



CHRONIC HYPOKALEMIA, HYPOMAGNESEMIA DUE TO GITELMAN SYNDROME: A CASE REPORT

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<p>Article Info <i>Received 15/03/2015</i> <i>Revised 27/04/2015</i> <i>Accepted 20/05/2015</i></p> <p>Key words: Gitelman Syndrome, Hypokalemia, Hypomagnesemia, Hypocalciuria and Metabolic alkalosis.</p>	<p>ABSTRACT Gitelman Syndrome is a genetic disorder of salt wasting causing Hypokalemia, Hypomagnesemia, Hypocalciuria and Metabolic alkalosis. It is an Autosomal recessive disorder, which runs in families. Patients present with muscle cramps weakness, pain, nausea, vomiting, loss of appetite and history of joint pains. Since patients have polyuria and polydipsia, it is very important to calculate the urinary losses to supplement potassium intravenously and simultaneously correcting magnesium deficiency. We report a case of 16 year old male who came to us with weakness of all the limbs, pain on movements, nausea, hypotension, Hypokalemia, Hypomagnesemia, who had polyuria and large losses of urinary potassium in spite of severe hypokalemia. It was a therapeutic challenge for us to supplement large amounts of potassium intravenously and magnesium simultaneously.</p>
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INTRODUCTION

Patients presenting with chronic hypokalemia and muscle weakness present as a therapeutic challenge as they have multiple electrolyte abnormalities and correction of these electrolyte disturbances would be difficult when they have large amounts of urinary losses especially if they have polyuria and polydipsia.

Bartter syndrome (BS) and Gitelman syndrome (GS) are two major variants of familial hypokalemic alkalosis. Gitelman syndrome is common among the two. The clinical sub division between the two has been used in the past. Genetic classification is increasingly used due to phenotypic overlap. These subsets of patients exhibit hypocalciuria rather than hypercalciuria seen in Bartter syndrome. Although, plasma rennin activity is increased, renal prostaglandin excretion is not elevated, which is another distinguishing feature between Bartter and Gitelman syndrome. Gitelman syndrome is milder than Bartter syndrome but patients do have significant morbidity mostly related to muscular symptoms and fatigue. The QT interval is frequently prolonged suggesting

increased risk of cardiac arrhythmia.[1] We present this case of Gitelman syndrome as a unique case because of difficulty in correcting Hypokalemia due to large losses of potassium in the urine, in spite of having severe hypokalemia. The prevalence of this syndrome is 1 in 40000.[2]

CASE REPORT

We present a case of 16 year old adolescent male who came to us with complaints of generalized weakness since 6 months of all the limbs. History of nausea, vomiting and pain in the limbs on movement. His admission history revealed that he had been admitted for the same reason at different hospital 3 months ago and was treated with intravenous fluids. His vital parameters on admission being pulse rate of 110 /min., blood pressure of 70 mm. of Hg. Systolic and SPO2 of 96% with general physical examination revealing him to have exophthalmos, poor visual activity, pectus carinatum, height of 168 cms. and weight of 36 kgs. His cardiovascular, respiratory and per abdomen findings were normal and there was



generalized muscle wasting of all the limbs and pain in the muscles on movements, with dropping of eyelids and all deep tendon reflexes being absent. His laboratory investigations revealed Hb-10.8 gms/dl. Total count of 12900 cells/cumm., platelet of 2.7 lacs/cumm., neutrophils of 80% and lymphocytes 20%, PCV 33.9%, blood urea 16 mg/dl. , Serum creatinine of 0.86 mg/dl. Serum uric acid of 3.9%, Na,-139.6 meq/ltr. K-2.2 meq/ltr. Cl-85.5 meq/ltr. Magnesium of 1.7 mg/dl. Calcium of 9.2mg/dl. Phosphorous of 4 mg/dl. and bicarbonate of 36 mmol/ltr. His urine examination showed Albumin 2+, Sugar nil, and 6-8 pus cells/hpf, 3-4 RBC/hpf, and urinary electrolytes being Na-65.4 meq/ltr., K-35 meq/ltr. and Cl-105 mmol/ltr. with urinary bicarbonate being 3.9 mmol/ltr. Magnesium-6.9 mg/100 ml, urinary calcium of 1.4 mg/100 ml. urinary phosphorous 45.2 mg/dl. His ABG report showed PH-7.668, PCO₂-50.3 mmHg, PO₂-104.6 mmHg, HCO₃-55.9mmol/ltr. Suggesting metabolic alkalosis with respiratory compensation. His ultrasound abdomen showed bilateral enlarged kidneys with right kidney 12.6X4.5cms & left kidney 12.4X4.7 cms. with no calcifications.

