

Gitelman syndrome DD thiazide diuretics abuse

Case Report

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Abstract: Introduction. Gitelman syndrome (GS) is a rare inherited disorder. Mutations in SLC12A3 gene that encode tubular Na⁺-Cl⁻ cotransporter (NCCT) cause hypokalemic metabolic alkalosis, salt loss, hypomagnesaemia and hypocalciuria. The symptoms include weakness, vertigo, hypotension, tetany, paresthesia and nausea. Diagnostic criteria are a normal urine concentrating ability, normal glomerular filtration rate (GFR), hypomagnesaemia (<0,65mmol/l), hypokalemia (<3,6mmol/l) and hypocalciuria (<0,1mmol/mmol creatinine). Previously, the diagnosis was made by exclusion. Today, genetic analysis can ensure diagnosis. Thiazide diuretics (TD) abuse with similar abnormalities can make the differential diagnosis difficult. Causal therapy of GS does not exist. The substitution of potassium and magnesium are therapeutic strategies. Case presentation. A 41-year-old obese woman presented at the emergency department with recurrent episodes of hypokalemia with concomitant weakness, muscle cramps, polyuria and collapse. The results of laboratory testing of blood and urine led to the suspected diagnosis of GS. In the follow-up examinations, the results were inconsistent. Therefore, a transient thiazide diuretics abuse was assumed. Discussion. This case demonstrates the difficulties in making the diagnosis of GS on the basis of only clinical and laboratory tests, without the use of genetic analysis. The differentiation between GS and thiazide diuretic abuse is especially difficult.

Keywords: *Gitelman • Hypokalemia • Hypomagnesaemia • Hypocalciuria • SLC12A3 • NaCl cotransporter*

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1. Introduction

Gitelman syndrome (GS) was first described by Gitelman et al. [1] in 1966 [1-6]. It is a rare inherited autosomal recessive renal disorder with decreased tubular resorption of Na⁺, Cl⁻, Mg²⁺ and K⁺ [3-5,7-18]. The prevalence of GS has been reported between 1:40000 to 1:52500 [6,12,19]. The disease often manifests in adult life [5,12]. Men and women are affected equally [4].

GS underlies one or more genetic mutations of the NCCT gene (SLC12A3-Gen/16q13) [3-7,9,10,12-14,16-21]. By now, more than 100 mutations of the SLC12A3 gene (associated with GS) have been identified [6,10,12,13,16,17,21]. Although an inherited autosomal recessive succession has been reported, 30-40% of

patients showed mutations at only one allele of the SLC12A3 gene [10,11].

Renal dysfunction causes blood and urine abnormalities typically characterized by hypokalemic metabolic alkalosis, salt loss, hypomagnesaemia and hypocalciuria [2-7,9,11,13-18,20]. These abnormalities are caused by dysfunction of thiazide-sensitive NCCT in distal convoluted tubuli [2-7,9,12,13,15,16,18-21]. However, dysfunction in NCCT is not directly responsible for all electrolyte abnormalities. Secondary ion resorption disorders are associated with NCCT dysfunction. Dysfunction of NCCT leads to salt loss, combined with reduced intravascular volume, activation of the renin-angiotensin-aldosterone system and increased aldosterone blood level [18,20]. Aldosterone increases renal K⁺ and proton loss in the collecting tubule, resulting in typical hypokalemic metabolic alkalosis [20]. Alkalosis of urine

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activates Na⁺-K⁺-ATPase in the collecting tubule with increased K⁺ diuresis and intensified hypokalemia [22]. Hypocalciuria is caused by increased Na⁺ transport in the proximal tubule [15]. Increased intracellular Na⁺ inflow is responsible for reduced extracellular volume, and it stimulates Ca²⁺ reabsorption, resulting in hypocalciuria [15]. It is presumed that a reduced Mg²⁺ reabsorption associated with hypokalemia causes hypomagnesaemia [9,15].

Patients with GS often show only a few symptoms over a long time period [13,20]. GS is frequently overlooked at its beginning [4,12]. The symptoms include adynamia, loss of muscle strength, fatigue, vertigo, hypotension, muscle spasm, tetania and paraesthesia [2,4,6-8,10,12,13,16,19,20]. Other rare symptoms are abdominal pain, nausea, vomiting and fever [4,12,13].

