INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 7; Issue 12(A); December 2021; Page No. 6076-6078
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20211081

Case Report

CASE REPORT: A 22 YEAR OLD FEMALE PRESENTING WITH HYPOKALEMIC PARALYSIS IN NEWLY DIAGNOSED GITELMAN SYNDROME

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ARTICLE INFO

Article History:
Received 6th September, 2021
Received in revised form 15th October, 2021
Accepted 12th November, 2021
Published online 28th December, 2021

Key words:
Gitelman syndrome, hypokalemia, Metabolic acidosis

ABSTRACT

Introduction: Gitelman syndrome (GS) is a rare, salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. The disease is recessively inherited, caused by inactivating mutations in the **SLC12A3** gene that encodes the thiazide-sensitive sodium-chloride cotransporter (NCC). GS is usually detected during adolescence or adulthood, either fortuitously or in association with mild or nonspecific symptoms or both. The disease is characterized by high phenotypic variability and a significant reduction in the quality of life, and it may be associated with severe manifestations. With a prevalence at ~1 to 10 per 40,000,(potentially higher in Asia) GS is arguably the most frequent inherited tubulopathy. To date, >350 mutations scattered throughout *SLC12A3* have been identified in GS patients **Material And Methods:** A 22 year old female patient presented for the first time in a tertiary health care center with decreased capacity to do routine work since childhood and episodes of periodic all 4 limb paresis, painful muscle spasms, primary infertility, pallor, polyuria and nocturia. Magnesium – 1.38 mg/dl, Potassium – 1.4 mEq/l, ABGA ph – 7.65, HCO3 – 55 Meq/l, potassium-to-creatinine ratio (K/Cr) – 3.9 mEq/ml, urine K–22 mEq/ml, Urine calcium (spot) -4.32mg/dl, Urine calcium 24 hrs – 32mg/24 hrs **Diagnosis:** Based on the clinical examination showing weakness of all 4 limbs hyporeflexia, decreased depth of respiration and the lab values of potassium less than 2mEq/ml suggesting severe hypokalaemia, a diagnosis of transient hypokalaemia paralysis was made. There was also drastic improvement in symptoms after potassium supplementation **Conclusion:** Because GS originates from the distal convoluted tubule, the salt and water losses in GS patients are less pronounced than in antenatal Barter syndrome because urinary concentrating ability is largely intact. GS patients are often asymptomatic or present with symptoms such as muscle weakness, fatigue, salt craving, thirst, nocturia, constipation, cramps, carpopedal spasms, or tetanic episodes triggered by hypomagnesemia. Blood pressure is typically low, particularly for patients with severe hypokalemia and hypomagnesemia. Treatment consisted of salt, potassium and magnesium supplementation.

INTRODUCTION

Gitelman syndrome (GS) is a rare, salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. The disease is recessively inherited, caused by inactivating mutations in the SLC12A3 gene that encodes the thiazide-sensitive sodium-chloride cotransporter (NCC). GS is usually detected during adolescence or adulthood, either fortuitously or in association with mild or nonspecific symptoms or both. The disease is characterized by high phenotypic variability and a significant reduction in the quality of life, and it may be associated with severe manifestations.

With a prevalence at ~1 to 10 per 40,000, (potentially higher in Asia) GS is arguably the most frequent inherited tubulopathy. To date, >350 mutations scattered throughout *SLC12A3* have been identified in GS patients. The majority of patients are compound heterozygous for *SLC12A3* mutations, but a significant number of GS patients are found to carry only a single *SLC12A3* mutation. The presence of both hypocalciuria and hypomagnesemia is highly predictive for the clinical diagnosis of GS.

MATERIALS AND METHODS

A 22 year old female patient presented for the first time in a tertiary health care center with decreased capacity to do routine work since childhood and episodes of periodic all 4 limb paresis, painful muscle spasms, primary infertility, severe pallor, polyuria and nocturia.

The following lab reports were obtained:

Haemoglobin – 8.8gm/dl
Creatinine – 1.0 mg /dl
Magnesium –1.38 mg/dl
Potassium – 1.4 mEq/l
Chloride : 122 mEq/l

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ABGA ph – 7.65
HCO3 – 55 Meq/l
pO2 – 98
urine osmolality : 220 mOsm/l
potassium-to-creatinine ratio (K/Cr) – 3.9 mEq/ml
urine K – 22 mEq/ml
Urine calcium (spot) -4.32mg/dl
Urine calcium 24 hrs – 32mg/24 hrs

Diagnosis

Based on the clinical examination showing weakness of all 4 limbs hyporeflexia, decreased depth of respiration and the lab values of potassium less than 2mEq/ml suggesting severe hypokalaemia, a diagnosis of transient hypokalaemia paralysis was made. There was also drastic improvement in symptoms after intravenous potassium supplementation.

