Journal of Clinical Cases and Reports

ISSN: 2582-0435 **Case Report** | Vol 3 Iss 4

Gitelman Syndrome: A Rare Cause of Persistent Hypokalemia

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Abstract

Gitelman syndrome is a rare autosomal recessive renal tubular disease, caused by mutations in the SLC12A3 gene, which encodes the renal thiazide-sensitive sodium-chloride cotransporter (NCCT) in the distal renal convoluted tubule.

We present a 48-years-old male referred to our observation after being considered not suitable to a previous proposed surgery due to persistent hypokalemia. No valued symptoms were described. Laboratory tests showed metabolic alkalosis, hypomagnesemia, hypokalemia and secondary hyperaldosteronism. Genetic test was performed and sequence analysis of the SLC12A3 gene revealed a homozygous mutation confirming this disease.

The aim of this report is to remind and increase awareness of the existence of GS, manage the condition properly and consider the risk of disease recurrence to the next generations.

Keywords: ***Gitelman syndrome; Tubulopathies; Hypokalemia***

Received Date: November 14, 2019; **Accepted Date:** November 28, 2019; **Published Date:** December 05, 2019

Introduction

Gitelman syndrome also referred to as familial hypokalaemia-hypomagnesemia, is an autosomal recessive salt-losing renal tubulopathy, with a prevalence of heterozygotes at ~1% in European populations making it one of the most frequent inherited renal tubular disorders [1]. In the vast majority of cases it's caused by inactivating mutations in the SLC12A3 gene coding for the thiazide-sensitive sodium-chloride cotransporter (NCCT), normally expressed in the apical membrane of the renal distal convoluted tubule [2].

Typically characterized by hypomagnesaemia, hypocalciuria, hyperreninemia, and hyperaldosteronism that induce hypokalaemia and metabolic alkalosis, patients with Gitelman syndrome are usually diagnosed in adulthood during routine investigation or based on clinical symptoms and biochemical abnormalities.

Citation: Duarte Lages da Silva, Gitelman Syndrome: A Rare Cause of Persistent Hypokalemia. J Clin Cases Rep 3(4): 146-149.

Case Report

We report a case of a 48-years-old male, with a past history of diabetes and hyperlipidemia, treated with sodium-glucose cotransporter type 2 and dipeptidyl peptidase-4 (DPP-4) inhibitors and a statin. At pre-operative study for inguinal hernia repair, a severe decreased plasma potassium concentration (2.4 mmol/l) was detected. The patient complained of polyuria and polydipsia attributed by the attending physician to diabetes. He had no previous history of fatigue, cramps or tetany; denied having any other diseases or taking any other medications and family medical history was unremarkable. Initial evaluation revealed normal neurological/physical examinations, except for relatively low blood pressure (systolic 90 mmHg - 107 mmHg; diastolic 55 mmHg - 69 mmHg). Laboratory investigations revealed, besides severe and sustained hypokalaemia (2.4 mmol/l - 2.6 mmol/l), hypomagnesemia (1.27 mmol/l), slight hiponatremia, metabolic alkalosis and secondary hyperaldosteronism. Biochemical data are summarized in Table 1.

Examination items	Result	Reference range
Serum biochemical		
Potassium (mmol/l)	2.4	3.5 - 5.1
Sodium (mmol/l)	134	136 - 145
Chloride (mmol/l)	97	98 - 107
Calcium (mmol/l)	9.7	8.6 - 10.3
Magnesium (mmol/l)	1.27	1.6 - 2.6
Phosphate (mmol/l)	2.98	2.5 - 4.9
Creatinine (mg/dl)	0.85	0.8 - 1.3
Urea (mg/dl)	52	17 - 43
Venous blood gas		
pH	7,53	7.35 - 7.45
HCO3 (mmol/l)	30.9	22 - 27
Potassium (mmol/l)	2.6	3.50 - 5.30
Iomized calcium (mmol/l)	0.98	1.13 - 1.32
24-hr urine		
Potassium (mmol/24h)	51	25 - 125
Calcium (mmol/24h)	167	100 - 300
Magnesium (mmol/24h)	114.4	73 - 122
Phosphate (mmol/24h)		
Creatinine (mmol/24h)		
Chloride (mmol/24h)	483	110 - 250
Sodium (mmol/24h)	492.5	40 - 220
RAAS system		
Plasma renin activity (ng/ml/h)	77.5	0.5 - 1.7
Aldosterona (pg/ml)	260	49.3 - 175
ARR	0.05	<3.7

