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GITELMAN SYNDROME AS A RARE CAUSE OF HYPOKALEMIA - CASE REPORT

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Gitelman syndrome is a rare autosomal recessive tubulopathy leading to hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria and low-to-normal blood pressure. Clinical signs are mostly secondary to chronic hypokalemia and include dizziness, fatigue, constipation and weakness. Patients can also present with muscle cramps, tetany and convulsions due to severe metabolic alkalosis or hypomagnesemia. Therefore, early recognition and treatment are important. Diagnosis of Gitelman syndrome is usually made incidentally during adolescence or early adulthood based on clinical and biochemical findings. In this paper we report a case of a young women with classic Gitelman syndrome. Treatment included magnesium and potassium salts and potassium saving diuretics. In general, the long-term prognosis of Gitelman syndrome is excellent. However, the severity of fatigue may seriously hamper some patients in their daily activities. *Acta Medica Medianae 2014;53(3):54-57.*

Key words: *Gitelman syndrome, tubulopathy, hypokalemia, hypomagnesemia, metabolic alkalosis*

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Introduction

Hypokalemia is a common clinical problem. It can result from reduced potassium intake, increased translocation from extracellular spaces into the cells (as a transient condition) or, most commonly, from increased gastrointestinal or urinary losses. Increased potassium secretion in the distal nephron may account for such losses, for example, with the intake of diuretics or because of mineralocorticoid excess.

Gitelman syndrome (GS), also referred to as familial hypokalemia-hypomagnesemia, is an salt-losing renal tubulopathy that is characterized by hypomagnesemia, hypocalciuria, and secondary aldosteronism, which is responsible for hypokalemia and metabolic alkalosis (1). The prevalence is estimated at ~25 per million and accordingly, the prevalence of heterozygotes is approximately 1% in Caucasian populations, making it one of the most frequent inherited renal tubular disorders. This renal syndrome is caused by mutations in the solute carrier family 12, member 3, SLC12A3 gene, which encodes the renal thiazide-sensitive sodium-chloride co-transporter (NCCT) that is expressed in the cells in the distal convoluted tubule (2).

Symptoms of Gitelman's syndrome reported in literature range from asymptomatic to mild symptoms of cramps and fatigue to severe manifestations such as tetany, paralysis, and rhabdomyolysis (3), especially during periods of fever or when extra magnesium is lost due to vomiting or diarrhea. However, the severity of fatigue in GS is not completely related to the degree of hypokalemia. Additionally, patients complain on salt craving, nocturia and polydipsia. Decreased reabsorption of sodium at the NCCT and subsequent increased potassium losses via the renal outer medullary potassium channel, largely driven by secondary aldosteronism, explain the hypokalemia and reportedly increased salt appetite in GS patients. Gitelman syndrome patients are usually diagnosed relatively late, because malaise, low blood pressure, hypokalemia, hypocalciuria, and hypomagnesemia are difficult to categorize clinically. However, a precise diagnosis permits a more exact, goal-directed clinical care.

Case report

A 23-year-old woman was admitted to hospital because of vomiting, weight loss, weakness of the legs, muscle cramping and anxiety. The same symptoms she had occasionally for the past 2 years and they were aggravated by physical activity and were associated with polyuria, polydipsia and thirst. There was no history of fever, diarrhea, rash or abdominal pain. The patient ate a regular diet without alcohol abuse and took no drugs. She denied self-induced vomiting – as with anorexia nervosa or bulimia and diuretic abuse. Her clinical examination revealed moderate dehydration and discrete paraparesis without

sensory loss. Otherwise, the physical findings were unremarkable except for low BMI (16.02 kg/m^2) and hypotension (110/60 mmHg). Marked hypokalemia (down to 2.2 mmol/L) was the most striking initial biochemical abnormality. Nonetheless, her electrocardiogram tracing showed normal sinus rhythm without features of hypokalemia (i.e. no flattening of T wave, inverted T wave, U wave, depression of ST segment, decreased QRS voltage or prolonged PR or QT interval) throughout the hospitalisation period. Further investigations (Table 1) in exploring the cause of hypokalemia were proceeded. Table 1 summarizes the results of the laboratory investigations conducted in the patient.

