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CASE REPORTS

GITELMAN SYNDROME, A RARE CONDITION: THREE CLINICAL CASES AND PATHOPHYSIOLOGY REVIEW

SÍNDROME DE GITELMAN, UMA CONDIÇÃO RARA: TRÊS CASOS CLÍNICOS E REVISÃO DA FISIOPATOLOGIA

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ABSTRACT

Introduction: Gitelman syndrome (GS) is a renal tubular disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Clinical manifestations are nonspecific. Herein are reported three cases of GS with different age of onset, clinical manifestations, and management.

Case Reports: Case 1 was a sixteen-year-old female, while Cases 2 and 3 presented at an atypical age (seven and eight years). Clinical manifestations mainly consisted of abdominal pain with vomits, together with past history of muscular weakness in Case 1. Diagnosis was based on usual electrolyte abnormalities, such as metabolic alkalosis with hypokalemia. Genetic diagnosis was confirmed in Case 3. Patients were treated with oral potassium, magnesium, and spironolactone, with symptom and electrolytic profile improvement.

Discussion/Conclusions: GS is a rare condition that should be considered in cases of metabolic alkalosis and hypokalemia and all pediatricians should be aware of. Diagnosis is established based on biochemical profile and treatment response.

Keywords: Gitelman syndrome; hypokalemia; metabolic alkalosis; tubular hypomagnesemia-hypokalemia with hypocalciuria; tubulopathy

RESUMO

Introdução: A síndrome de Gitelman (GS) é uma patologia tubular renal, caracterizada por hipocaliémia, alcalose metabólica, hipomagnesiemia e hipocalciúria. As manifestações clínicas são inespecíficas. São descritos três casos de GS com diferentes idades de apresentação, manifestações clínicas e abordagem.

Casos clínicos: O Caso 1 refere-se a uma adolescente de dezasseis anos de idade e os Casos 2 e 3 a crianças com manifestações em idade atípica (sete e oitos anos). As principais manifestações clínicas foram dor abdominal com vómitos e, no Caso 1, história de fraqueza muscular. O diagnóstico baseou-se em alterações eletrolíticas habituais, como alcalose metabólica com hipocaliémia. Foi confirmado diagnóstico genético no Caso 3. Os doentes foram tratados com potássio, magnésio e espironolactona por via oral, com melhoria dos sintomas e perfil eletrolítico.

Discussão/Conclusões: A GS é uma condição rara que deve ser considerada em situações de alcalose metabólica com hipocaliémia e para a qual os pediatras devem estar em alerta. O perfil analítico e a resposta ao tratamento sugerem o diagnóstico.

Palavras-chave: alcalose metabólica; hipocaliémia; hipomagnesemia-hipocaliémia tubular com hipocalciúria; síndrome de Gitelman

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INTRODUCTION

Gitelman syndrome (GS), described in 1966 by Gitelman and colleagues, is an inherited renal tubular disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. GS is probably the most frequent inherited tubulopathy, with an estimated prevalence of 1 to 10 per 40.000 people.[1,2]

GS patients have a NaCl co-transporter (NCCT) dysfunction on the apical membrane of the distal convoluted tubule, resulting in potassium and magnesium loss. Secondary biological adaptations include alkalosis, stimulation of renin–angiotensin–aldosterone system, and prostaglandin hypersecretion.

Clinical manifestation occurs in late infancy or adolescence/early adulthood and may include transitory paraesthesia or muscular weakness episodes. In several cases, patients remain asymptomatic for long periods and are usually accidentally diagnosed. Due to nonspecific symptoms and high phenotypic variability, diagnosis is challenging and often suspected in patients with unexplained hypokalemia, metabolic alkalosis, and normal or low blood pressure.

GS treatment is lifelong and aims to minimize the effects of extracellular volume depletion and correct electrolyte abnormalities, which can be life threatening if not managed early.

The authors herein report three clinical cases of GS with different age of onset, clinical manifestations, and management.

CASE REPORT

CASE 1

A sixteen-year-old female, born at term from unrelated parents, with no relevant past clinical history except for an episode of muscular weakness three years before with normal laboratory results. Observed in the Emergency Department due to fever, cough, and diarrhea. She reported muscular weakness and lack of strength in the inferior members, pain in the lower extremities, and intermittent abdominal pain.

