Gitelman-like Syndrome with Kanamycin Toxicity

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Abstract

A 22 year-old lady with multi-drug-resistant pulmonary tuberculosis was on Kanamycin, Cycloserine, Ethionamide, Pyrazinamide and Moxifloxacin since more than two months. She presented with muscle cramps and carpopedal spasm. Investigation revealed hypokalemia and metabolic alkalosis. She also had hypomagnesemia, hypochloremia and hypocalciuria. Serum urea and creatinine levels were normal. Patient was treated with intravenous and oral potassium chloride. Kanamycin was stopped. Metabolic alkalosis and hypokalemia improved gradually over one month. Biochemical parameters were like Gitelman’s syndrome but it reversed with stoppage of Kanamycin. Gitelman-like syndrome with Kanamycin toxicity has not been reported in literature previously.

Introduction

Barter’s and Gitelman’s syndromes are autosomal recessive renal tubular genetic diseases associated with metabolic alkalosis and hypokalemia with normal blood pressure. Here we report a patient with prolonged Kanamycin usage, who developed metabolic alkalosis and severe hypokalemia along with hypocalciuria. There are only few reports of other drug (aminoglycoside, cisplatin) causing Barter or Gitelman like syndromes. But Kanamycin induced Gitelman-like syndrome has not been reported in literature till now.

Case Report

A 22 year-old lady came to our emergency department with the complaints of painful muscles cramps in all four limb with upper limb predominance and severe generalized weakness. She had no difficulty in breathing and had no symptoms of facial or ocular muscle involvement. Bulbar or bladder/bowel symptoms were absent. There was no similar past or family history.

The patient had been diagnosed as a case of sputum positive pulmonary tuberculosis in 9 months before (Figure 1). A standard four drug regime was started with isoniazid, rifampicin, ethambutol and pyrazinamide. But she developed drug-induced hepatitis after three weeks of intensive phase. After normalization of liver function tests (LFT), initial four drugs regime was restarted. But the persistent sputum positivity for acid fast bacilli (AFB) and non-resolving opacities in chest x-ray raised the suspicion of drug resistant tuberculosis, which was confirmed by sputum culture for AFB and drug sensitivity report. The organism isolated from her sputum was resistant to isoniazid and rifampicin. Then she was put on injection Kanamycin 1gm OD, tab. Cycloserine 250mg BD, tab. Pyrazinamide 1.5 gm OD, tab. Ethionamide 250mg BD and tab. Moxifloxacin 400mg OD from the end of January 2014. Chest symptoms and signs improved along with radiological improvements in chest x-ray after one month (Figure 2).

After two months of initiation of modified regime patient had tingling sensation of all four limbs associated with intermittent painful spasm of limb muscles. These symptoms gradually increased in intensity. The intensity of muscle spasms caused her to be brought to the emergency department, the patient was anxious, had tachycardia (120/min) and tachypnea (28/min). She was normotensive and was in afebrile state with a SpO2 of 96% in room air. Examination of her cardiovascular and gastrointestinal systems revealed no specific abnormality, but respiratory system examination revealed few coarse crackles in the right base.

Her arterial blood gas (ABG) and serum electrolytes analysis revealed mixed metabolic and respiratory alkalosis with severe hypokalemia. ABG analysis revealed a pH of 7.553, PCO2 30.8 mm of Hg, PO2 96 mm of Hg, HCO3 1.6 meq/L, Na+ 134 meq/L, K+ 1.6 meq/L, Ca2+ 0.72 mmol/L (normal 1.12-1.32 mmol/L). Serum magnesium was 1.3 mg/dl (N: 1.5–2.3 mg/dl). Serum chloride was 84 mEq/L (N: 98-108 mEq/L). ECG showed sinus rhythm and prominent U waves. We started her on intravenous (IV) potassium infusion immediately with continuous ECG monitoring. IV calcium gluconate was also given. She was given 4 gm magnesium sulphate IV. She got substantial relief from the spasms on the very next day. We continued electrolyte replacement and her anti-tubercular drugs (ATT) was also continued. We repeated analysis of all electrolytes in blood and urine and also repeated the ABGs. It came out as persistent hypokalemia with metabolic alkalosis and with low-normal serum sodium level. Initial coexistent respiratory alkalosis was likely due to anxiety hyperventilation as it disappeared with reassurance. Repeat ABG analysis revealed a pH of 7.52, PCO2 43 mm of Hg, PO2 96 mm of Hg, HCO3 32 mEq/L, Na+ 135 meq/L, K+ 2.6 meq/L. Routine urine examination revealed pus cells 5-6/HPF, albumin 1+ and trace amount of blood. Eosinophils and casts were not found in urine. 24

![Fig. 1: Chest x-ray showing patchy opacity in right mid and lower zones](image-url)
and July, 2014 she had no recurrence stopped. At follow up visits in June and July, 2014 also showed absence of growth of tubercle bacilli. According to Naranjo causality scale, this case scores 6 (2 for adverse reaction after drug was given, 1 for improvement following stopping the drug, 1 for absence of similar reaction on administering placebo, in this case other anti-TB drugs, and 2 for absence of alternative causes). We concluded the case as toxicity of Kanamycin manifesting as Gitelman-like syndrome.

