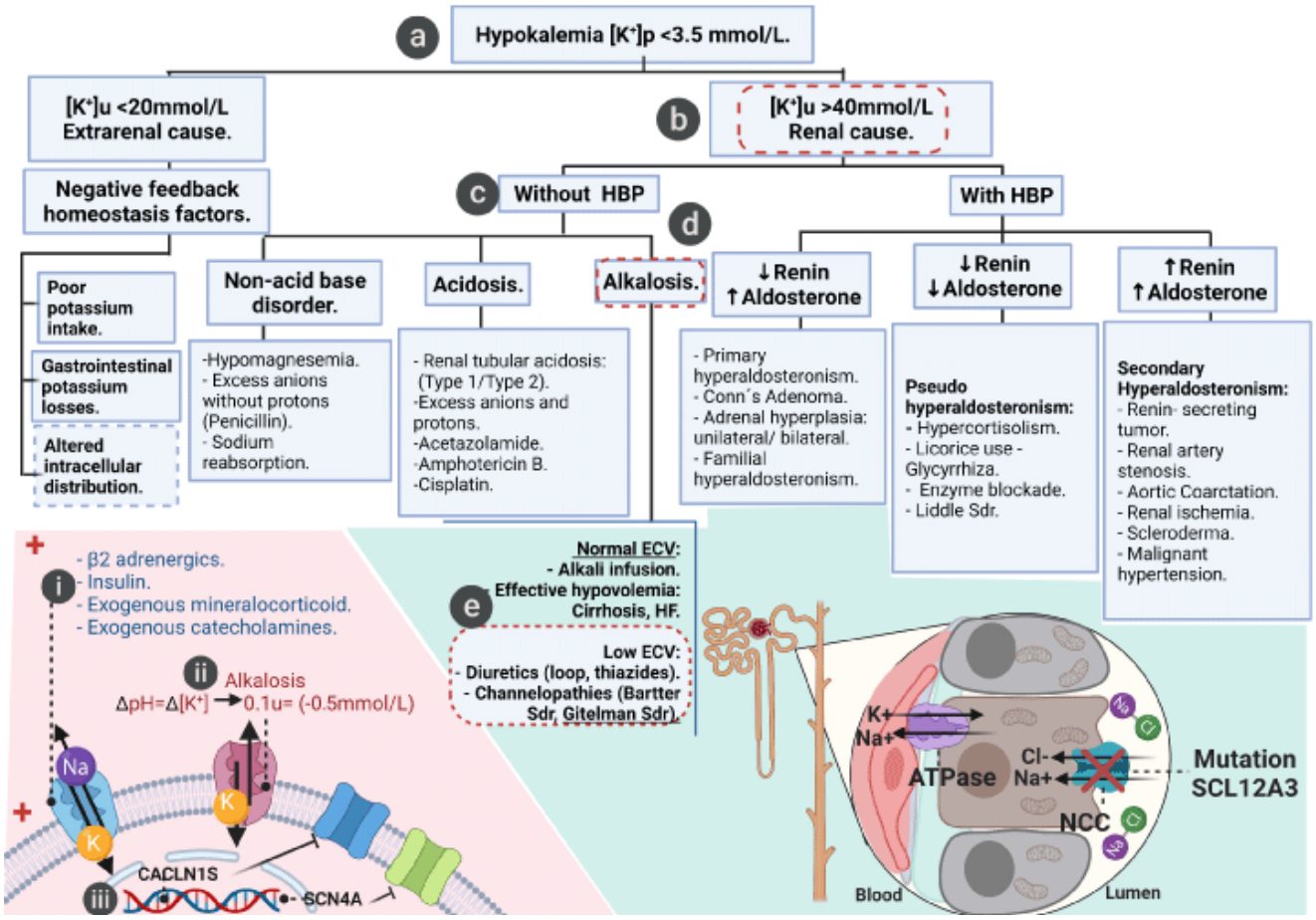

Figure 1. Hypokalemia diagnostic algorithm.
K: potassium; HBP: high blood pressure; ECV: extracellular volume; HF: heart failure.
Source: Elaboration based on Vidal-Petiot *et al.*[12] The image was created using BioRender.com

Ethical considerations

The patient's informed consent was obtained for the preparation of this case report.

Conflicts of interest

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References

1. Seyberth HW, Schlingmann KP. Bartter- and Gitelman like syndromes: salt-losing tubulopathies with loop or DCT defects. Pediatr Nephrol. 2011;26(10):1789-802. https://doi.org/fctr2h.

2. Ji W, Foo J, O'Roak BJ, Zhao H, Larson MG, Simon DB, *et al.* Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nature Genetics. 2008;40(5):592-9. https://doi.org/b227sx.
3. Serna-Higuita LM, Betancur-Londoño LM, Medina-Vásquez CM, Urbano L, García AM, Pineda-Trujillo N, *et al.* Phenotypic Characterization of 14 Colombian Families with Bartter and Gitelman's Syndromes. JOJ uro & nephron. 2017;3(3). https://doi.org/hxqc.
4. Blanchard A, Bockenhauer D, Bolignano D, Calò, LA, Cosyns E, Devuyst O, *et al.* Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017;91(1):24-33. https://doi.org/f9j5tk.
5. Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. Trans Assoc Am Physicians. 1966;79:221-35.
6. Fujimura J, Nozu K, Yamamura T, Minamikawa S, Nakanishi K, Horinouchi T, *et al.* Clinical and genetic characteristics in patients with Gitelman syndrome. Kidney Int Rep. 2018;4(1):119-25. https://doi.org/hwgd.
7. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB. Gitelman's syndrome revisited: an evaluation of symptoms and health- related quality of life. Kidney Int. 2001;59(2):710-7. https://doi.org/bwms8t.
8. Bettinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, Appiani AC, *et al.* Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. J Pediatr. 1992;120(1):38-43. https://doi.org/fvvkjh.
9. 263800 Gitelman Syndrome. OMIM® Online Mendelian Inheritance in Man®. An Online Catalog of Human Genes and Genetic Disorders. Baltimore: Johns Hopkins University; [cited 2020 Jul 8]. Available from: https://bit.ly/3wRJDei.
10. Jeck N, Schlingmann KP, Reinalter SC, Kömhoff M, Peters M, Waldegger S, *et al.* Salt handling in the distal nephron: lessons learned from inherited human disorders. Am J Physiol Regul Integr Comp Physiol. 2005;288(4):R782-95. https://doi.org/b2n2m7.
11. Cotovio P, Silva C, Oliveira N, Costa F. Gitelman syndrome. BMJ Case Rep. 2013;2013:bcr2013009095. https://doi.org/gbcsnk.
12. Vidal-Petiot E, Ayari H, Flamant M. Hipopotasemia. EMC - Tratado de medicina. 2017;21(2):1-7. https://doi.org/hwgg.
13. Knoers NV, Levtchenko EN. Gitelman syndrome. Orphanet J Rare Dis. 2008;3(1):22. https://doi.org/dqk35h.
14. Vargas-Poussou R, Dahan K, Kahila D, Venisse A, Riveira-Munoz E, Debaix H, *et al.* Spectrum of mutations in Gitelman syndrome. J Am Soc Nephrol. 2011;22(4):693-703. https://doi.org/dvbz7t.
15. Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, Molina AM, *et al.* Gitelman's variant of Bartter's syndrome, inherited hypokalemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet. 1996;12(1):24-30. https://doi.org/fwh3pz.