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Gitelman syndrome patient managed with amiloride during pregnancy and lactation

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Abstract

Gitelman Syndrome (GS) is a rare autosomal-recessive tubular disorder characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, hyperreninemic hyperaldosteronism, and normotension. Management of GS during pregnancy is particularly challenging due to pregnancy-associated renal physiological changes and due to controversial safety profiles regarding teratogenicity of medications commonly used for GS management in non-pregnant patients. We report a case of a 20-year-old female patient diagnosed of GS who was treated with amiloride during pregnancy and lactation due to persistent hypokalemia resistant to oral supplementation therapy. Use of amiloride facilitated control of hypokalemia and hypomagnesemia in the mother without causing any noticeable side effects in the newborn.

Keywords Gitelman, Pregnancy, Amiloride, Hypokalemia, Hypomagnesemia

Case report

Presentation

A 20-year-old woman presented to the nephrology clinic with profound hypokalemia. 6 weeks before her presentation, she presented to the emergency department with lower back pain due to a fall injury, which resulted in an L1 vertebral burst fracture. At the time of her admission for her fall injury, she was found to be profoundly hypokalemic (2.2 mmol/L) and hypomagnesemic (1.2 mg/dL). Bicarbonate concentration was 27 mmol/L. Her blood pressure was 90s/60s mmHg. She was started on potassium and magnesium oral supplementation 30mEq potassium chloride and 400 mg magnesium oxide twice daily. Despite oral supplementation therapy, at the time she presented to our clinic, her potassium was 2.6 mmol/L, magnesium was 1.2 mg/dl, chloride was 100 mmol/L, and sodium was 140 mmol/L. Moreover, her trans-tubular potassium gradient (TTKG) was 10.4 and her fractional excretion of magnesium was 6.25%, supporting renal potassium and magnesium wasting, respectively. Her urinary magnesium excretion was 154 mg/day with a range between 51 and 270 mg/day. Urinary sodium was 123 mEq/day with a range between 41 and 227 mEq/day and urinary calcium was low at 46 mg/day. Plasma renin was elevated, 56.3 pg/ml (Reference range: 2.5–45.7 pg/mL), suggesting volume contraction, while aldosterone was 25.7 ng/dL (4.0–31.0 ng/dL) when plasma potassium was 2.8 mmol/L. The combination of low/normal blood pressure with hyperreninemia, hypokalemia, hypomagnesemia and hypocalciuria with renal potassium and magnesium wasting strongly suggested a diagnosis of GS (**Blanchard A et al. KI 2017 91: 24–33**). Refer to Table 1.

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Table 1 Maternal electrolytes level at the time of diagnosis

	Electrolyte	Normal Range	Result at Time of Diagnosis
1	Serum Potassium (mmol/L)	3.5–5.0	2.6
2	Serum Magnesium (mg/dL)	1.7–2.2	1.2
3	Serum Chloride (mmol/L)	98–107	100
4	Serum Bicarbonate (mEq/L)	22–28	27
5	Serum Creatinine (mg/dL)	0.6–1.1	0.82
6	Serum Sodium (mmol/L)	135–145	140
7	Plasma Renin (pg/mL)	2.5–45.7	56.3
8	Aldosterone (ng/dL)	4.0–31.0	25.7
9	Trans-tubular potassium gradient (TTKG)	>6	10.4
10	Fractional excretion of Magnesium (%)	2–5	6.25
11	Urinary Magnesium (mg/day)	20–60	154
12	Urinary Sodium (mEq/day)	40–220	123
13	Urinary Calcium (mg/day)	100–300	46

Genetic diagnosis

GS diagnosis was confirmed by DNA sequencing of the *SLC12A3* gene, which identified two previously reported heterozygous pathogenic variations. The first variation, c.1180+1G>T, is predicted to result in aberrant splicing of the *SLC12A3* transcript. This variation has been reported before in Roma families (**Coto E et al.:*A new mutation (intron 9+1 G>T) in the SLC12A3 gene is linked to Gitelman syndrome in Gypsies*, Kidney Int. 2004 Jan 65(1):25–9.** https://doi.org/10.1111/j.1523-1755.2004.00388.xThe second variation identified in our patient, p.Gly741Arg, has been previously reported (**Ji W et al.**: ***Rare independent mutations in renal salt handling genes contribute to blood pressure variation*, Nat Genet. 2008 May ; 40(5): 592–599.** https://doi.org/10.1038/ng.118 Like our patient, the majority of patients with GS are compound heterozygous for *SLC12A3* variations (**Blanchard A et al. KI 2017 91: 24–33)**.