**Discussion**

Gitelman’s syndrome (GS) is a rare genetic renal disease due to mutations in the thiazide-sensitive NaCl co-transporter (NCCT) in the distal convoluted tubule. It is characterized by hypokalemia, hypomagnesemia, metabolic alkalosis and hypocalciuria. It may present at any age and the clinical and laboratory features are variable. Treatment entails lifelong electrolyte replacement and high doses of spironolactone or amiloride.

The manifestations of GS are said to be similar to the effect of thiazide diuretics. However, other drugs with similar effect on the kidney have only rarely been reported. A case report from USA described a patient receiving cisplatin who developed GS like syndrome. However; in that case, the syndrome was permanent while in our case, the patient recovered after stopping the drug. Cisplatin causes focal tubular necrosis in distal tubule and collecting ducts. It is also thought that it can cause direct DNA damage of the NCCT gene and precipitate this GS like episode.

Kanamycin is an aminoglycoside. Its mechanism of nephrotoxicity is by binding of the cationic drug with negatively charged acidic phosphoinositide of tubular epithelium brush borders. This complex is internalized and disrupts various cellular processes. Hypokalemia and hypomagnesemia have been reported in aminoglycoside toxicity. However, full blown GS like episode, as in our patient, is rare. Very rarely, other distal tubular disorders like Bartter-like syndrome have been reported with amikacin or gentamicin. But there is no report of Kanamycin presenting with similar symptoms. Capreomycin, another aminoglycoside used in multi-drug resistant tuberculosis, has also been reported to cause renal potassium and magnesium wasting with alkalosis. This had case responded to spironolactone and was resistant to indomethacin. In contrast, our patient responded only to omission of Kanamycin.

GS-like condition can also occur in some other conditions like malignancy. A case of paraneoplastic GS associated with pancreatic carcinoma was reported from Romania in 2011. This patient also had persistent GS and needed spironolactone support. Other causes of acquired GS are autoimmune disorders and renal transplantation. Among the autoimmune diseases, the highest number of cases was reported with Sjogren’s syndrome. In these patients, treatment of the underlying disease led to resolution of electrolyte abnormalities. In some of the cases, circulating antibodies to NCCT have been documented.

While proximal tubular damage due to aminoglycosides show typical histological features on biopsy, distal tubular syndromes like Gitelman do not show any specific histological features. The exact mechanism of biochemical alteration in Gitelman-like syndrome is still unknown. Gentamicin has been implicated in distal tubular syndromes and in one report from Taiwan, four cases of gentamicin induced Bartter syndrome-like state reversed spontaneously after stopping the drug. This group of renal adverse reaction seems to be more common in females, as per the published cases. Thus, it is very difficult to assess the extent of renal damage in these conditions and often, the clinicians have to wait for response after stopping the drug. However, as with genetic Bartter or Gitelman syndrome, the electrolyte alterations can be life-threatening and standard electrolyte replacement protocols should be followed before further diagnostic studies are attempted. Invasive renal tests are not always helpful and our patient refused renal biopsy. However, it should also be remembered that Gitelman syndrome may first present in adult age. Hence, further follow up after stopping the drugs is needed before labeling a case as drug induced Gitelman like...
syndrome, as in genetic syndromes lifelong electrolyte replacement is needed. Aminoglycoside induced nephrotoxicity (AIN) is a common differential diagnosis in these cases, along with genetic Gitelman syndrome and Gitelman-like syndrome. However in AIN, serum creatinine generally rises, while in our patient it was persistently normal. Hypokalemia and hypomagnesemia are common to both conditions. But in AIN, we usually find hypercalciuria and eventually cast excretion. Also metabolic acidosis is more common in AIN while in Gitelman syndrome, as in our case, there is metabolic alkalosis. AIN is mainly due to damage to proximal tubular cells while Bartter or Gitelman like syndromes are presumably due to distal tubular damage. However, AIN can also be reversed by simply stopping the drug in initial stages. To differentiate between them, regular blood pressure measurement, urine examination and serum creatinine estimation should be done.

**Conclusion**

Kanamycin can have reversible adverse effects on distal tubular function and can cause significant morbidity. Toxicity of Kanamycin or aminoglycoside should be considered in a patient with GS like electrolyte abnormalities.

**References**