Case study

CASE REPORT ON RECURRENT EPISODES OF DYSELECTROLYTEMIA DIAGNOSED AS GITLEMAN SYNDROME.

ABSTRACT

Background: Gitleman syndrome (GS) is also known as familial hypokalaemia-hypomagnesemia, which is a rare genetic disorder. It is an autosomal recessive disease that is characterized by hypokalaemia, hypomagnesemia, metabolic alkalosis, hypocalciuric hypercalcemia and hyperaldosteronism.

Case report: 70-year-old female patient who was diagnosed with Gitelman syndrome with the symptoms of loss of appetite, muscle weakness, and abdominal pain. Electrolyte levels were low. After inconclusive evidence from laboratory investigation, genetic testing was performed. The detection of the *SLC12A3* gene mutation confirmed the diagnosis of GS. No pathological variant of CLCNKB for Bartter syndrome has been found.

Keywords: Gitleman syndrome, renal tubulopathy, hypomagnesemia, hypokalaemia,

INTRODUCTION

Gitleman syndrome (GS) is a heritable renal disorder that is characterized by hypokalaemia, hypomagnesemia, hypocalciuric hypercalcemia, and hyperaldosteronism. It impairs the kidney's function to reabsorb salt and causes an imbalance in electrolyte concentration. The electrolytes primarily affected are potassium, calcium, magnesium, sodium, and chloride. Gitleman syndrome affects both female and male populations equally. It is the most commonly occurring tubulopathy. The prevalence of GS is 1 to 10 per 40,000 people. It is found to be potentially more common in Asian countries [(1)].

GS can occur anywhere from late childhood (over 6 years) to early adulthood. Gitleman syndrome is caused by biallelic inactivating mutations. Mutations occur in some of the genes encoding for magnesium, chloride, and sodium carried in the apical membrane of the distal

convoluted tubule. This tubule is responsible for about 7–10% of tubular absorption of electrolytes. The mutations involve two main genes, which are

1. The SLC12A3 gene encodes for thiazide-sensitive sodium cotransporter (NCCT).
2. The TRPM6 gene encodes for distal tubular magnesium transport.

The majority of Gitleman syndrome is caused by mutations in the SLC12A3 gene. In some patients, GS is caused by mutations in the CLCNKB gene, which encodes for the chloride channel ClC-Kb. This precipitates hypocalciuric hypercalcemia and hypomagnesemia, which overlaps with Bartter syndrome [(2,3)].

The signs and symptoms of this disorder are highly variable. Some people can develop chronic symptoms that will affect their quality of life, while others can remain asymptomatic throughout their lives. The most common symptoms of Gittleman syndrome are cramps, muscle weakness, and spasms. Patients also experience dizziness, fatigue, and tetany. Cramps and spasms of particular muscles like the hands and feet characterize tetany. This can be provoked by hyperventilation.

Other symptomatic episodes include abdominal pain, constipation, diarrhea, fever, and vomiting. Occurrence of seizure or facial paraesthesia are the most common reasons for patients to seek medical assistance. Some uncommon symptoms include polydipsia, polyuria, hypotension, chondrocalcinosis, joint swelling, cardiac arrhythmias, and rhabdomyolysis [(1)].

CASE REPORT

A 70-year-old female patient came to the hospital with complaints of fever, vomiting on and off (6 episodes per day), loss of appetite for 1-month, abdominal pain, and generalized weakness. Six months ago, she was hospitalized for continuous vomiting and giddiness, diagnosed as dyselectrolytemia, corrected with electrolyte parenteral therapy. She felt symptomatically better and was discharged. For the past 3 months, the symptoms recurred, the patient was hospitalized often for the same condition, she was on a semi-solid diet and treated with IV fluids, and she was continuing spironolactone 25mg once daily. Then the patient was admitted to our hospital for further evaluation.Known case of hypertension, diabetes, and hypothyroidism for 15 years. History of cholelithiasis in 2020.

Physical examination at the time of admission revealed that the patient is dehydrated. Her blood pressure was 140/80 mmHg, her pulse rate was 96 beats/min, her respiratory rate was 26 breaths/min, and her body temperature was normal. No additional heart sounds, murmurs, or arrhythmias were detected in the cardiovascular system examination, and other system examinations were not remarkable.