Except for hypotension, physical examination is usually normal [4,7,12,18,20]. Recommended laboratory examinations are blood electrolytes, kidney parameters, blood-pH, acid-base balance, electrolytes in a 24h specimen of urine (Na⁺, Cl⁻, K⁺, Ca²⁺, Mg²⁺), urine concentrating ability of kidneys, aldosterone level and renin level [12].

Bettinelli et al. [23] formulated clinical diagnostic criteria for GS [23]. These criteria include normal urine concentrating ability of the kidneys and normal GFR, hypomagnesaemia <0,65mmol/l, hypokalemia <3,6mmol/l and hypocalciuria <0,1mmol/mmol creatinine [10,13,14,23]. Hypomagnesaemia and hypocalciuria have a high probability for the diagnosis [6]. In rare cases typical hypomagnesaemia is lacking [12,24]. Secondary aldosteronism and elevated angiotensin II and renin levels are seen [12,14,16,25].

Patients with GS are insensitive to thiazide diuretics (TD) [4,8]. This fact could be used for diagnostic purposes [4,8]. If patients with GS (with sufficient hydration) take a test dose of TD, the normal effect of increased Na⁺, Cl⁻ and K⁺ diuresis fails to appear [2,4,8,9,12,24,26]. Conversely, loop diuretics increase Na⁺ and Cl⁻ diuresis [2,8,12,26]. The reported test sensitivity is 93% and specificity 100% [24].

Typical symptoms and laboratory deviations point to the right diagnosis [8,12]. Previously, the diagnosis of GS was made only by exclusion. Today, the diagnosis can be secured by SLC12A3 gene analysis [4,12,13,24].

Causal therapy of GS does not exist [3,4,8,9,17]. Electrolyte substitution is the most important therapeutic option [3,4,9,12,17,25]. Patients should maintain a diet rich in Na⁺ and K⁺ [12,19]. If diet is not sufficient to compensate the K⁺ loss, K⁺ should be substituted in relation to the serum electrolytes [3,4,8,9]. Moreover, Mg²⁺ substitution therapy is recommended [3,9,12,19,25].

Amiloride, spironolactone or triamterene could be helpful in reducing hypokalemia [3,17].

Most asymptomatic GS patients who follow the recommended diet do not need any medical therapy [12]. They should be regularly evaluated by a nephrologist, and there should be an awareness of complications, like arrhythmias caused by the electrolyte changes [12].

There is discordance about the prognosis of these patients. On one hand, a favourable prognosis has been reported for most patients with GS [4,9,12] with a normal life expectancy [4], but a reduced quality of life [3]. On the other hand, in the last decade, cases with life-threatening arrhythmias and sudden cardiac death have been reported [27,28]. Although sudden cardiac death also occurred with normal potassium blood levels, [27] hypokaliemia and QTc prolongation are the most frequently suggested mechanisms of sudden cardiac death caused by arrhythmia [27,28]. Therefore, medications that prolong the QT duration should be avoided in GS patients. Moreover, GS has been associated with left ventricular dysfunction and exercise-induced reduction of the cardiac index [27,29]. Because of the salt and fluid loss, it can be assumed that GS is also connected with a higher frequency of thromboembolic events.

2. Case report

A 41-year-old obese woman presented at the emergency department with muscle cramps, muscle pain, vertigo, headache, polyuria and collapse. She had already been treated with K⁺ substitution because of hypokalemia of undetermined cause.

On physical examination, her general condition was appeared sick, the body mass index (BMI) was increased (39.8kg/m²), pulse rate 80 beats/min and blood pressure 135/110mmHg.