The girl had lost 10 kg over the last few months. No history of medication usage, including diuretics and laxatives, or consumption of other substances was identified.

Physical examination showed a reasonable general state, normotension, and normal cardiovascular examination. No abdominal tenderness, hepatosplenomegaly, or peripheral edema were identified. Neurologic examination revealed no sensory or motor deficit. Chvostek and Trousseau signs were absent.

Laboratory tests revealed metabolic alkalosis with hypokalemia: pH 7.44; potassium 2.1 mmol/L; bicarbonate 34 mmol/L; PaCO2 51 mmHg; urea 15 mg/dL; creatinine 0.7 mg/dL; and magnesium 1.2 mg/dl. Alkalosis and hypokalemia persisted, despite fluids and KCl supplementation (K+ max. 2.8 mmol/l). The patient was admitted to the Pediatric Nephrology Department due to tubulopathy suspicion.

Further evaluations were normal, including complete blood count and C-reactive protein (CRP), parathyroid hormone, 25-hidroxi vitamin D, liver enzymes, total cholesterol, triglycerides, iron metabolism, total serum proteins and albumin, urine calcium/creatinine ratio, and urine uric acid/creatinine ratio. Plasmatic renin activity was 115.6 pg/ml (normal range, 2.4–21.9 pg/ml) and plasmatic aldosterone was 47 pg/ml (normal range, 42–202 pg/ml). Pelvic ultrasound was also normal.

During hospitalization, the patient was treated with intravenous fluids with potassium supplementation at increasing doses (max. 4800 mg per day), calcium carbonate (500 mg per day), and magnesium and spironolactone (max. 3 mg/kg/day). Alkalosis gradually improved, but mild hypokalemia persisted (K+ 2.5–3.0 mmol/l), despite KCl supplementation.

During the two-year follow-up, the patient was admitted twice due to hypokalemia in the context of an enteritis and a pharyngitis episode.

The girl is currently asymptomatic regarding muscular weakness, paraesthesia, and abdominal pain. Daily medication includes potassium chloride 2400 mg per day, magnesium supplementation 3000 mg per day, and spironolactone 100 mg per day. No genetic diagnosis was performed.

CASE 2

A seven-year-old female, born at term, daughter of first-degree cousin parents, with normal growth and psychomotor development, without relevant clinical history, was observed at the Emergency Department due to fever, persistent vomiting (four episodes), abdominal pain, and cramps in both hands.

The girl had been admitted twice before due to vomiting episodes and treated with intravenous fluids. No diarrhea or other symptoms were reported and no laboratory tests were performed.

Physical examination was normal, except for dry tongue and diffuse pain in abdomen palpation. No other signs of dehydration were found.

Cardiovascular examination was normal and blood pressure was within the normal range. No hepatosplenomegaly or peripheral edema was reported. Neurologic examination revealed no sensory or motor deficit. On admission, the patient had cramps in both hands.

Due to symptom recurrence, laboratory tests were conducted, showing hypokalemia (2.0 mmol/l), hypomagnesemia (1.4 mmol/l), alkalosis (pH 7.49; bicarbonate 26.7 mmol/l, base excess 5.3), and microalbuminuria (urine albumin 4.8 mg/L, creatinine/protein ratio 0.3). Plasma renin activity was not evaluated, and plasma aldosterone was normal, as were the abdominal ultrasound and abdominal-pelvic tomography.

The girl was transferred to the Pediatric Nephrology Department and treated with intravenous fluids and potassium supplementation (max. 2400 mg per day) and spironolactone (max. 3.1 mg/kg per day), with gradual electrolytic improvement. No vomits were reported

since the first day of admission.

After diagnosis, the patient was admitted twice due to hypokalemia in vomiting/enteritis context. Daily medication currently includes oral potassium (max. 4800 mg per day), magnesium supplementation, and spironolactone (max. 62.5mg per day). The girl is asymptomatic, with adequate weight and growth (P25 for weight and P50 for height), with no daily activity limitations. Laboratory study shows occasional hypokalemia persistence (2.5–4.0 mmol/l), but compliance is doubtful.

Due to irregular follow-up, genetic testing could not be performed during the nine years following diagnosis.