Laboratory investigation showed that haemoglobin was 12.3 g/dl, hemocrit was 33.6%, white blood cells were 5400/mm3, neutrophils were 60%, the platelet count was 230000, random blood glucose (160 mg/dl)and HBA1Cwas7.5 increased. triiodothyronine was reduced (29 ng/dl), thyroxine was 5.4 g/dl, TSH was increased (56.87 lU/m), urea, creatinine and BUN were normal. Renin value in standing was increased(220 U/m) aldosterone value in standing was increased(25 ng/dl) and 25-hydroxycholecalciferol level is low(14 ng/ml). The electrolyte levels were repeated daily, and their values are shown (Table 1) (Fig 1).

Table 1: Electrolyte levels

S.NO	ELECTROLYTES	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8
1.	SODIUM (mmol/L)	122	124	126	125	122	122	122	132
2.	POTASSIUM (mmol/L)	2.9	3.3	2.9	3.1	4.1	4.1	3.6	3.9
3.	BICARBONATE (mmol/L)	24	25	24	23	21	21	21	23
4.	CHLORIDE (mmol/L)	88	90	91	92	88	88	91	99

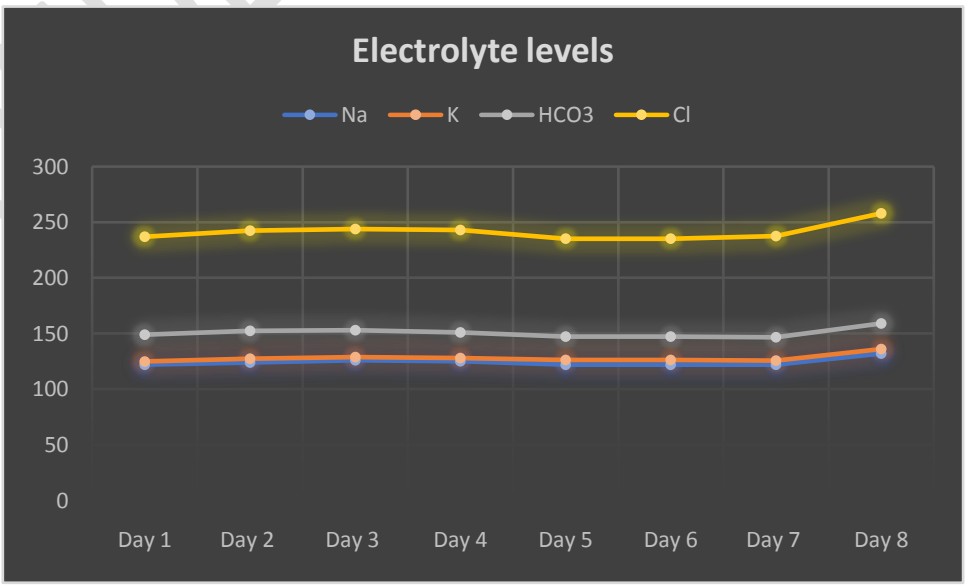

Fig 1: Electrolyte levels

At the time of admission, her calcium (7.5 mg/dl) and magnesium (0.98 mg/dl) levels were low. The arterial blood gas value showed metabolic alkalosis. pH 7.532, HCO3 31.4 mmol/L, pCO2 43.2 mmHg, and pO2 92 mmHg. The trans tubular potassium gradient (TTKG) value is 10. Troponin was negative, and the ECG showed sinus tachycardia. A chest X-ray revealed no illness. The liver and spleen appeared normal on ultrasonography. The pancreas, gall bladder, kidneys, ureters, and bladder were all free of pathology. The liver function test was normal. Hepatitis B virus (HBV) and HIV-specific antibodies were negative.

Microscopic urine analysis revealed no pathology, Urine osmolarity was 365 mOsm/kg, urine sodium was 145 mmol, and urine potassium was 50.9 mmol.Proteinuria was absent.

A normotensive patient with hypokalaemia, hypomagnesemia, hypochloraemia, hyponatremia, increased renin-angiotensin-aldosterone activity, hyperchloremic metabolic alkalosis, hyperreninemia, and hypocalciuric hypercalcemia was suspected to have the diagnosis of Gitelman Syndrome, which was also correlated with clinical and laboratory findings. After getting informed consent, genetic testing was performed. The detection of the *SLC12A3* gene mutation confirmed the diagnosis of GS. No pathological variant of CLCNKB for Bartter syndrome has been found.