Treatment

The patient was started on liberal salt intake, 60mEq potassium chloride supplementation, and 800 mg magnesium oxide supplementation daily. A month later, her potassium was 2.8 mmol/L and her magnesium was 1.6 mg/dl. Her serum magnesium levels were closely monitored by her primary care physician, obstetrician, and nephrologist. Intravenous magnesium was administered as needed to manage the persistent hypomagnesemia. Potassium and magnesium supplementation continued, and the patient was started on 5 mg Amiloride daily to decrease renal magnesium and potassium excretion. 2 weeks later, amiloride was increased to 10 mg daily. After around 6 months of treatment the patient was found to be pregnant and was counselled about the risks and benefits of using amiloride during pregnancy to maintain stable serum electrolytes levels. Amiloride was discontinued during the first trimester of pregnancy and resumed thereafter. The patient had an uneventful spontaneous vaginal delivery at 39 weeks of gestation, giving birth to a healthy infant. The infant's birth weight was 3.2 kg, height was 50 cm, and Apgar scores were 8 at 1 min and 9 at 5 min. There were no obvious external body malformations observed. Amiloride was initially discontinued during breastfeeding because of the absence of literature in support of using it. After a 6 weeks period it was resumed due to persistent hypokalemia. The baby's electrolytes were monitored thereafter for the effects of the maternal medication on the baby. While on amiloride, the baby's labs showed a serum potassium of 5.8 mmol/L and a magnesium concentration of 2.3 mg/dl. Spot urine concentrations of magnesium were <1.4 mg/dl, urine creatinine was 5 mg/dl, and urine potassium was 5 mmol/L. Amiloride was stopped for one week and labs were repeated, which showed a serum potassium of 4.8mmol/L, magnesium 2.2 mg/dL and a urine magnesium of 1.7 mg/dl, while urine creatinine was 8 mg/dl, and urine potassium 6mmol/L. Refer to Fig. 1.

Discussion

Gitelman Syndrome is a rare autosomal recessive hereditary tubular disorder characterized by metabolic alkalosis, hypokalemia, hypomagnesemia [1], and normal blood pressure [2], first described in 1966 by Gitelman and his colleagues [3]. GS is caused by loss of function mutations in the *SCL12A3* gene, which encodes the thiazide-sensitive sodium chloride cotransporter that reabsorbs sodium chloride in the apical membrane of the distal convoluted tubule [4, 5]. Over 350 variations in the *SLC12A3* gene have been identified until now [6]. The majority of these are missense mutations, but splicing, nonsense mutations, and deletions and duplications have also been identified (ref: Vargas-Poussou et al. JASN 2011, 22: 693–703).

Hypokalemia, a key manifestation of GS, is a result of two underlying mechanisms. First, loss of function of the sodium chloride cotransporter results in decreased sodium chloride reabsorptionin the distal convoluted tubule and increased sodium delivery to the downstreamconnecting tubule and cortical collecting duct, which comprise the aldosterone-sensitive distal nephron. Increased sodium reabsorption by the epithelial sodium channel provides an increased driving force for potassium secretion through the potassium secretory channels, ROMK (Renal Outer Medullary Potassium) and BK (Big Potassium, also known as Maxi-K). This is potentiated by volume depletion, which activates the epithelial sodium channel via aldosterone and angiotensin II, as well as increased tubular flow, which stimulates the epithelial sodium channel and BK [4].Second, hypomagnesemia relieves gating of ROMK by magnesium, allowing