We started to correct his electrolyte abnormality with intravenous potassium chloride infusions of 40meq/ in 500 ml of 0.9% saline and started to measure his urine output over next 24 hrs. His urine output was 4.5 ltrs over next 24 hrs. and we calculated urinary losses of potassium. We found that patient was losing 140meq of potassium in his urine over 24 hrs. Next day, we found that his potassium to be 1.5 meq/ltr. and magnesium 1.5 mg./dl. Since the requirements of potassium was large we had to increase the concentration of our replacement fluid from 40 meq/ 500ml. 0.9% NS to 60 meq/500ml. 0.9% NS. Along with intravenous magnesium supplementation in the form of magnesium sulphate in 0.9% NS. Patient required intravenous potassium for 6 days to correct the deficit from baseline of 1.5 meq/ltr to 3.5 meq/ltr. Serum magnesium however remained around 1.2 mg./dl. Hence, we started patient on oral magnesium supplementation in the form of magnesium oxide and oral potassium supplementation in the form of potassium chloride by 5th day of admission. After correcting potassium levels to 3.4meq./ltr, patient's symptoms improved and muscle power began to normalize and pain subsided. His ECG initially which showed to have prolonged QT interval had normalized. He was discharged on 7th day of admission with oral magnesium and potassium supplementation.

Patient's data was analyzed and clinical features assessed. Patient had hypocalciuria with urinary calcium being 1.4mg/100ml. and urinary creatinine of 10.75 mg/dl. With urinary calcium creatinine ratio of 0.130 mmol/mol. of creatinine. Patient had features of chondro calcinosis on X-ray of chest and knees with corneal opacities which could be due to choroidal calcification. From these features and laboratory values we came to conclusion that patient had Gitelman Syndrome which usually presents after 6 years of age and typical presentation is in adolescent children.

DISCUSSION AND CONCLUSION

Gitelman syndrome (GS), (OMIM 263800), also referred as familial hypokalemia-hypomagnesemia, is an autosomal recessive salt-losing renal tubulopathy characterized by hypomagnesemia, hypocalciuria and secondary aldosteronism, which is responsible for hypokalemia and metabolic alkalosis [1]. It has got a prevalence of 1 in 40,000, and it is most frequent inherited tubular disorder.

Clinically it will present above the age of 6, and mostly in adults, as in our case when the age of our patient was 16 years. The most common symptom is tetany and muscular pain which was the presentation in our case. Due to pain, there was limitation of movements in our patient, who had serum potassium of 1.5 meq/ltr. on the second day of admission. His height was 168 cms. which was normal for that age and there was no stunted growth. In general Gitelman syndrome (GS) patients have normal growth, however it can be delayed in patients of severe hypokalemia and hypomagnesemia [2]. Our patient also had chondrocalcinosis on the chest X-ray and his cornea had opacities, which could not be found in the literature we searched and found that patients can have choroidal calcification.

The evaluation of 50 adult patients by Cruz and colleagues of quality of life(QOL) and comparing with 25 age and sex matched controls have challenged the general belief that GS is a mild disorder [3]. They found that the quality of life was significantly impaired in these patients due to muscular cramps, tetany, pain and fatigue.

