Case study

Gitelman Syndrome presenting as Hypokalemic Periodic Paralysis: A Case Report

ABSTRACT

GitelmanSyndrome is a type of inherited tubulopathy that results in hypokalemia, hypomagnesemia, hypocalciuria and metabolic alkalosis. It is generally due to loss of function mutation of theSLC12A3 Gene. The prevalence is estimated at approximately 1:40,000. It usually presents abovesix years of age and in many cases, the diagnosis is only made at adult age. Some patients experience severe fatigue interfering with daily activities, while others never complain of tiredness.The symptoms and severity can even vary among members of the same family. Blood pressure is lower than that in the general population. The prognosis of patients withGitelman Syndrome is excellent, except a few patients may be at risk for Cardiac arrhythmias. Potassium and Magnesium depletion increases the risk of ventricular arrhythmia. Sudden cardiac arrest has been reported occasionally. We describeacase of a man in his early 40's having severe hypokalemia but only mild muscular weakness without any acid-base abnormality.

KEYWORDS : Hypokalemic periodic paralysis, Gitelman Syndrome, Inherited Tubulopathy, Metabolic Alkalosis, Hypomagnesemia, Hypocalciuria

INTRODUCTION

Gitelman syndrome is an inherited hypokalemic salt-losing tubulopathy, characterized by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria, secondary aldosteronism, a high urinary chloride concentration and an absence of thiazides from the urine.It was first described by Gitelman in 1966. It is generally inherited as an autosomal recessive trait due to abiallelic inactivatingmutation in theSLC12A3 gene that encodes the thiazide-sensitive sodium chloride cotransporter (NCC) expressed in the distal convoluted tubule

of the kidney. The abnormal luminal membrane transporters are shed into the urine in nanovesicles called urine exosomes. Reduced NCC activity in urine exosomes has been described in patients with Gitelman syndrome, and this may be utilized in the future as a diagnostic test. In a small minority of GS patients, mutations in the CLCNKB gene, encoding the chloride channel ClC-Kb have been identified. Antenatal diagnosis for GS is technically feasible but not advised because of the good prognosis inthe majority of patients.

The main symptoms include mild muscular weakness and cramps, hypotension, salt craving, chondrocalcinosis of the knees, occasional episodes of tetany, constipation, abdominal pain and vomiting.First-line therapy is always oral supplementation with a generous dose of sodium chloride or potassium chloride. Magnesium supplementation is necessary as hypomagnesemia worsens renal potassium wasting. Potassium-sparing diuretics (Spironolactone, Eplerenone, Amiloride) are generally the next line of therapy when supplementation alone is insufficient. NSAIDs, typically Indomethacin may be helpful. ACEI reduces aldosterone levels and therefore renal potassium loss.

CASE REPORT

A 40-year-old male patient, not a known case of any comorbidity, presented on 17thMarch 2023 with chief complaints of generalized weakness, decreased appetite, constipation and tetany.The patient was thin and lean,well built but poor nourishment. [height =164 cm and weight =45 kg (BMI-16.73 kg/m^2)].The patient works as a farmer. The patient is a tobacco chewer for 10 years (one packet in two days). There is no history of smoking, alcohol or drug abuse. The patientwas born out of non-consanguineous marriage, a full-term child, delivered by normal vaginal delivery. The patient is having one elder brother. There is no history of similar illness in the family.

Past History:

In October 2020, the patient was having similar complaints of generalized weakness and was diagnosed as having hypokalemic periodic paralysis. Serum potassium was 1.73 and the patient was given intravenous supplementation of

potassium chloride. At the time of discharge, he was advised to continue oral supplementation of potassium chloride.

Until one week before admission, the patient was relatively in good health after which he complained of generalized weakness, decreased appetite, constipation and tetany, and soughtan outside medical facility on 14thMarch, 2023.

Table 1. Pathological report in premedication periods.

Investigation	14/03/23	15/03/23	16/03/23	17/03/23
Hb	11			11
TC	11,400			
Platelets	3.86			
RBS	70			
S. TSH		2.86		
S. sodium	129.2	128.4	133.9	133.2
S. potassium	1.82	1.58	2.18	2.0
S. chloride	70	90	96	95
U. sodium			40.10	
U. potassium			16.44	
S. magnesium	1.6			

It is important to place the reference values of laboratory tests.