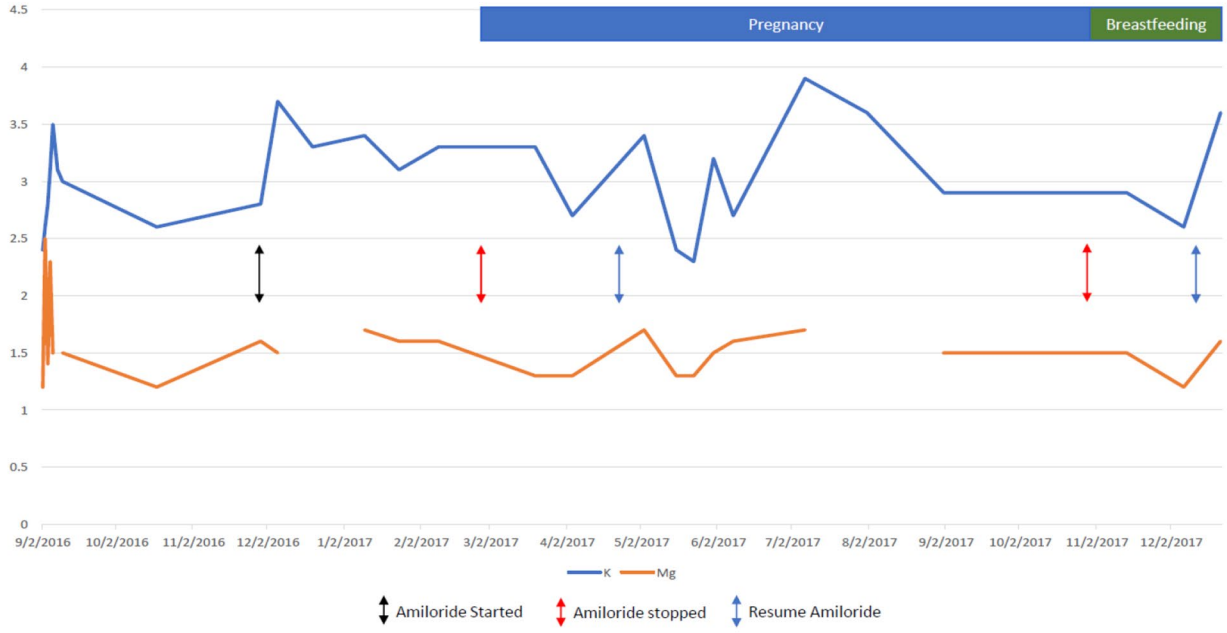

Fig. 1 Maternal serum potassium and magnesium levels during pregnancy and breastfeeding in correlation with amiloride treatment

increased potassium efflux from the principal cells of the aldosterone-sensitive distal nephron [7].

Although hypomagnesemia is another key manifestation of GS, its underlying cause is not very well understood. The TRPM6 (transient receptor potential cation channel subfamily M member 6) magnesium channel, which is located on the apical membrane of distal convoluted tubule epithelial cells, reabsorbs magnesium in that segment (ref: de BaaijPhysiol Rev 2015, 95: 1–46). In mice that are chronically treated with thiazide diuretics, which inhibit the sodium chloride cotransporter, or which have genetic deletion of the sodium chloride cotransporter, there is downregulation of TRPM6, possibly due to the atrophy of the distal convoluted tubule that occurs with loss or inhibition of the sodium chloride cotransporter (ref: Nijenjuis T et al., J Clin Invest 2005, 115: 1651–1658). Decreased TRPM6 in the distal convoluted tubule could explain renal magnesium wasting and hypomagnesemia.

Potassium and magnesium supplementation is the basis of GS treatment. However, in cases where electrolyte level correction via supplementation is insufficient, potassium-sparing diuretics such as amiloride, spironolactone, and eplerenonemay be useful [8]. Amiloride is a potassium and magnesium-sparing diuretic that acts primarily by blocking sodium transport in the aldosterone-sensitive distal nephron, which in turn inhibits sodium-potassium exchange [9]. Physiologically, sodium reabsorption in the distal tubules via epithelial sodium channels (ENaC) results in apical membrane depolarization, which acts as a driving force for potassium secretion [7]. Therefore, asamiloride directly inhibits ENaC, it hyperpolarizes the apical membrane which decreases the electrochemical driving force for potassium efflux, and results in its antikaliuretic potassium-sparing effects [10]. It is classified as a category B drug by the Food and Drug Administration in terms of teratogenicity. Although teratogenicity evaluation in rodent models is reassuring, amiloride is concentrated in breast milk and thus it is not recommended to be used during breastfeeding unless it is strongly indicated [11]. To the best of our knowledge, there are no reports of amiloride levels in human breast milk, and assays for measuring amiloride concentration in breast milk are not commercially available. However, in our case, the infant's relatively elevated serum potassium, and low urinary potassium and magnesium concentrations, suggested a systemic effect of amiloride.