CASE 3

An eight-year-old female, without relevant family history, daughter of unrelated parents, with normal growth and psychomotor development, was observed at the Emergency Department due to abdominal pain and loss of appetite with seven days of evolution. In the first five days, the girl had diarrhea and sporadic vomiting. On physical examination, she presented poor general condition, redness of the pharynx, and temperature of 38.6ºC. Parents reported that she had a preference for salty food and high diuresis.

Blood analyses revealed metabolic alkalosis (pH 7.65, bicarbonate 29.4 mmol/l), hypokalemia (1.9 mmol/l), hyponatremia (131 mmol/l), hypochloremia (89 mmol/l); calcium of 2.27 mmol/l, hypophosphatemia (0.99 mmol/l), hypomagnesemia (0.58 mmol/l), normal renal function, normal blood count, and negative inflammatory markers (CRP).

Electrocardiogram (ECG) showed ST depression, shallow T waves and prolonged QTc interval.

The patient was hospital admitted and started intravenous electrolyte correction. However, due to difficulty in hypokalemia correction, she was transferred to the Pediatric Intensive Care Unit (PICU), where she maintained potassium, phosphorus, calcium, and magnesium intake by oral and central venous access. Urinalysis revealed an incipient sediment, increased urinary potassium excretion (139.5 mmol/l), and decreased calcium excretion (1.78 mmol/l), with normal urine osmolarity (632 mOsm/kg) and concentration (1.015). Renin was increased (280.9 pg/ml) and aldosterone was normal (187 pg/ml). Abdominal ultrasound, including renal, adrenal gland, and vesical evaluation, was normal.

Treatment with spironolactone 1 mg/kg/day was added to the intravenous electrolyte correction.

A gradual normalization of electrolytic findings was observed, and in the second day of admission ECG was also normal, besides constant normal blood pressure and diuresis.

Genetic study showed two SLC12A3 heterozygous gene variants: c.2221G>A p.(Gly741Arg) and c.3053G>A p.(Arg1018Gln), described in Gitelman syndrome (MIM 263800).

Two years later, the girl is followed as an outpatient and is asymptomatic with daily oral spironolactone (25 mg/day), potassium supplementation (3600 mg/day), and weekly magnesium supplementation (121.5 mg/day).

DISCUSSION

GS is a recessive autosomal distal tubulopathy. Simon *et al*. first demonstrated complete linkage of GS to the NCCT gene, with subsequent studies mapping SLC12A3 to chromosome 16q13 and establishing GS as an autosomal recessive disorder with 99% penetrance.[3-6] The association with 16q13 chromosome was later confirmed by other studies.[6-8] Additionally, no differences have been reported regarding gender or ethnic prevalence in GS.

Similar electrolyte changes are reported with diuretic abuse and GS. In GS, NCCT function is modified. This dysfunction leads to NaCl wasting and hypovolemia, stimulating the renin-angiotensin-aldosterone system and causing an increase in apical Na reabsorption and stimulation of the basolateral Na+-K+-ATPase, with potassium wasting. The increase in aldosterone levels stimulates activity of H-ATPase pumps in the cortical collector and medullary collecting ducts, with subsequent increase in apical hydrogen secretion. Potassium and hydrogen excretion increase as potassium enters in the basolateral membrane via Na+-K+-ATPase, resulting in hypokalemic metabolic alkalosis.[8]

Sodium reabsorption via sodium channels is accompanied by potassium and hydrogen excretion, also leading to hypokalemia and metabolic alkalosis. NaCl reabsorption through the apical membrane decreases, whereas intracellular sodium continuously leaves cells via Na+-K+-ATPase at the basolateral membrane. This sodium flow results in the decrease of its intracellular concentration, hyperpolarizing distal convoluted tubular cells and causing Ca2+ to enter the apical membrane through Ca2+ channels.[8]

Similarly, loss of NCCT function can inhibit magnesium reabsorption via Na+/Mg2+ exchanger.[9] As the distal convoluted tubules reabsorb 5% of filtered magnesium and reabsorption is load-dependent, this mechanism would lead to magnesium wasting and, thereby, hypomagnesemia. A recent study suggested that magnesium loss may be due to lower expression of magnesium channel TRPM6 in distal tubules.[10]

Patients with GS can be asymptomatic during long periods of infancy and adulthood. Often, they are diagnosed in adolescence or early adulthood. In the cases here described, diagnosis varied between the ages of 7 and 16 years, with two of the three patients being under the age of ten.

