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# Gitelman's Syndrome: A Hereditary Disorder Characterized by Hypokalemia and Hypomagnesaemia

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## ABSTRACT

Gitelman's syndrome is a type of hereditary tubular disorder, which is caused by inactive mutations in the gene, which encodes thiazide sensitive sodium chloride cotransporter (SLC12A3) in the distal convoluted tubule. Biochemical characteristic is comparable to effect of thiazide diuretics: hypokalemia, hypomagnesaemia, hypocalciuria, hypokalemic alkalosis and blood pressure is normal or lower. Gitelman's syndrome is typically diagnosed accidentally (hypokalemia) in adolescents or adults and the course is benign. If present, the most prominent symptoms are muscular fatigue or occasional tetany. Treatment includes magnesium and potassium salts and potassium saving diuretics. We report here a case of an adult patient with Gitelman's syndrome. The patient was a bearer of three heterozygote mutations in the gene, which encodes thiazide sensitive sodium chloride cotransporter (SLC12A3) in the distal convoluted tubule.

**Key words:** Gitelman's syndrome, hypokalemia, hypomagnesaemia, hereditary tubulopathy.

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## INTRODUCTION

Gitelman's syndrome represents the clinical manifestation of inactive mutations in the gene, which encodes thiazide sensitive sodium chloride cotransporter (SLC12A3) in the distal convoluted tubule (1, 2). Until the genetic background was clarified in 1996, Gitelman's syndrome was often mistaken for Bartter's syndrome, which is now attributed to defects in the transportation system in the thick ascending limb of Henle's loop (2). In Bartter's syndrome hypomagnesaemia is not a constant finding and urinary calcium excretion is normal or high. Bartter's syndrome is often diagnosed in neonatal period and it is followed by growth retardation and nephrocalcinosis (2). Gitelman's syndrome is typically diagnosed ac-

cidentally (hypokalemia) in adolescents or adults and the course is benign (1-5).

### CASE REPORT

38-year-old female with 9-year anamnesis of hypokalemia and hypomagnesaemia of unclear etiology (also eliminated surreptitious, self-induced vomiting - as with anorexia nervosa or bulimia and diuretic abuse) with clinical symptoms of gradually increasing whole - body fatigue, weakness and lassitude, episodes of muscular softness - loss of muscular strength and cramps, sporadic heart palpitation. The patient was admitted at the Department of Internal Medicine of Teaching Hospital for diagnostic stay with the aim to exclude or confirm secondary hyperaldosteronism in hereditary tubulopathy of the Gitelman's syndrome characteristic.

The systolic blood pressure in-patient was 90 mm Hg and the diastolic blood pressure was 60 mm Hg. The electrocardiogram was negative. The initial serum electrolyte values were following: sodium 138 mmol/l, chloride 95 mmol/l, potassium 2,9 mmol/l, magnesium 0,50 mmol/l, calcium 2,26 mmol/l, urea 6,7 mmol/l, creatinine 66 umol/l. The initial urinary electrolyte values were following: sodium 126 mmol/day, chloride 119 mmol/day, potassium 32 mmol/day, magnesium 1,2 mmol/day, calcium 0,07 mmol/l and 0,25 mmol/day, phosphate 6,3 mmol/l and 22,7 mmol/day, urea 73mmol/day, creatinine 5,8 mmol/day. The values of the capillary blood acid-base investigation were following: pH 7,445, pCO<sub>2</sub> 6,52 kPa, and pO<sub>2</sub> 5,4 kPa. The serum aldosterone level was 0,86 nmol/l and the serum plasma renin activity was 14,48 nmol/l.

