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Gitelman's Syndrome–Salt Wasting Nephropathy: An Inherited Kidney Disease

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Abstract: Gitelman's syndrome (GS) is a rare genetic disorder and also known as familial hypokalemia-hypomagnesemia with low urinary calcium excretion. This defect impairs the kidney's ability to reabsorb salt and causes changes in various electrolyte concentrations, the electrolytes affected are primarily mineral ions, specifically potassium, calcium, magnesium, sodium, and chloride. The severity and symptoms of the disorder can vary greatly from one person to another and can range from mild to severe, even vary greatly among members of the same family. Transitory episodes of muscle weakness and tetany, periodically followed by abdominal pain, vomiting and fever are usually seen in GS patients. Here we describing a case of 28 years female patient who presented with weakness, muscle cramps, palpitations, constipation, and increased frequency of urine output, multiple episodes of vomitings, eventually the diagnosis of Gitelman's syndrome was established.

Keywords: Gitelman's syndrome**,** familial hypokalemia, familial hypomagnesemia, electrolytes, salt wasting nephropathy.

INTRODUCTION

Gitelman's syndrome is a kidney function disorder that causes an imbalance of charged atoms (ions) in the body, including ions of potassium, magnesium, and calcium which is usually diagnosed during late childhood or adulthood [1-3]. It is an autosomal recessive inherited disease of renal tubules with mutations in the solute carrier family12, member 3 gene, *SLC12A3*, which encodes the thiazide-sensitive NaCl cotransporter (NCC) which is important for electrolyte homeostasis.

This cotransporter mediates sodium and chloride reabsorption in the distal convoluted tubule. Mutations in this gene lead to hypokalemic alkalosis combined with hypomagnesemia, low urinary calcium, and increased renin activity associated with normal or low blood pressure. This cotransporter is the target for thiazide diuretics that are used for treating high blood pressure. Multiple transcript variants encoding different isoforms (more than 140 different NCC mutations) have been found for this gene whereas *mutations in the CLCNKB* gene, encodes chloride channel ClC-Kb have also been identified in rare cases of GS [4].

Correlation between Gitelman's Syndrome and Bartter Syndrome

Bartter syndrome (BS), especially type III, is the most important genetic disorder to consider in the differential diagnosis of GS and in specific cases, it is extremely difficult to distinguish between these disorders. BS occurs as a result of mutations in genes coding for proteins mainly responsible for salt and water reabsorption in the thick ascending loop of Henle (TAL), while dysfunction of the sodium chloride co-transporter in the distal convoluted tubule (DCT) results in GS.

Some researchers believe it is better to consider the Bartter syndrome and Gitelman syndrome as a spectrum of disease rather than distinct disorders where Gitelman syndrome causes metabolic abnormalities resembling treatment with high dosage of thiazide diuretics while Bartter syndrome resembles treatment with high dosage of loop diuretics [5].

The biochemical features of both syndromes include hypokalemic hypochloremic metabolic alkalosis associated with high plasma renin activity and high aldosterone concentration [6]. Both patients with BS and GS present with complaints of constipation, muscle cramps and weakness secondary to chronic hypokalemia. Patients with either syndrome may also present with non-specific dizziness and fatigue [6]. GS is usually diagnosed during adolescence or adulthood and clinical signs are rarely apparent before the age of

five. It is also associated with less severe failure to thrive and milder growth retardation. BS can be further subdivided based on the underlying genetics shown in table-1 [7-9].

Table-1: Clinical and genetic classification of BS and GS

Clinical phenotype	Genetic Subtype	Gene	Protein	Features
Antenatal BS	Type I	*SLC12A1*	NKCC2	Polyhydramnios, prematurity, polyuria, nephrocalcinosis, failure to thrive
Antenatal BS	Type II	*KCNJ1*	ROMK1	Polyhydramnios, prematurity, polyuria, nephrocalcinosis, failure to thrive, transient hyperkalaemia
Classic BS	Type III	*CLCNKB*	CLC-Kb	Failure to thrive, hypomagnesaemia
Antenatal BS with sensorineural deafness	Type IV	*BSND*	Barttin	Polyhydramnios, prematurity, polyuria, nephrocalcinosis, failure to thrive, sensorineural deafness
GS	GS	*SLC12A3*	NCCT	Hypocalciuria, hypomagnesaemia
Transient antenatal BS	Type V	*MAGED2*	MAGED2	Severe polyhydramnios, prematurity, hypercalciuria, spontaneous resolution

Some people with GS may be at risk of developing cardiac arrhythmias. Those with severe hypokalemia are more susceptible to cardiac arrhythmias, which can be life-threatening when combined with severe hypomagnesemia (low magnesium) and alkalosis. Therefore, an in-depth cardiac work-up is strongly recommended to identify which people with Gitelman syndrome may be at risk. Competitive sports should be avoided because sudden death can be precipitated by intense physical activity that induces potassium and magnesium loss by sweating [10]. Individualized lifelong oral potassium or magnesium supplementation or both is the mainstay of treatment for patients with GS [11].