Parameters	Value	Reference range (unit)
Complete blood count		
Haemoglobin	11.6	11.5-15.5 (g/dL)
White blood cells	12.4	6.0-10.0 x 10^9 (/L)
Neutrophils	10.5	1.8-8.0 x 10^9 (/L)
Platelet	402	150-400 x 10^9 (/L)
Serum chemistry		
Sodium	129	135-144 (mmol/L)
Potassium	2.2	3.8-5.3 (mmol/L)
Urea	4.7	2.5-6.5 (mmol/L)
Creatinine	65	53-97 (mmol/L)
Serum proteins	78	60-80 (g/L)
Serum albumins	49	35-50 (g/L)
C-reactive protein	10.3	<5 (mg/L)
Calcium (adjusted)	2.36	2.25-2.75 (mmol/L)
Phosphate	1.25	0.8-1.45 (mmol/L)
Magnesium	0.53	0.73-1.06 (mmol/L)
Chloride	97	95-105 (mmol/L)
Glucose, random	3.91	3.9-6.1 (mmol/L)
Osmolarity	266	275-295 (mOsm/kg)
Blood gas venous		
pH	7.53	7.35-7.45
HCO_3	33	(mmol/L)
PCO_2	48	(mmHg)
PO_2 (mmHg)	10.70	(mmHg)
Base excess	2.9	(mmol/L)
Spot urine		
Sodium	19	N/A(mmol/L)
Potassium	64	N/A (mmol/L)
Calcium	0.68	N/A (mmol/L)
Creatinine	3.50	N/A (mmol/L)
Osmolarity	331	50-1400 (mOsm/kg)
pH	5	4.5-8.0
Hormonal examination		
Cortizol	291.5	131-642 (nmol/L)
ACTH	10.3	10-90 (ng/L)
Aldosterone	290.7	42-201.5 (pmol/L)
Renin	17.9	0.2-2.8 (nmol/l/h)
TSH	2.0	0.28-4.3 (mIU/L)

N/A: not applicable

Renal ultrasound was normal. No abnormality was found on an abdominal X-ray, chest X-ray or brain magnetic resonance imaging. Proximal endoscopy revealed healed gastric ulcer.

Her high urine potassium (64 mmol/l) suggests renal loss. A low urine sodium level (< 20 mmol/L) with a high urine potassium level indicates the presence of secondary hyperaldosteronism which was confirmed by elevated levels of active renin and aldosterone in blood testing. Morning cortisol was within the normal range.

Under these circumstances, a tubulopathy causing renal potassium loss was considered. The biochemical constellation of normal renal function, hypokalemia, hypomagnesemia and metabolic alkalosis was suggestive of Gitelman's syndrome. Unfortunately, for the definite confirmation of Gitelman's syndrome diagnosis, cytogenetic examination was not carried out due to technical reasons.

She was started on fluid replacement and high doses of parenteral potassium chloride. However, this could only transiently maintain her serum potassium level. She had rebound hypokalemia one day after initial normalisation, till a new bolus of parenteral potassium chloride was given. In addition, she was treated with parenteral magnesium and spironolactone. Within 72 hours, her potassium level began to rise.

She was discharged with the following medications: spironolactone 50 mg daily, supplementation with potassium 6 grams daily and supplementation with magnesium 500-750 mg daily depending on the tolerance as well as high salt diet.

The control values of potassium three months after were in range 3,5-3,8 mmol/l and the control values of magnesium were in range 0,78-0,85 mmol/l. The control electrocardiogram was negative.

Discussion

Once vomiting, diuretic and laxative abuse are excluded from the differential diagnosis of a nonhypertensive patient presenting with hypokalemia, rare conditions such as renal tubular acidosis, Bartter's syndrome or Gittelman's syndrome need to be considered.

Gitelman et al. first described a familial salt-losing tubulopathy that was associated with hypokalemic metabolic alkalosis and hypomagnesemia. Bettinelli et al. (4) in 1992 found that in addition to hypomagnesemia, this syndrome was also associated with hypocalciuria. Four years later, the molecular defect in GS was identified when it was demonstrated that GS was the result of loss of function mutations in the SLC12A3 gene located on the long arm of chromosome 16 (5). Epidemiologic studies have demonstrated that there is no ethnic predilection for GS, and both sexes are equally affected.