The patient was treated with parenteral normal saline, potassium chloride, Arachitol, spironolactone, metoclopramide, and MgD3 (magnesium glycinate and vitamin D3). Diabetes and hypothyroidism were treated with Vildagliptin 50mg and Thyronorm 100 mcg. After discharge, the intravenous medicines were shifted to oral, and the patient was followed up with serum electrolyte levels in our institute.

DISCUSSION:

Gitelman syndrome is a rare, autosomal recessive genetic disorder identified as an individual condition by Gitelman in 1966, and its diagnosis is based on clinical symptoms, biochemical abnormalities, and genetic testing[(2)].

Tetany, cramping, painful muscle spasms, fatigue, dizziness, and a craving for salt are the main symptoms of Gitleman syndrome. Other symptoms also include fainting, polyuria,

arthralgia, chondrocalcinosis, vertigo, seizures, paraesthesia's, etc. Our patient has the symptoms of fatigue, loss of appetite, abdominal pain, fever, and vomiting[(2)].

The patient's common presentation on the medical floor includes a combination of hypokalaemia, hypomagnesemia, and metabolic alkalosis. The differential diagnosis in such instances always include GS and Bartter syndrome. Because both are inherited renal tubulopathies, they differ in the mechanisms, presence of urinary concentrating defect, level of urinary calcium excretion, age of onset, and severity of clinical manifestations, but share the biochemical characteristics of hypokalaemia and metabolic alkalosis.

GS can be related to structural and/or functional abnormalities of the sodium-chloride cotransporter (NCCT) due to a loss-of-function mutation in the gene SLCI2A3, which codes for the thiazide-sensitive Na+-Cl cotransporter (NCCT) in the apical membrane of the cells lining the distal convoluted tubule (DCT). In addition to the detected SLC12A3 mutation, phenotypic variability is linked to the coexistence of other modifier genes, the presence of compensatory mechanisms, sex, and dietary and environmental variables.[(4)]

For identifying hypokalaemia, the TTKG test is useful. The typical range for TTKG is 4–8. If urine K is greater than 30 mmol/L or TTKG is high, hypokalaemia is thought to be secondary to renal loss. Hypokalaemia may be brought on by either an extrarenal loss or a transcellular K shift when urine K is below 30 mmol/L or TTKG is low. Here, the patient's urine potassium level is approximately 50.9 mmol, and the TTKG level is 10. The strong evidence for renal K loss as the root cause of hypokalaemia comes from this high TTKG value.

Diuretics, hyperaldosteronism, hypomagnesemia, renal tubular acidosis types 1 and 2, and specific medications, such as amphotericin and aminoglycosides, are other major causes of renal potassium loss [(6)].

Absar Ali et al. published a case report on GS with hyponatremia and hypophosphatemia, which is similar to this case. Where our patient has hyponatremia with a serum sodium level of 122 mmol/L, it has been suggested that renal sodium wasting, hypovolemia, and an intracellular potassium deficit play a role in the development of hyponatremia [(6)].

Hydrochlorothiazide-induced hyponatremia: GS performs the same physiological process as hydrochlorothiazide by impairing the free water excretion by thiazide diuretics, leading to

slight volume expansion as a primary event. This, in turn, triggers or aggravates hyponatraemia. A similar phenomenon may be responsible for hyponatraemia in patients with GS, but it is difficult to distinguish from SIADH (syndrome of inappropriate secretion of antidiuretic hormone).

In GS cases, hypocalcaemia was rarely documented. Due to the low levels of calcium excretion in urine, hypomagnesemia may explain hypocalcaemia by affecting cyclic AMP production in the parathyroid glands and PTH target organs. This impairs PTH secretion and increases end-organ resistance to PTH. Therefore, PTH increases serum magnesium by increasing absorption in the GI tract and bones. That is why the patient with hypocalcaemia has low PTH, and their normal level will be regained soon [(7)(8)].

In our patient, her calcium (7.5 mg/dl) and magnesium (0.98 mg/dl) levels were low. After correction with magnesium glycinate and vitamin D3, their levels returned to normal (calcium 8.4 mg/dl, magnesium 1.8 mg/dl).