Due to potassium and magnesium depletion the action potential duration and QT interval prolongation is seen in 50% of cases. Our patient too had QT prolongation and U wave in ECG, available literature revealed that GS is not associated with clinically relevant cardiac arrhythmias in majority [4], barring 2 reports of aborted sudden cardiac death in Bartters/Gitelmans syndrome by Scognamiglio R, et al.[5].

The Blood pressure in GS patients is lower than the general population and our patient's blood pressure was around 70mm of Hg to 80mm Hg systolic, during the period of admission. Even the carriers of GS gene are protected from hypertension [6]. The findings of low blood pressure were correlating with the findings of Cruz DN, and Colleagues who found to have low blood pressure in patient with SLC12A3 mutation allele [7].

Genetics of GS : Most cases of GS are caused by mutation in the solute carrier family 12, member 3, SLC12A3 gene, which codes for Thiazide –sensitive sodium-chloride co-transporter NCC located in apical membrane cells of Distal convoluted tubules.[8] NCC is a Polypeptide of 1021 Amino acids with 12 trans-membrane domain and intracellular carboxy and Amino terminus. More than 140 different mutations like missense, nonsense, frameshift and splice-site mutations are found in the whole protein. There is extreme phenotypic variability and



severity of symptoms in GS not correlating with the mutation in SLC12A3 gene [9].

Dejong and coworkers have found NCC misfolding and defective trafficking in some mutation.[10] And also proved that transcriptional regulator 4-phenyl butyrate, may be a potential pharmacological chaperone for future use to traffic the NCC protein to the cell membrane.[11] A small minority of patients have mutations in the CLCNKB gene which codes renal chloride channel CLC-Kb, located in the basolateral region of cell of thick ascending limb (TAL) and Distal tubules.

The loss of function of NCC and mutations of CLC-Kb leads to decreased or absent NaCl absorption in DCT delivering more Na⁺ to collecting duct, causing volume contraction and activation of Renin angiotensin and Aldosterone axis. This increased Aldosterone causes increased sodium Absorption at cortical collecting duct at the expense of Hydrogen and potassium, causing Hypokalemia and metabolic alkalosis. The hypomagnesemia is due to reduced abundance of epithelial Mg⁺ channel TRPM6 in DCT and Hypocalciuria due to passive Ca²⁺ reabsorption in proximal tubule [12].

Diagnosis and differential diagnosis

The diagnosis is based on biochemical abnormalities like hypokalemia, hypomagnesemia, metabolic alkalosis and hypocalciuria. In our patient, we had serum potassium of 2.2Meq/ltr., magnesium of 1.7 mg/dl, which later decreased to 1.5mg/dl. and his urinary calcium being 1/4mg./100ml. and urinary creatinine of 10.7 mg/dl. and urinary calcium creatinine ratio of 0.130 mmol/mol of creatinine and described in literature to be

less than 0.2mmol/mol of creatinine.[13] Definitive Confirmation is done by DNA analysis. Barter syndrome type III is the most common differential diagnosis followed by laxative abuse and chronic vomiting

Management

Since patient had severe hypokalemia and hypomagnesemia we started correcting intravenously by potassium chloride infusion and magnesium sulphate infusion. Urinary losses were assessed by 24 hrs urinary volume measurement which came to 140 meq. of potassium /day. Simultaneous correction by both oral and intravenous potassium supplementation were started due to heavy urinary losses, along with magnesium sulphate infusions, although recommendation is to use magnesium chloride intravenously. Due to easy availability of magnesium sulphate we used it effectively to increase magnesium and potassium. We discharged our patient on magnesium oxide preparation dividing it in 2-3 doses per day. The benefit of magnesium supplementation is that it also prevents chondrocalcinosis[14].

The other recommended drugs apart from magnesium are Amiloride (5-10mg / 1.73^{m2}/day) and KCL (1 -3mmol/kg/day in 3-4 divided doses). In children apart from magnesium and potassium Indomethacin is recommended as it promotes growth[15].

Prognosis

Long term prognosis is excellent with only one patient progressing to end stage kidney disease being reported [16].

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