Based on the urine examination showing increased fractional excretion of potassium along with ABGA findings suggestive of alkalosis, hypomagnesemia and normal Renal Function Test suggested a renal reabsobtion defect and the diagnosis of Gitelman was postulated.

Criteria for suspecting a diagnosis of GS

1. Chronic hypokalemia (<3.5 mmol/l) with inappropriate renal potassium wasting (spot potassium-creatinine ratio >2.0 mmol/mmol [>18 mmol/g])
2. Metabolic alkalosis
3. Hypomagnesemia (<0.7 mmol/l [<1.70 mg/dl]) with inappropriate renal magnesium wasting (fractional excretion of magnesium >4%)
4. Hypocalciuria (spot calcium-creatinine ratio <0.2 mmol/mmol [<0.07 mg/mg]) in adults.
5. High plasma renin activity or levels
6. Fractional excretion of chloride > 0.5%
7. Low or normal-low blood pressure
8. Normal renal ultrasound

CONCLUSION

Because GS originates from the distal convoluted tubule, the salt and water losses in GS patients are less pronounced than in antenatal Barter syndrome because urinary concentrating ability is largely intact. GS patients are often asymptomatic or present with symptoms such as muscle weakness, fatigue, salt craving, thirst, nocturia, constipation, cramps, carpopedal spasms, or tetanic episodes triggered by hypomagnesemia. Blood pressure is typically low, particularly for patients with severe hypokalemia and hypomagnesemia.

Complications of GS include chondrocalcinosis and sclerochoroidalcalcifications. This is because magnesium ions increase the solubility of calcium pyrophosphate crystals and are important activators for tissue-nonspecific alkaline phosphatase, which hydrolyzes pyrophosphates (PPi) into inorganic phosphate (Pi), hence hypomagnesemia may promote the formation of calcium pyrophosphate crystals in joints and sclera.

The differential diagnosis of GS also includes diuretic and/or laxative abuse, which is unusual in children, and chronic vomiting. Measurement of urinary chloride (e.g., < 25 mEq/l for surreptitious vomiting) and a urine screen for diuretics (e.g., by mass spectrometry) can help exclude GS in these patients. The association of hypokalemic metabolic alkalosis with hyperreninemic secondary aldosteronism is also seen .GS-like manifestations have been reported as a rare complication of the use of cisplatin. Typical features of GS have been associated with autoimmune disorders including iritis and arthritis and Sjögren syndrome.

Treatment

Because GitelmanSyndrome is caused by a primary defect in a sodium-chloride cotransporter, *ad libitum* NaCl intake should be strongly advocated. Encourage patients to follow their propensity for salt consumption.

Individualized lifelong oral potassium or magnesium supplementation or both is the mainstay of treatment for patients with GS. In the presence of hypomagnesemia, magnesium supplementation should be considered first, because magnesium repletion will facilitate potassium repletion and reduce the risk of tetany and other complications.

A reasonable target for potassium may be 3.0 mmol/l and magnesium 0.6 mmol/l (1.46 mg/dl). Potassium supplements should be given as chloride (KCl) because chloride is the main anion lost in the urine and patients are alkalotic. A starting dose of ≥40 mmol KCl (1–2 mmol/kg in children), in divided doses throughout the day, is suggested. Potassium supplements should not be taken on an empty stomach to minimize gastrointestinal irritation or damage. KCl supplements can be administered in water, as syrup, or in a slow-release formulation according to each patient's preference. Potassium-rich foods should be recommended.

Intravenous KCl may be necessary either when the patient cannot take oral drugs or when the potassium deficit is very severe, causing cardiac arrhythmias, quadriplegia, respiratory failure, or rhabdomyolysis.

Intravenous infusion of magnesium should be reserved either for patients presenting with acute, severe complications of hypomagnesemia (e.g., tetany, cardiac arrhythmias), or in cases of digestive intolerance to oral supplements.

The potassium-sparing diuretics amiloride, spironolactone, eplerenone can be useful, both to increase serum potassium levels in patients resistant to supplements and to treat magnesium depletion that is worsened by elevated aldosterone levels.

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How to cite this article:

Mohita Shah* and Prafful Kothari (2021) 'Case Report: A 22 Year Old Female Presenting With Hypokalemic Paralysis In Newly Diagnosed Gitelman Syndrome', *International Journal of Current Medical and Pharmaceutical Research,* 07(12), pp 6076-6078.

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