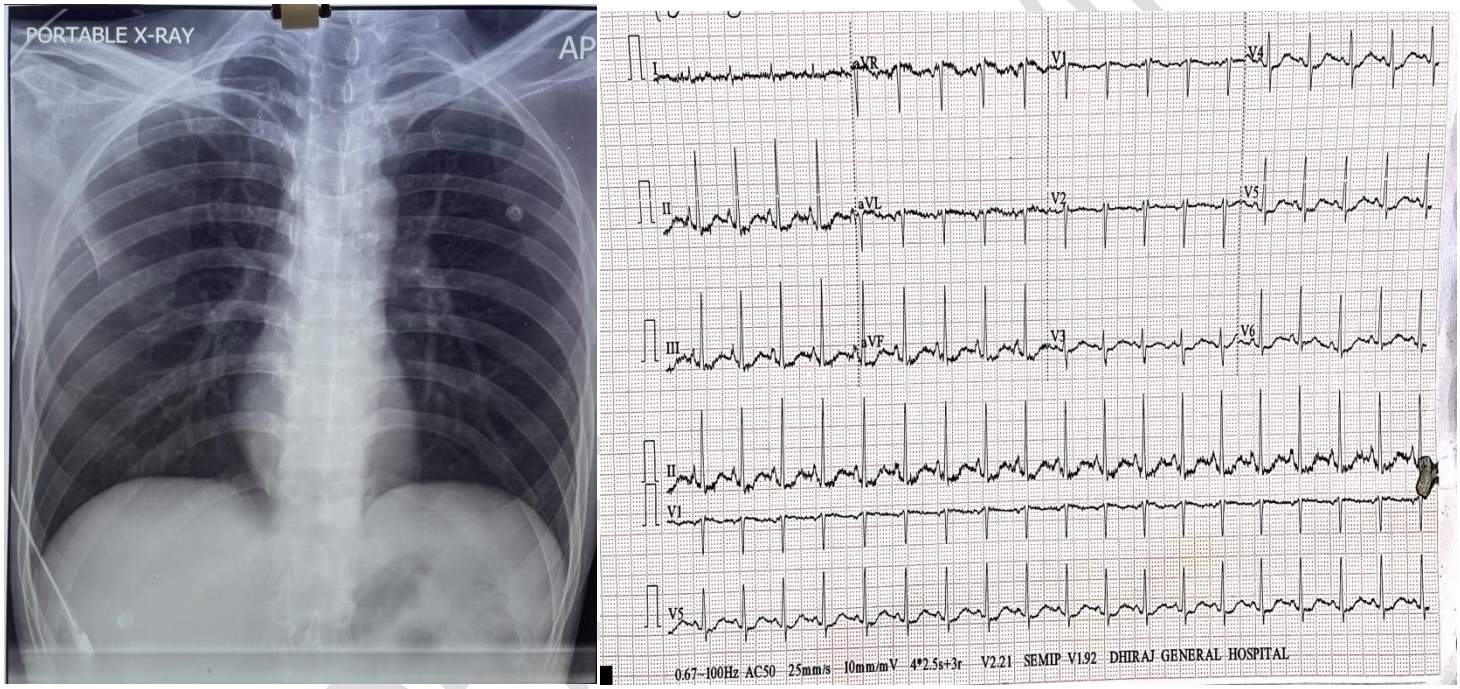
Management:

The patient was given potassium chloride supplementation (40 mEq) intravenously. The patient was started on Dopamine and Noradrenaline support and referred.

On presentation to our hospital, the patient was afebrile.He was having a pulse rate of 120 beats per minute.His blood pressure was 106/60 mmHg on Noradrenaline (0.48 mg/hour) and Dopamine (20 mg/hour) support. His respiratory rate was 18 per minute. Oxygen saturation was 100% on room air. There was no evidence of pallor, icterusor edema. Systemic examination revealed no abnormality. Neurological examination was completely normal.Patients' blood and urine samples were sent for analysis on admission and an immediate ECG was done.The ECG was showing diminished T wave andprominent U wave, suggestive of hypokalemia. On ultrasound, bilateral

kidneys showed raised cortical echotexture with few tiny (2-3 mm) concretions in the left kidney (10*5.8 cm) and few simple cortical cysts (largest of size 17*16 mm) in the lower pole of the right kidney (9.8*5.9 cm). Echocardiography was completely normal. ABG was inconclusive. Urine Routine Micro was normal. ANA Profile was Negative.

Fig 1. X-Ray plate and ECG report (page 1) of a patient.