Pregnancy is associated with many renal physiological changes, including positive balance of both sodium and potassium, which could be complicated by renal sodium and potassium losses in Gitelman's syndrome. Renin, angiotensin II, and aldosterone levels are known to increase during pregnancy. However, the increased progesterone levels during pregnancy would counteract the effects of increased activation of the renin angiotensin-aldosterone system on potassium excretion due to its anti-mineralocorticoid effects [12]. Nonetheless, the compensatory mechanism of progesterone on potassium excretion may be inadequate to prevent excessive

potassium excretion in pregnant women with GS [12]. Moreover, potassium wasting may be exacerbated during pregnancy due to additional physiological changes, such as increased fetal demand, and vomiting [13].

Although in rodent models, magnesium deficiency during pregnancy has been associated with significantly increased neonatal mortality and morbidity [14], it appears that GS represents no significant risk to the fetus in human clinical reports [15]. Thus, the main therapeutic goal for patients with GS is to maintain their potassium and magnesium serum levels and prevent symptoms [13, 15]. Additionally, electrolyte correction is critical to prevent potentially fatal maternal complications such as ventricular arrhythmias.

Although the cornerstone for GS treatment during pregnancy is liberal salt intake, potassium and magnesium supplementation, it appears that it is more difficult to achieve stable normal serum levels of these electrolytes in pregnant patients [16].

The use of medications such as Spironolactone, amiloride, and eplerenone has been rarely reported due to their controversial safety profile during pregnancy [16]. In the rat, the epithelial sodium channel is activated during pregnancy to allow net positive sodium balance and the plasma volume expansion that is characteristic of pregnancy, and pharmacological inhibition of the epithelial sodium channel prevents plasma volume expansion (West C et al. Am J PhysiolRegulIntegr Comp Physiol 299: R1326-R1332, 2010). However, amiloride has been successfully used for managing hypokalemia in a few pregnant patients with Bartter's Syndrome [17] and Liddle's Syndrome [18].

We are aware of only four previous reports of amiloride use during pregnancy in GS patients [19–22]. In all cases amiloride was used due to persistent hypokalemia unresponsive to potassium and magnesium supplementation alone. All pregnancies resulted in healthy newborns; however, one pregnancy required labor induction at 38 weeks of gestation due to oligohydramnios [19]. The use of amiloride in our case was necessary to maintain adequate potassium and magnesium serum levels in our patient and thus to prevent further serious complications.

Although amiloride is classified by the FDA as category B in terms of teratogenicity, no randomized clinical trials have been conducted to investigate their actual safety profile in humans during pregnancy and breastfeeding.

In conclusion, we report a safe and effective use of amiloride during pregnancy in a GS patient which facilitated control of her persistent hypokalemia and hypomagnesemia despite oral supplementation therapy. However, due to the uncertainty regarding its safety during breastfeeding and the limited available literature, we cannot make a definitive recommendation for amiloride use during this period. Accordingly, we suggest that more clinical studies are needed to evaluate the safety profile of amiloride therapy during pregnancy and breastfeeding.

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Author contributions
A. I. contributed to patient care, data collection, manuscript drafting, and critical revision of the manuscript. C. W. participated in the design of the study, data interpretation, and critically reviewed the manuscript. A. R. was involved in genetic analysis, data interpretation, and manuscript preparation. L. Al-R. managed the patient's treatment, contributed to the conception of the report, and drafted and revised the manuscript critically for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Data availability
The patient data during the current case report are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Consent obtained under Institutional Review Board (IRB): IRB_00117828.