CASE REPORT

Subjective Evidence

A 28 years female patient was admitted to the KIMS hospital Ongole on April 2018 presented with weakness, muscle cramps, palpitations, constipation, and increased frequency of urine output, multiple episodes of vomitings. The past history of the patient reveals that she was not a known diabetic, hypertensive, asthamtic and epileptic. No relevant family history was found and no other similar illness in other family members.

Objective examination

Vitals of the patient were found to be BP: 110/70 mm of Hg, Pulse Rate: 90 bpm, RR: 23 cpm. Laboratory findings revealed that hemoglobin was 9.7gm, RBC was 3.34 million/cmm, platelets was 3.96 lakhs/cmm, WBC was 7,700 cells/cmm , serum sodium was 138 meq/l (normal- 136 - 144), serum pottasium was 2.7 meq/l (normal- 3.6 - 5.1meq/l), serum chloride was 99 meq/l (normal- 98 - 107 meq/l), serum calcium was 7.5 meq/l (normal- 8.5 - 10.5 meq/l), serum magnesium was 0.7 meq/l (normal- 1.6 - 2.6 meq/l), and total volume of 24 hrs urine sample was 3800ml/day(1000 - 2000 ml/day) and 24 hrs urinary sodium, potassium, calcium and creatinine was 3534.0 mmol/day (normal- 40-200 mmol/day), 433.2 mmol/day (normal- 25- 125mmol/day), 440 mg/day (normal- 150 - 200 mg/day), 615.6 mg/day (normal 1000-2000mg/day) respectively.

LFT's and RFT's and Thyroid tests were normal. Peripheral smear showed mild Erythropenia Normocytic Normochromic. Arterial blood gases and chest x-ray were normal.

Diagnosis

Based on the subjective and objective evidence, the patient was diagnosed as “GITELMAN SYNDROME”.

Treatment

The patient was treated with the oral pottasium and magnesium supplements, non-steroidal anti-inflammatory drugs, other supportive medications and she was encouraged to maintain a high-sodium and high-potassium diet.

Outcome and Follow-up

The patient was got relieved from the symptoms on oral supplementation, but hypomagnesemia and hypocalciuria persists and was discharged with Tab. Magvion 400mg, Tab. Aldactone 25mg, Tab. Bio D3 0.2mg, and was asked to come back for review after a month. On follow up the patient recovered, symptom free and had normokalaemia levels and again in month of November, patient came to the hospital with the complaints of vomitings, severe right sided abdominal pain and amenorrhea in the last 2

months. Trans vaginal ultrasound showed that Bilateral polycystic ovarian pattern, elongated uterus and partially exophytic right ovarian cyst. The patient was treated with Inj. Tramadol 50mg thrice daily, Inj. Drotin 40mg twice daily, Inj. Pantop 40mg once daily. She was symptomatically stable and was discharged with Tab. Deviry 10mg and Tab. Mefthal spas 250 mg daily.

DISCUSSION

In Gitelman's syndrome, mutations in the thiazide sensitive Nacl transporter made reduced sodium reabsorption in the distal convoluted tubule leads to volume depletion and hypokalemia. Loss of activity of the thiazide sensitive transport increases tubule calcium reabsorption, leading to the classic finding of hypocalciuria in Gitelman's syndrome.

In our patient, diagnosis of Gitelman's syndrome was done based on clinical findings and laboratory findings like hypocalciuria, hypokalemia and hypermagnesuria. *Rodriguez-Soriano et al.* suggests that hypocalciuria may be useful in distinguishing the Gitelman's syndrome from classic Bartter's syndrome [12]. The greater urinary calcium excretion in patients with classic Bartter's syndrome is consistent with impaired reabsorption in the ascending limb of loop of Henle. Alternatively, the hypocalciuria of Gitelman's syndrome suggests the involvement of the distal convoluted tubule, where reduced chloride absorption is associated with augmented calcium absorption [13]**.** The patient also presented with right ovarian cyst but no significance was found between GS and ovarian cyst on review of literature in databases.

Most asymptomatic patients remain untreated and undergo ambulatory monitoring with low frequency. Concerning treatment, supplementation with magnesium is indicated, along with a high sodium and high potassium diet. If symptomatic hypokalaemia is not corrected, the drugs that antagonise aldosterone activity or block the sodium channel in the collecting duct will be preferred and therapeutic option is the combination of amiloride, spironolactone with potassium chloride. Patients are encouraged to maintain a high-salt diet [11].

CONCLUSION

Hypokalemia is the cause for Gitelman's syndrome and it seems a challenge for physicians in case differentiation of GS from other tubulopathies (genetic as well as acquired), and other causes of hypokalemia. Familial history can reveal asymptomatic patients with GS. With adequate treatment, GS patients have an excellent prognosis. The long-term prognosis of Gitelman's syndrome, in terms of growth and life expectancy is favorable.

LIST OF ABBREVATIONS

- BP - Blood Pressure
- BS - Bartter syndrome
- DCT - Distal convoluted tubule
- GS - Gitelman's syndrome
- Hg - Hydrargyrum
- LFT's – Liver Function Tests
- NaCl – Sodium Chloride
- NCC – Sodium Chloride Cotransporter
- RBC – Red Blood Cell
- RFT's – Renal Function Test's
- WBC – White Blood Cell

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