While an increase in aldosterone can increase the reabsorption of sodium ions and water molecules while decreasing potassium ion absorption, this can result in hypokalaemia and metabolic alkalosis. Decreased sodium chloride reabsorption can further activate the renin-angiotensin-aldosterone system. In addition, a spike in aldosterone secretion will cause a decrease in intestinal and renal tubular absorption of magnesium ions, which will increase urine magnesium and result in hypomagnesemia. Hypokalaemia, hypomagnesemia, hypocalcaemia, metabolic alkalosis, and growth retardation in children are therefore the predominant clinical symptoms of GS patients. Additionally, some of the patients suffer from proteinuria and impaired renal function.

The goal of GS treatment is to reduce symptoms and enhance patients' quality of life. Electrolyte replacement therapy is the major mode of treatment. In addition to a diet high in salt and dietary supplements taken regularly, potassium and magnesium supplements are necessary to keep the levels of serum potassium and magnesium stable. Serum magnesium and potassium levels in GS patients are typically thought to be greater than 0.6 mmol/L and more than 3.0 mmol/L, respectively. The use of non-steroidal anti-inflammatory drugs, potassium-sparing diuretics, and medications that block the renin-angiotensin-aldosterone pathway may also be investigated as further therapeutic options.

A liberal salt diet was avoided because the patient had hypertension, and an aldosterone receptor antagonist was started after symptoms of hypokalaemia reappeared while using potassium supplements [(9)].

CONCLUSION:

This report shows a patient with hypokalaemia, hyponatremia, hypomagnesemia, metabolic alkalosis, and other characteristic features of GS. There are various differential diagnosis for Gitleman syndrome. Concrete diagnosis is arrived at by the means of genetic testing. The first stage in making a precise diagnosis that will be supported by genetic testing is to raise clinical suspicion by observing characteristic biochemical features.

REFERENCES

1.Parmar MS, Muppidi V, Bashir K. Gitelman syndrome.

2.Yang W, Zhao S, Xie Y, Mo Z. A novel SLC12A3 homozygous c2039delG mutation in Gitelman syndrome with hypocalcemia. BMC nephrology. 2018 Dec;19:1-6.

3.Simon DB, Nelson-Williams C, Johnson Bia M, Ellison D, Karet FE, Morey Molina A, Vaara I, Iwata F, Cushner HM, Koolen M, Gainza FJ. Gitelman's variant of Barter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na–Cl cotransporter. Nature genetics. 1996 Jan 1;12(1):24-30.

4.Blanchard A, Bockenhauer D, Bolignano D, Calo LA, Cosyns E, Devuyst O, Ellison DH, Frankl FE, Knoers NV, Konrad M, Lin SH. Gitelman syndrome: consensus and guidance from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney international. 2017 Jan 1;91(1):24-33.

5.Riveira-Munoz E, Chang Q, Bindels RJ, Devuyst O. Gitelman's syndrome: towards genotype-phenotype correlations?. Pediatric Nephrology. 2007 Mar;22:326-32.

6.Ali A, Masood Q, Yaqub S, Kashif W. A case of Gitelman syndrome with severe hyponatraemia and hypophosphataemia. Singapore Med J. 2013 Jan 1;54(1):e18-20.

7.RUDE RK, Oldham SB, SINGER FR. Functional hypoparathyroidism and parathyroid hormone end- organ resistance in human magnesium deficiency. Clinical endocrinology. 1976 May;5(3):209-24.

8.Sanda S, Schlingmann KP, Newfield RS. Autosomal dominant hypoparathyroidism with severe hypomagnesemia and hypocalcemia, successfully treated with recombinant PTH and continuous subcutaneous magnesium infusion. Journal of Pediatric Endocrinology and Metabolism. 2008 Apr;21(4):385-92.

9.Ying J, Wu H, Zhang R, Wu P, Sui F, Li Z. A case report of Gitelman syndrome in children. Medicine. 2023 Apr 4;102(15).

ABBREVIATIONS

GS	Gitleman syndrome
CLCNKB	Chloride channel KB
TRPM6	Transient receptor potential cation channel subfamily M member
IV	Intravenous
HbA1C	Glycated haemoglobin
TSH	Thyriod stimulating hormone
BUN	Blood urea nitrogen
ECG	Electrocardiogram
HIV	Human immunodeficiency virus
NCCT	Sodium chloride Co transporter
TTKG	Trans-tubular potassium gradient
K	Potasium
PTH	Parathyroid hormone

AMP	Adenosine monophosphate
GI	Gastrointestinal