Consent for publication
Informed consent for publication was obtained from patient for the publication of this case report.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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References

1. Graziani G, et al. Gitelman syndrome: pathophysiological and clinical aspects. QJM. 2010;103(10):741–8.
2. Naesens M, et al. Bartter's and Gitelman's syndromes: from gene to clinic. Nephron Physiol. 2004;96(3):p65–78.
3. Gitelman HJ, Welt GJ. LG., *A new familial disorder characterized by hypokalemia and hypomagnesemia.* Proceedings of the Association of American Physicians, 1966. 79: pp. 221–235.
4. Filippatos TD, et al. Gitelman syndrome: an analysis of the underlying pathophysiologic mechanisms of acid-base and electrolyte abnormalities. Int Urol Nephrol; 2017.
5. Simon DB, Bia N-WC, Ellison MJ, Karet D, Molina FE, Vaara AM, Iwata I, Cushner F, Koolen HM, Gainza M, Gitelman FJ. Lifton RP *Gitelman's variant of Bartter's syndrome, inherited hypokalemic alkalosis, is caused by muta- tions in the thiazide sensitive Na-Cl cotransporter.* Nat Genet. 1996;12:24–30.
6. Riveira-Munoz E, et al. Gitelman's syndrome: towards genotype-phenotype correlations? Pediatr Nephrol. 2007;22(3):326–32.
7. Chou-Long Huang EK. Mechanism of Hypokalemia in Magnesium Deficiency. J Am Soc Nephrol. 2007;18(10):2649–52.
8. Blanchard A, et al. Indomethacin, amiloride, or eplerenone for treating hypokalemia in Gitelman syndrome. J Am Soc Nephrol. 2015;26(2):468–75.
9. Vidt DG. *Mechanism of Action, Pharmacokinetics, Adverse Effects, and Therapeutic Uses of Amiloride Hydrochloride, A New Potassium-Sparing Diuretic.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 1981. 1(3): pp. 179–187.
10. Kleyman TR. The mechanism of action of Amiloride. Semin Nephrol. 1988;8(3):242–8.

11. Ainsworth SB. Maternal medication and the baby. Neonatal Formulary: drug use in pregnancy and the First Year of Life. Wiley; 2014. p. 562.
12. Baylis C. The normal renal physiological changes which occur during pregnancy. Oxford textbook of clinical nephrology. C.-e.J. Davison AM, Grünfeld JP, Ponticelli C, Ritz E, Winearls CG, van Yperseele C, Oxford: Oxford University Press; 2005. pp. 2213–31.
13. de Arriba G, Sanchez-Heras M, Basterrechea MA. Gitelman syndrome during pregnancy: a therapeutic challenge. Arch Gynecol Obstet. 2009;280(5):807–9.
14. Almonte RA, Whitehall HDL, Russell J, Patole MJ, Vink S. Gestational Magnesium Deficiency is deleterious to fetal outcome. Neonatology. 1999;76(1):26–32.
15. Moustakakis MN, Bockorny M. Gitelman syndrome and pregnancy. Clin Kidney J. 2012;5(6):552–5.
16. Elkoundi A, et al. Gitelman syndrome: a rare life-threatening case of hypokalemic paralysis mimicking Guillain-Barre syndrome during pregnancy and review of the literature. Clin Case Rep. 2017;5(10):1597–603.
17. Deruelle P, et al. Maternal Bartter's syndrome in pregnancy treated by amiloride. Eur J Obstet Gynecol Reprod Biol. 2004;115(1):106–7.
18. Caretto A, et al. A therapeutic challenge: Liddle's syndrome managed with amiloride during pregnancy. Case Rep Obstet Gynecol. 2014;2014:156250.
19. McCarthy FP, et al. Gitelman's syndrome in pregnancy: case report and review of the literature. Nephrol Dial Transpl. 2010;25(4):1338–40.
20. Raffi F, et al. Pregnancy with Gitelman's syndrome. Obstet Med. 2011;4(1):39–41.
21. Mascetti L, et al. Pregnancy in inherited hypokalemic salt-losing renal tubular disorder. Obstet Gynecol. 2011;117(2 Pt 2):512–6.
22. Mathen S, Venning M, Gillham J. *Outpatient management of Gitelman's syndrome in pregnancy.* BMJ Case Rep, 2013. 2013.

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