

Case Report

Gitelman's Syndrome: A Separate Disorder or a Variant of Bartter's Syndrome

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ABSTRACT

Gitelman's Syndrome (GS) is described as a separate entity of potassium (K) losing nephropathy that has to be distinguished from Bartter's Syndrome (BS). We present a case report followed by a short review of

patients with chronic hypokalemia and the differentiating features of these two K - losing nephropathies.

Key words: Bartter's syndrome, chronic hypokalemia, Gitelman's syndrome

INTRODUCTION

Hypokalemia, defined as serum potassium (SK) < 3.6 mmol/l, is found in over 20% of hospitalized patients. It is the most common electrolyte abnormality encountered in clinical practice. However, when it comes to chronic hypokalemia, its occurrence is infrequent but it presents a clinical challenge in finding the cause^[1]. It is well established that the term familial BS includes a variety of tubular transport disorders. The classical BS is referred to as hypokalaemic alkalosis with normocalciuria or hypercalciuria; while GS is referred to as hypokalaemic alkalosis with hypomagnesaemia and hypocalciuria. We report a case of GS and review the differential work up of these two syndromes.

CASE REPORT

Mr FT, a 52-year-old Indian male patient was admitted to the medical ward in Amiri Hospital to investigate an accidental discovery of confirmed hypokalemia on routine blood collection, after he presented to the medical casualty with fever and follicular tonsillitis. He had adequate dietary intake, was on no drugs and had no other positive symptoms. His past medical and family history was unremarkable. Physical examination was normal apart from congested tonsils. Basic investigations showed normal renal function tests with SK of 2.5 mmol/l. He had mild elevated S. calcium of 2.6 mmol/l [normal range (nr) 2.2 - 2.65] and low S. magnesium (SMg) 0.3 mmol/l (nr 0.8 - 1.2). Arterial blood gases (ABG) showed mild metabolic alkalosis with pH of 7.5, normal pO₂ and

pCO₂ with S. bicarbonate of 32 mmol/l (nr 21 - 28). Other investigations like electrocardiogram, chest X-ray, complete blood count and liver function tests were normal.

He was treated with high doses (> 180 mmol/d) of i.v. potassium chloride. However, this could not correct his hypokalemia. Once hypomagnesaemia was noticed and corrected first, by i.v. Mg sulfate for three days, his S.K returned to normal on much lower doses.

Further investigations were as follow: ultrasound of the kidneys and suprarenals was normal; 24hour urine for metabolic screen showed the following:

K - 27 mmol/d (nr 20-100), Mg 8.96 mmol/d (nr 3.0 - 5.0), Calcium 1.3 mmol/d (nr 2.5 - 8), aldosterone 197.7 pmol/l (nr 111 - 863) - ambulatory, S-rennin 92 ng/ml/hr (nr 7 - 76).

This patient was labeled as GS. He was discharged later on oral slow K, 1200 mg three times/day and oral Mg oxide 500-mg twice/day with SK of 3.8 mmol/l and S. Mg of 0.79/l.

DISCUSSION

Hypokalemia is classified as mild (3.0 - 3.5 mmol/l) usually asymptomatic; moderate (2.5 - 3.0 mmol/l) with non-specific symptoms; and severe (below 2.5 mmol/l) where it can cause ascending paralysis and muscle necrosis. In patients with underlying cardiac disease, cardiac arrhythmias are more common even with mild hypokalemia^[2].

Chronic hypokalemia is less likely to induce symptoms, as rapidity of decrease in SK is very much correlated with induction of symptoms^[2]. Hypokalemia is almost the result of K depletion

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induced by abnormal losses in urine or stool. Uncommonly, it can be attributed to redistribution of K between extracellular and intracellular spaces. Inadequate intake is another possible cause^[2,3].

Hypomagnesaemia, induced either by dietary restriction or abnormal losses, reduces the intracellular K concentration or leads to renal K wasting. Mg depletion often co-exists with K depletion as a result of drugs or disease process (e.g., diarrhea) making it difficult to assess whether it is an independent effect. However, the ability to correct K deficiency is impaired when the S. Mg is below 0.5 mmol/l. Repletion of Mg improves the co-existent K deficit^[2,4].

The first step in management of hypokalemia is to review the patient, his drug and dietary record. In surreptitious vomiting, hypochloremia, low urine chloride and mild renal impairment are supportive. High urine chloride is indicative of diuretic abuse; while high stool weight and low urine sodium indicate laxative abuse. If urine K is > 20.0 mmol/l, it usually points to a renal cause. ABG is also useful in the diagnostic work up. The finding of metabolic alkalosis can exclude renal tubular acidosis and laxative abuse^[3].