Table 1: Clinical tests of the patient.

Calcemia, calciuria, thyroid function tests and glucocorticoid level were within the normal range. His electrocardiogram revealed sinus rhythm (70 beats/minute) with normal QT interval; thoracic x-ray and abdominal CT were normal.

We measured the 24-hrs. urinary electrolyte excretion levels since her renal function was normal. A renal tubular disorder, namely Gitelman syndrome, was suspected. Genetic testing was performed and sequence analysis of the SLC12A3 gene revealed a homozygous mutation (c.1195C>T), which is predicted to substitute the arginine at codon 399 by a cysteine residue (p.Arg399Cys, R399C), and is considered to be a recurrent disease causing mutation.

The prescribed therapy included potassium chloride (2,400 mg/day), spironolactone (25 mg/day) and magnesium L-aspartate hydrochloride one packet (1229.6 mg) 3 times daily.

At the last evaluation an increased was observed with a potassium serum concentration of 3.0 mmol/l. The patient underwent uneventful surgery.

Discussion

Tubulopathies, like Gitelman or Bartter syndrome, are often suspected in patients with unexplained hypokalaemia, metabolic alkalosis, and a normal or low blood pressure. It demands the exclusion of the more common causes of unexplained hypokalaemia and metabolic alkalosis through a careful history evaluation (vomiting, diuretic and laxative abuse), physical examination and laboratorial study [2]. Those causes were excluded by measuring a high urinary chloride excretion and by a negative history of diuretic and laxative use. The remaining hypotheses would be tubulopathies of which, Bartter seemed unlikely because it usually has an earlier onset, a more severe phenotype and the serum magnesium is normal or mildly reduced [3].

The present report describes the case of a patient with hypokalaemia, hypomagnesemia and metabolic alkalosis diagnosed as Gitelman syndrome, confirmed at molecular level after genetic testing. Commonly, this syndrome is diagnosed in late childhood or even adulthood, in a patent with mild symptoms (muscle cramps, paresthesias and fatigue) or, as in our patient, accidentally discovered during routine investigation [4]. In a contradictory way, no hypocalciuria (another classical feature of this syndrome) has been documented. Even so, previous descriptions suggest that hypomagnesemia and hypocalciuria may not be invariant in this disorder [2].

Most asymptomatic patients remain untreated and undergo ambulatory monitoring with low frequency. Of note, chondrocalcinosis occurs later in life and may be the consequence of hypomagnesaemia [4]. This assumption is a clear argument for lifelong supplementation of magnesium, along with a high sodium and high potassium diet. If symptomatic hypokalaemia is not corrected, it can be associated drugs that antagonise aldosterone activity or block the sodium channel ENaC in the collecting duct [2]. Long-term prognosis of Gitelman syndrome is excellent and progression to renal insufficiency is extremely rare [5].

Conclusion

The authors present a case of Gitelman syndrome, one of the rare causes of hypokalaemia, and it seems a challenge for physicians. Genetic counselling in an appropriate set is important and familial history can reveal asymptomatic patients. Our patient had no sibling and was a father of two. Adult patients with GS have a low risk of having children with GS (~1 in 400),

unless consanguinity exists, but genetic test were performed (still ongoing). We highlight that suitable treatment protects patients from potentially dangerous complications [2].

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