Two provocation tests with thiazide and furosemide were carried out for assessment of sodium and chloride fraction excretions. Before provocation tests we discontinued potassium saving diuretics. The first provocation test with thiazide was based on peroral application of hydrochlorothiazide 100 mg 1 hour after previous intensive per oral and parenteral hydration with repeated - 30 min. intervals - laboratory collection of serum and urine sodium, chloride and creatinine. Hydrochlorothiazide inhibits sodium chloride reabsorption by competing for the chloride site on the apical sodium chloride cotransporter in the distal tubule. The distal tubule is also the major site of active calcium reabsorption. Calcium enters the cell via a calcium transporter that is probably a

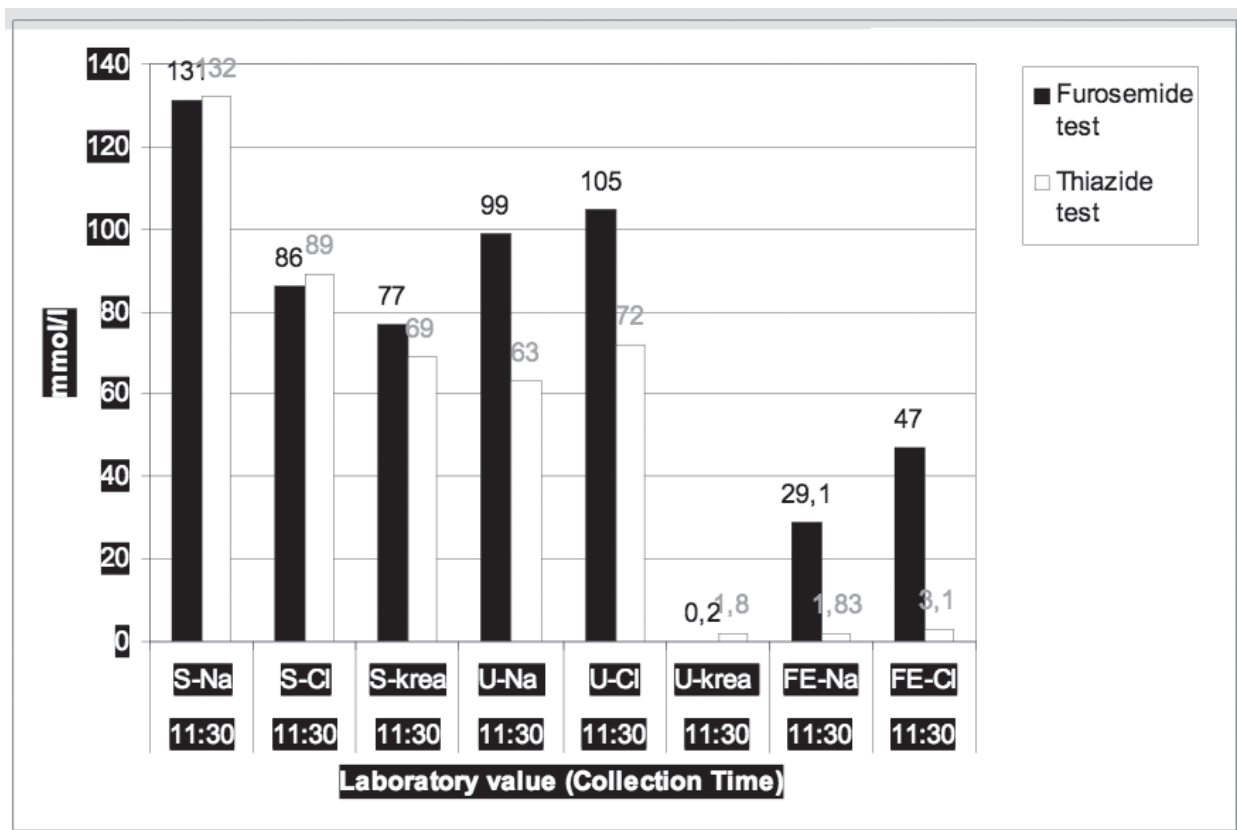
calcium channel. The second provocation test with furosemide was based on parenteral administration of furosemide 10 mg 1 hour after previous intensive per oral and parenteral hydration with repeated - 30 min. intervals - laboratory collection of serum and urine sodium, chloride and creatinine. Furosemide inhibits sodium, potassium, chloride, and calcium and magnesium reabsorption by competing for the chloride site on neutral sodium-potassium-chloride cotransporter in the apical (luminal) membrane in the ascending limb of the loop of Henle. Calculation of sodium and chloride fraction excretions after administration of hydrochlorothiazide and furosemide shows low sodium and chloride fraction excretions after administration of hydrochlorothiazide and on the contrary high sodium and chloride fraction excretions after administration of furosemide (Figure 1).