When none of the usual causes apply and when urine K is high, then BS is often suspected. GS should also be considered although there are only a few reports in the literature.

Bartter's first description of his syndrome was in 1962; it is characterized by hypokalaemic metabolic alkalosis, hyperprostaglandin production, hyperreninemia, secondary hyperaldosteronism with juxta-glomerular hyperplasia and normal blood pressure^[5]. It is associated with high urinary prostaglandin levels. It has an autosomal recessive mode of inheritance but sporadic cases have been reported^[5,6].

Recent advances in the field of molecular genetics have demonstrated that there are four genetically distinct abnormalities, which result from mutations in renal electrolyte transporters and channels.

Neonatal Bartter syndrome affects neonates and is characterized by polyhydramnios, premature delivery, severe electrolyte derangement, growth retardation, and hypercalciuria leading to nephrocalcinosis. It may be caused by a mutation in the gene encoding the Na-K-2Cl cotransporter. Classic Bartter syndrome is due to a mutation in the gene encoding the chloride channel, and typically presents in infancy or early childhood with failure to thrive. Nephrocalcinosis is typically absent despite hypercalciuria. The hypocalciuric, hypomagnesaemic variant of Bartter syndrome (Gitelman syndrome), presents in early adulthood with predominantly musculoskeletal symptoms

and is due to mutations in the gene encoding the Na-Cl cotransporter^[7].

GS was first described in 1971 in three patients. Several reports came after. These patients are unlikely to present with symptoms except for tetany or muscle weakness. Histopathology usually shows minimal changes of the juxta-glomerular apparatus^[5]. GS has been noted to have an autosomal mode of inheritance^[1].

GS represents the clinical manifestations of inactivating mutations in the gene encoding for the thiazide sensitive sodium chloride cotransporter in the distal convoluted tubule. Thus, the biochemical characteristics resemble those seen with thiazide diuretics: hypokalemia, hypomagnesaemia, hypocalciuria, metabolic alkalosis and blood pressure in the low normal range. Until the genetic background was clarified in 1996, GS was often mistaken for BS, which is now attributed to defects in the ion transportation system in the thick ascending limb of Henle's loop^[8].

A further distinguishing feature was the demonstration of hypercalciuria in patients with BS while those with GS had abnormally low urinary calcium excretion^[5]. Hypomagnesaemia, usually of a mild degree, is a major feature of GS but it is also present in one fifth of patients with BS^[4].

BS is an abnormality of chloride transport in the thick ascending limb of the loop of Henle which leads to loss of calcium and sodium, activation of the rennin angiotensin aldosterone system and loss of K. It resembles a state produced by furosemide. In contrast, GS resembles a state produced by a thiazide diuretic. Most probably the defect is in the distal cortical convoluted tubule. The renal Mg wasting in GS remains to be explained^[4,5].

In BS, prostaglandin production is almost a constant feature and many features of BS can be improved by the use of cyclo-oxygenase inhibitors. This has not been demonstrated in GS^[1]. Even though our understanding of these disorders has been greatly advanced by these discoveries, the pathophysiology remains to be completely defined.

In conclusion, this case report presents a classical case of GS. The patient had all the definite criteria including hypokalaemic metabolic alkalosis, hypomagnesaemia, and increased Mg excretion in the urine, hypocalciuria, and high rennin level with no evidence of hyperaldosteronism. His age group combined with normal physical examination further establishes the diagnosis.

REFERENCES

1. C Luchy MTA, A Bettinelli, S Iseln. Normal Prostaglandinuria E2 in Gitelman's syndrome. *Am J Kidney Dis* 1995; 25:824-828.
2. F John Gennari. Hypokalemia. *NEJM* 1998; 339:451-457.

3. U Gladziwa, R Schwarz, AH Gitter. Chronic hypokalemia of adults: Gitelman's Syndrome is frequent but classical Bartter's Syndrome is rare. *Nephrol Dial Transplant* 1995; 10:1607-1613.
4. Gary A Quamme. Renal magnesium handling: New insights in understanding old problems. *Kidney International* 1997; 52:1180-1195.
5. DA Mc Credie. Variants of Bartter's Syndrome. *Ped Nephrol* 1996; 10:419-421.
6. GH Malik, J Alwakeel, S Almohaya. Bartter's Syndrome in two successive Generations of a Saudi Family. *Am J Nephrol* 1997; 17:459-498.
7. Shaer AJ. Inherited Primary renal tubular hypokalemic alkalosis: review of Bartter's syndrome and Gitelman's syndrome. *Am J Med Sci* 2001; 322:316-332.
8. Hansen KW, Mosekilde L. Gitelman's syndrome, an overlooked disease with chronic hypokalemia and hypomagnesaemia in adults. *Ugeskr Laeger* 2003; 165:1123-1127.