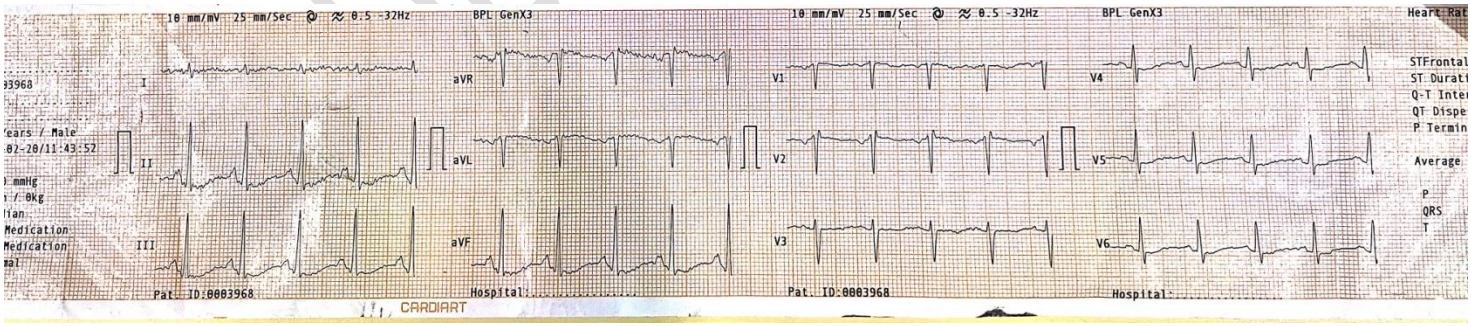


Fig 2. ECG report (page 2) of a patient.

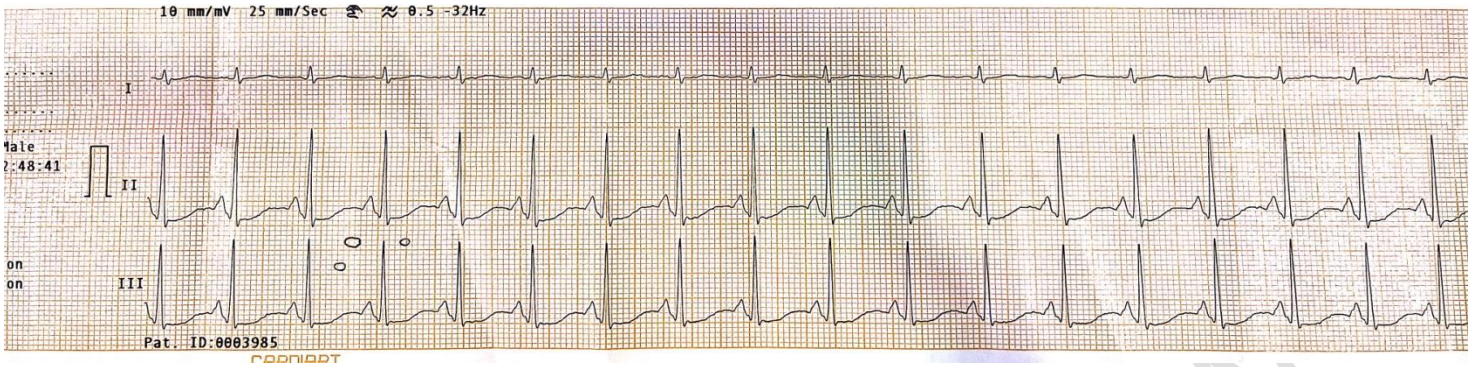


Fig 3.ECG report (page 3) of a patient.

Table 2. Pathological report in postmedication periods.

INVESTIGATION	17/03/2023	19/03/2023	21/03/2023	23/03/2023
Hb	12.6	12.8	12.3	
TC	10,000	13,000	11,000	
Platelets	4.0	3.72	3.25	
S. Sodium	134	138	136	137
S. Potassium	1.8	2.9	3.1	3.5
S. Chloride	96	93	91	96
S. Creatinine	0.6	0.6	0.7	
S. Calcium	7.2			
S. Magnesium	2.0			
U. Sodium	119			
U. Potassium	23			
24 Hrs Urinary K			202.4	
U. Chloride	68			
U. Ca/Creat		0.08		
U. Mg/Creat			314	
U. Osmolality			215	
U. Ph			6.5	
S. Bicarbonate			27.2	
S. Cortisol				15.1

The patient was started on Infusion of potassium chloride intravenously which continued till serum potassium became >4. Serum electrolytes were monitored 12 hourly. The patient's muscular weakness and constipation were improved with potassium supplementation. The patient was also given calcium and magnesium supplementation intravenously with which tetany improved. Gradually, Noradrenaline and Dopamine support was tapered off.A nephrology consultation was done and a probable diagnosis of RTA Type II v/s Gitelman Syndrome was given.