Laboratory results showed hypokalemia of 2.9mmol/l (normal: 3.5-5.1mmol/l), hypomagnesaemia of 0.56mmol/l (normal: 0.85-1.15mmol/l), normal creatinine of 0.6mg/dl (normal: 0.6-1.1mg/dl), and normal phosphate of 4.0mg/dl (normal: 2.3-4.7mg/dl). The venous blood gas had a pH of 7.49, PCO₂ of 38.1mmHg, PO₂ of 46.5mmHg, and HCO₃⁻ of 29.6mmol/l. The plasma aldosterone concentration was elevated to 185pg/ml (normal: 7.5-150pg/ml), and the renin level at rest to 118.0μU/ml (5-26.7μU/ml). A 24h specimen of urine showed an increase of K⁺ diuresis to 344.4mmol/24h (normal: 35-80mmol/24h) and hypocalciuria of 0.59mmol/24h (normal: 2.5-6.2mmol/24h). The urine osmolality was normal. Morbus Cushing was excluded by a dexamethasone test. Abdominal ultrasound

examination was normal, including the kidneys. An ECG did not show a prolongation of QT-time.

Because of vertigo, the patient already had an MRI of the head, a 24h-ECG and echocardiography. Beside diastolic dysfunction, results were normal. Moreover, an ENT specialist excluded a vestibular genesis of the vertigo.

We presumed the diagnosis of GS and treated with the substitution of K^+ and Mg^{2+} and spironolactone. With this therapy, we achieved an improvement in symptoms. Although diuretic or antiemetic use was denied, there were several inconsistent laboratory results in the patient's history. Therefore, we deferred the genetic testing for GS and performed first a follow up 24h-urine examination 3 weeks after she left the hospital. Results were inconsistent with our previous findings. No typical changes of GS were found. Therefore, temporary TD abuse in order to lose weight was presumed. An examination of the urine for diuretic agents was at that time not helpful, because intermittent diuretic use was suggested. The patient was further evaluated by an ambulatory nephrologist. Genetic testing and examination of the urine for diuretic agents were recommended, if symptoms recurred.

3. Discussion

The patient in our case report presented with typical symptoms of GS. Also, the findings in the blood and urine in the first analysis were consistent with the typical findings of GS. In the follow-up examinations 3 weeks later results were inconsistent with the first analysis, especially the urinary electrolytes. In contrast to the first examination, they were in the normal range. Therefore, although the patient had denied diuretic or antiemetic drug use, TD abuse was suggested.

Important differential diagnoses for GS are eating disorders, long-term laxative abuse, TD abuse, renal tubular acidosis and Bartter syndrome (BS) [4,6,8,30-33]. In order to exclude those differential diagnosis without expensive genetic testing, recurrent examinations are necessary [4]. Inconsistent results of laboratory examinations make GS as the genetic cause for dysfunction improbable.

Most patients with anorexia and bulimia are underweight [4]. Recurrent vomiting decreases Cl^- serum levels, causes metabolic alkalosis, and increases kidney laboratory parameters [4]. Contrary to GS, serum hypomagnesaemia and hypocalciuria do not occur and Cl^- urine levels are decreased [4].

Metabolic acidosis is the main difference between GS and long-term laxative abuse, as well as renal tubular acidosis [4]. Long-term laxative abuse typically reveals decreased Cl^- levels in urine [4].

BS occurs frequently in childhood with distinct impairments [4-6]. BS is connected with normal or slightly reduced Mg^{2+} levels [4,5,13]. Typically, hypocalciuria does exist in GS but not in BS [4,8,13]. If patients with BS are tested with TD, increased Na^+ and Cl^- levels in urine are seen [24].

The most difficult diagnosis to exclude in the differential diagnosis of GS is TD abuse [4,13]. In patients with TD abuse, NCCT is inhibited [34]. Abnormalities in electrolyte tubular transport are similar to those seen in GS [4,13,15,34]. Sometimes the creatinine level is elevated [4,35]. TD abuse is often found in cases of eating disorders, weight-loss attempts and sport doping [30-34,36].

Exclusion of diuretics abuse is based mainly on a careful interrogation [34]. Examination of urine for diuretic agents is helpful to confirm diuretics abuse [4,34-36].

Our case demonstrates the difficulties in making the diagnosis of GS on the basis of clinical and laboratory tests only, without the use of genetic analysis, and the differentiation between GS and TD abuse is difficult.

4. Conclusions

GS is a rare inherited autosomal recessive renal disorder. To diagnose GS based on clinical and laboratory findings without genetic analysis is not always simple and obvious, especially because TD abuse is difficult to distinguish from GS.

Conflict of interest

Karsten Keller, Johannes Beule, and Wolfgang Dippold declare that they have no conflict of interest.

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