This disease is sometimes diagnosed in almost asymptomatic adults who have hypokalemia and unexplained transient periods of weakness, tetany, abdominal pain, vomiting and fever (6,7). Nocturia, polyuria or polydipsia are relatively rare. Severe manifestations of GS

include early onset (before the age of 6), growth retardation, tetany, chondrocalcinosis, rhabdomyolysis and seizures. These patients often have a normal to low blood pressure with a tendency toward hyper-reninemic hyperaldosteronism. Progression to end stage renal disease is however rare (8). Patients may suffer from carpopedal spasms especially during periods of fever or when extra magnesium is lost by vomiting or diarrhea. Paraesthesias, especially of the face, frequently occur. Some patients experience severe fatigue interfering with daily activities, while others never complain of tiredness (9,10). Some adult patients suffer from chondrocalcinosis, which is assumed to result from chronic hypomagnesemia (11). Hypokalemia and hypomagnesemia prolong the duration of the action potential of cardiomyocytes and consequently increase the risk of ventricular arrhythmia. Electrocardiograms of patients with GS have shown that, in about 50% of cases, the QT interval is indeed slightly to moderately prolonged (12).

Biochemically, GS is characterized by hypokalemia with increased urinary potassium excretion, hypochloremic metabolic alkalosis, hypocalciuria and hypomagnesemia. Serum calcium is usually normal.

The diagnosis of GS is made on the basis of clinical, biochemical and molecular findings. Disease-free intervals may be prolonged resulting in delay of diagnosis until adulthood. The tubular defect in GS itself cannot be corrected so that adequate supplementation of magnesium and potassium remains the cornerstone of treatment in addition to potassium sparing effect of spironolactone or amiloride; some authors have also reported a beneficial effect of indomethacin. However, oral therapy may be difficult, since large quantity of potassium chloride may be required, and oral magnesium salts may cause diarrhea. It is sometimes not possible to normalize serum levels of the minerals completely and it is more beneficial to focus attention on the amelioration of patients' complaints.

Conclusion

Most asymptomatic patients with GS remain untreated and undergo ambulatory monitoring, once a year, generally by nephrologists. Lifelong supplementation of magnesium and potassium is mandatory. Cardiac work-up should be performed to screen for risk factors of cardiac arrhythmias. All Gitelman syndome patients are encouraged to maintain a high-sodium diet. In general, the long-term prognosis of GS is excellent.

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GITELMANOV SINDROM KAO REDAK UZROK HIPOKALEMIJE - PRIKAZ BOLESNIKA

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Gitelmanov sindrom je retka, autozomno recesivna tubulopatija, koja dovodi do hipokalijemije, metaboličke alkaloze, hipomagnezijemije, hipokalciurije i nižeg-do normalnog krvnog pritiska. Klinički znaci su uglavnom posledica hronične hipokalijemije i podrazumevaju vrtoglavicu, umor, opstipaciju i opštu slabost. Bolesnici, takođe, mogu imati mičićne grčeve, tetaniju i konvulzije zbog teške metaboličke alkaloze i/ili hipomagnezijemije. Stoga, od izuzetne je važnosti rano otkrivanje i lečenje. Dijagnoza Gitelmanovog sindroma se obično postavi slučajno, tokom adolescencije ili ranog odraslog doba, a na temelju kliničkih i biohemijskih nalaza. U ovom radu prikazana je mlada žena s klasičnom slikom Gitelmanovog sindroma. Lečenje podrazumeva primenu magnezijuma i kalujuma kao i diuretika koji štede kalijum. Ddugoročna prognoza obolelih od Gitelmanovog sindroma je odlična. Međutim, izražena malaksalost može ozbiljno ometati neke bolesnike u njihovim svakodnevnim aktivnostima. *Acta Medica Medianae 2014;53(3):54-57.*

Ključne reči: *Gitelmanov sindrom, tubulopatija, hipokalijemija, hipomagnezijemija, metabolička alkaloza*