The achieved results indicate the tubular renal disorder, which has most likely a character of Gitelman's syndrome. The diagnosis of this syndrome is proved by chronic hypokalemia and hypomagnesaemia - in spite of intensive supplementation of both minerals - hypocalciuria, hypokalemic alkalosis, secondary hyperaldosteronism and low sodium and chloride fraction excretions after administration of hydrochlorothiazide. For the definite confirmation of Gitelman's syndrome diagnosis, there was carried out a cytogenetic examination with patient's approval in Centre of cytogenetic investigations of Teaching Hospital. The three heterozygote mutations in the gene, that encodes thiazide sensitive sodium chloride cotransporter (SLC12A3) in the distal convoluted tubule was identified: 1<sup>st</sup> heterozygote mutation was c. 1315 G >A, p. Gly439Ser, 2<sup>nd</sup> mutation was c. 1664 C>T, p. SER555Leu and 3<sup>rd</sup> mutation was c. 2711 G>A, p. Arg904Glu.

Therapeutically recommended amilorid 10 mg daily and spironolacton 50 mg daily, supplementation with potassium 7 grams daily and supplementation with magnesium 500-750 mg daily according to the tolerance. Patient's endocrinological dispensarisation once in six months. The control values of potassium in this treatment after six months were in range 3,7-4,1 mmol/l and the control values of magnesium were in range 0,58-0,67 mmol/l. The control electrocardiogram was negative.

### DISCUSSION

Gitelman's syndrome is a rare disease for its low incidence, i.e. approximately 1:50000 inhabitants.



**Figure 1.** Changes of sodium and chloride fraction excretions after administration of hydrochlorothiazide and furosemide 30 min. after administration of hydrochlorothiazide 100 mg and furosemide 10 mg.

#### Comments to Graph 1

**S-Na:** Serum sodium value (mmol/l), **S-Cl:** Serum chloride value (mmol/l), **S-crea:** Serum creatinine value (umol/l), **U-Na:** Urine sodium value (mmol/l), **U-Cl:** Urine chloride value (mmol/l), **U-crea:** Urine creatinine value (umol/l), **FE-Na:** Calculated sodium fraction excretion value, **FE-Cl:** Calculated chloride fraction excretion value.

Calculation of sodium and chloride fraction excretions after administration of hydrochlorothiazide and furosemide shows low sodium and chloride fraction excretions after administration of hydrochlorothiazide and on the contrary high sodium and chloride fraction excretions after administration of furosemide.

Clinical symptoms are manifested in early adulthood. Differences in sex have not been found (1). Laboratory characteristic and clinical signs of this renal tubular disorder include hypomagnesaemia, hypokalemia, hypokalemic alkalosis, normotension or hypotension, episodes of muscular softness even cramps, gradually increasing whole-body fatigue and weakness, palpitation, tremor and fasciculation and the last but not least the incidence of chronic dermatitis and dermatosis of unclear etiology is described as well (1, 2, 4). Hypokalemia could be associated with severe cardiac complications and sudden death (4). Diagnosis of Gitelman's syndrome is based on anamnestic data,

clinical picture, repeated lab. detection of hypokalemia, hypomagnesaemia, hypokalemic alkalosis, hypocalciuria, chondrocalcinosis, secondary hyperaldosteronism, low sodium and chloride fraction excretion after administration of hydrochlorothiazide as well as on cytogenetic examination with the detection of mutation in the gene encoding for the thiazide sensitive sodium chloride cotransporter (SLC12A3) in the distal convoluted tubule (1-5).

Therapy of Gitelman's syndrome is purely symptomatic, i.e. supplementation with potassium, magnesium, potassium saving diuretics, inhibitors of angiotensin-converting enzyme, inhibitors of prostaglandin syn-

thetasis (1,2,4). Prognosis of Gitelman's syndrome is favorable because it is a chronic benign disease, however a lifelong nephrological or endocrinological dispensarisation is inevitable (1,2,4).

In conclusion, in the present report we describe the Gitelman's syndrome in an adult patient with 9-year anamnesis of hypokalemia and hypomagnesaemia.

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