This disorder has a great clinical heterogeneity and can be accidentally diagnosed in asymptomatic patients through laboratory findings or in patients with infections or intermittent symptoms of muscular weakness, fatigue, and cramps. More serious symptoms, as tetany, rhabdomyolysis, or paralysis, have been reported in some studies, as well as recurrent episodes of abdominal pain, vomits, and fever.[11-13]

In Case 1, the patient had fever and vomits (enteritis-like symptoms)

and reported an episode of muscular weakness and paraesthesia approximately three years earlier, as well as a 10-kg weight loss in the past 12 months. Electrolyte disturbances, including metabolic alkalosis with hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia, were suggestive of GS. In Case 2, the patient was younger (seven years old) and was observed at the Emergency Department for vomits, abdominal pain, and fever. Laboratory tests evidenced hypokalemia, hypomagnesemia, and metabolic alkalosis, establishing GS diagnosis. Similarly, patient from Case 3 was an eight-year-old girl observed for abdominal pain and loss of appetite following an episode of gastroenteritis. Laboratory tests revealed metabolic alkalosis, hypomagnesemia, hypophosphatemia, and hypokalemia of difficult correction. ECG changes on admission were typical of hypokalemia and resolved with ionic correction.

In all three cases, patients displayed atypical symptoms. In a systematic review about GS, 30% of patients reported unspecific symptoms, like muscle cramps, weakness, and anorexia (observed in Case 1 but on a prior episode, three years before diagnosis), and only 5.7% reported gastrointestinal (GI)-related symptoms, such as vomiting, constipation, abdominal pain, and weight loss, similarly to the present three cases.[14] Although Case 1 presented weight loss, all cases had GI-related symptoms, which is infrequent in GS diagnosis.[14]

Due to nonspecific symptoms, GS is often diagnosed by chance during routine blood analyses. It is therefore important to check serum potassium and magnesium levels in conditions as epilepsy, growth retardation, pubertal delay, and neuromuscular disorders.[3]

These patients were treated with intravenous fluids, potassium and magnesium supplementation, and spironolactone, with gradual improvement. All patients required inward hospital care and all were advised to maintain follow-up with a pediatric nephrologist.

Regarding complications, only Case 3 reported ECG changes related with GS, with no clinical consequences. No patient reported other complications described in literature, such as renal pathology (glomerulonephritides, tubulointerstitial nephritis, or renal tubular acidosis) or thyrotoxic and hypokalemic periodic paralysis.[14]

GS differs from Bartter syndrome (BS) by the severity of clinical presentation and laboratory findings. BS patients typically have symptoms before the age of six, including dehydration and growth retardation. Serum magnesium and urinary calcium levels help in the differential diagnosis between GS and BS, as hypomagnesemia and hypocalciuria are observed in the first. Additionally, genetic analysis may further differentiate both syndromes, with linkage to the NCCT-encoding locus on chromosome 16q1 reported on GS. Diagnosis should be confirmed by genetic study, through identification of biallelic inactivating SLC12A3 mutations.[3] In this study, genetic testing was performed in two patients. One had a positive genetic mutation and the other is waiting results.

GS treatment in outpatient setting consists in oral potassium supplementation, but hypokalemia is usually very difficult to treat and high doses of oral potassium are required (sometimes up to 10 mmol/kg/day in children and 500 mmol/day in adults).[13] Potassium-sparing diuretics should be reserved for resistant cases, as Case 2.[15]

These patients should additionally take oral magnesium supplementation, administered 4–5 times daily. Magnesium not only corrects hypomagnesemia, but also improves hypokalemia.[16,17] All patients are advised to maintain a high-sodium diet. Lifelong potassium and magnesium supplementation is required.[18] Regular annual follow-up by a nephrologist to assess potential complications is a reasonable approach.

With this study, the authors intend to share three clinical cases of GS with different and infrequent clinical manifestations and heterogeneous patient ages. Although rare, GS should be considered in situations of metabolic alkalosis with hypokalemia and hypomagnesemia. GS is considered a benign tubulopathy with excellent prognosis, but associated with significant quality of life impairment.

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