DISCUSSION

We have a case of an adult patient who was having symptoms suggestive of hypokalemia forthe last three years. After excluding pseudohypokalemia, on the basis of history, physical examination and basic laboratory tests, hypokalemia due to decreased intake and/or redistribution into cells was ruled out.24-hoururinary potassium of morethan 15millimole/day was suggestive of renal loss of potassium.TTKG(trans tubular potassium gradient) more than 4 (here, it was 7) was explaining increased distal potassium secretion. In a hypotensive patient with inconclusive acid-base status and urinary chloride of more than 20, an extremely low urinary calcium to creatinine ratio clinched the diagnosis of Gitelman Syndrome. The tetany responded to calcium and magnesium supplementation.

In Gitelman Syndrome, loss of NCC function results in Na^+ and Cl^- wasting from DCT leading to hypovolemia with secondary activation RAAS. The resulting increase in collecting tubule Na^+ reabsorption is counterbalanced by K^+ and H^+ excretion causing hypokalemic alkalosis. The hypocalciuria is due to the associated plasma volume contraction. The renal magnesium wasting is caused by the downregulation of the epithelial Mg^{2+} channel Trpm6 in DCT.

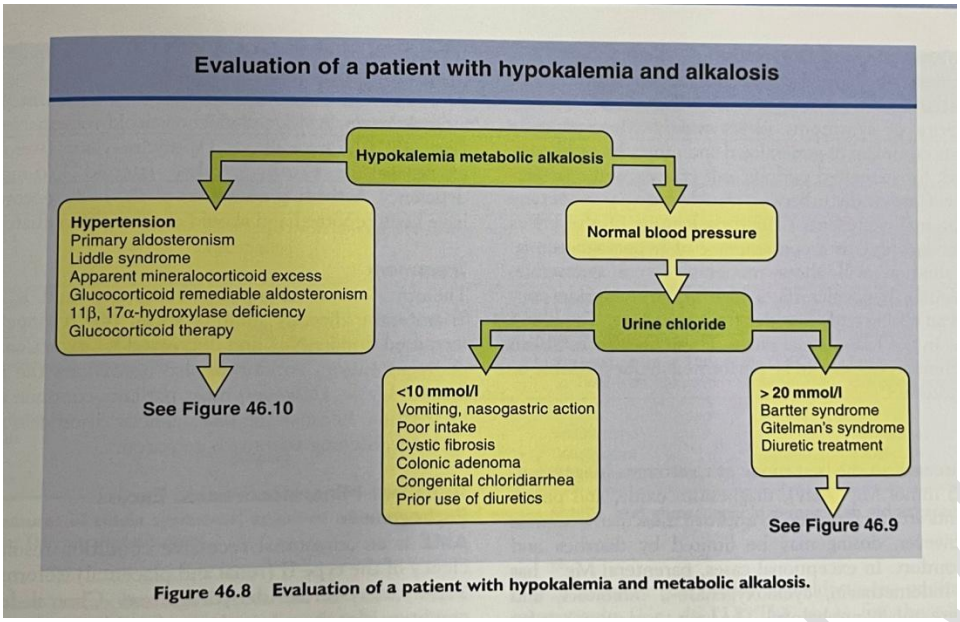


Fig 4. Evaluation of a patient with hypokalemia and metabolic alkalosis.

Barter Syndrome type 3 and Gitelman Syndrome are both usually present in adolescence or early adulthood. Measurement of urine calcium/creatinine ratio and urine magnesium/creatinine ratio can help differentiate between these two. Urine calcium excretion is high-normal or elevated in Barter syndrome type 3 but reduced with Gitelman syndrome. Renal magnesium wasting and hypomagnesemia is present in Gitelman syndrome but is usually not seen with Barter syndrome type 3.Inthe absence of genetic confirmation, it can be difficult to differentiate these disorders.

CONCLUSION

We discussed the case of a patient who will require lifelong supplementation of potassium and magnesium salts. Periodically, he was developing muscular weakness associated with severe hypokalemia, improving with potassium supplementation. We can conclude that lifelong potassium supplementationwould prevent the symptoms of such patients and provide a better quality of life. Carbonic anhydrase inhibitors such as Acetazolamide or a potassium-sparing diuretic such as Spironolactone are also useful.

ABBREVATIONS

GS: GitelmanSyndrome ;**NCC :** Sodium Chloride Co-Transporter; **TTKG:** Trans Tubular Potassium Gradient ;**ECG :** Electrocardiogram; **ABG:** Arterial Blood Gas Analysis ; **DCT** : Distal Convoluted Tubule ; **RAAS** : Renin Angiotensin Aldosterone System

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