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Case Report

Management of childhood Gitelman syndrome: a case study

Risky Vitria Prasetyo, Putu Dian Saraswati, Ninik Asmaningsih Soemyarso, Mohammad Sjaifullah Noer

Gitelman syndrome is a rare, autosomal recessive, renal tubular salt wasting disorder characterized by hypokalemia, and metabolic alkalosis in combination with significant hypomagnesemia and hypocalciuria.[1,2] The prevalence is estimated to be 1 in 40,000 individuals. The condition affects both males and females of all ethnic backgrounds. The prevalence of heterozygotes is approximately 1% in Caucasian populations.[2,3]

In the majority of cases, symptoms do not appear before the age of six years and the disease is usually diagnosed during adolescence or adulthood. Symptoms, such as transient episodes of muscle weakness and tetany, sometimes accompanied by abdominal pain, vomiting and fever, are often seen in Gitelman syndrome patients. Paresthesias, especially in the face, frequently occur. Remarkably, some patients are completely asymptomatic except for the appearance of chondrocalcinosis at adult age that causes swelling, local heat, and tenderness over the affected joints. Blood pressure is lower than that in the general population. Sudden cardiac arrest has been reported occasionally. In general, growth is normal but can be delayed in those Gitelman syndrome patients with severe hypokalemia and hypomagnesemia.[2,4]

Gitelman syndrome is transmitted as an autosomal recessive trait. Mutations involve the SLC 12A3 gene, located on chromosome 16q13, which encodes the thiazide-sensitive NaCl cotransporter (NCC) in the distal tubule. [2,4-6]

Diagnosis of Gitelman syndrome is based on the clinical symptoms (transient episodes of muscle weakness and cramps, occasional episodes of tetany, abdominal pain, vomiting, constipation, and fever) as well as biochemical abnormalities (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).[2,5,7] Bartter syndrome (especially type III) is the most important genetic disorder to consider in the differential diagnosis of Gitelman syndrome. Genetic counseling is important for patients with Gitelman syndrome. Antenatal diagnosis for Gitelman syndrome is technically feasible, but not advised because of the good prognosis in the majority of patients.[2]

Keywords: *Gitelman syndrome; management; child*

From the Department of Child Health, Airlangga University Medical School/Dr. Soetomo Hospital, Surabaya, Indonesia.

Reprint requests to: Risky Vitria Prasetyo, Department of Child Health, Airlangga University Medical School/Dr. Soetomo Hospital, Jalan Kertajaya Indah Tengah 6/14, Surabaya 60116, Indonesia. Telp. +62-81-6507203; Email: kikiprasetyo14@gmail.com.

Treatment of Gitelman syndrome consists of oral supplementation of magnesium and potassium. Magnesium therapy not only corrects the hypomagnesemia but also improves the hypokalemia. A potassium-sparing diuretic or a combination with anti-aldosterone medication and prostaglandin inhibitors may also be used.[2,4,5,7-9] Lifelong supplementation of magnesium (magnesium-oxide and magnesium-sulfate) is recommended. A cardiac workup should be offered to screen for risk factors of cardiac arrythmias. All Gitelman syndrome patients are encouraged to maintain a high-sodium and high-potassium diet. In general, the long term prognosis of Gitelman syndrome is excellent.[2,7]

The purpose of this paper is to present a rare case of Gitelman syndrome in a child, focusing on diagnosis and management.

The case

A 13-year-old boy was referred to Pediatric Emergency Department at Dr. Soetomo Hospital on May 1, 2013 from Bangkalan Hospital with the diagnosis of weakness and refractory hypokalemia. The patient's main complaint was vomiting. Vomiting had occurred for 1 week prior to admission at Bangkalan Hospital and was followed by weakness for 4 days before admission that worsened to the point that he could only lie down on the bed. He vomited 3-4 times per day with 50-100 cc each time. The patient had no appetite and was subfebrile for 1 week before admission. There was a history of falling in the bathroom during his hospitalization in Bangkalan Hospital.

He was the second child of non-consanguineous parents. There was no history of illness or taking of herbal medications during pregnancy. The antenatal period was unremarkable. He was clinically well until the age of 10 years when he started to have recurrent nausea and vomiting episodes that required 14 hospital admissions in the 3 years prior. He received intravenous potassium correction during those admissions, but none was given following discharge. He drank more than 5 liters water per day in the 8 months prior, after he was treated with a combination of antacids, cetirizine and vitamins for 3 months to stop the vomiting episodes.

His basic immunizations were complete. His development milestones were delayed as he was not able to walk until the age of 2 years nor talk until 3 years. He had not attended any school. The mother said that his friends tried to bully him during his first days in the first grade of primary school, so he did not want to go back to school. Home schooling was not feasible due to the high hospital costs for his recurrent admissions. Family history was unremarkable.

On admission to our ward, he was alert. His height was 155 cm (25^{th}–50^{th} centile) and weight was 39 kg (25^{th}–50^{th} centile). He was not tachypneic or tachycardic. His blood pressure was 100/60 mmHg (less than 95^{th} centile BP for his age and height, which would have corresponded to 126/81 mmHg), pulse was 90 beats per minute, respiratory rate was 24 times per minute, and temperature was 37.4ºC. Chest examination was normal with clear lungs. The abdomen was normal without any organomegaly. No pedal edema was noted. Neurological examination showed weakened motoric strength in the lower limbs, but normal physiological reflexes were seen. His urine output was 6-7 mL/kg/hour.

Laboratory examinations revealed hemoglobin level 7.5 g/dL, hematocrit 22.5%, leukocyte count 7,500/mm^3, platelet count 461,000/mm^3, serum sodium 133 mmol/L, serum potassium 2.3 mmol/L, serum chloride 91 mmol/L, serum calcium 8.7 mmol/L, serum glutamic oxaloacetic transaminase (SGOT) 87 U/L , serum glutamic pyruvic transaminase (SGPT) 45 U/L, albumin 3.19 g/dL, creatinine serum 0.78 mg/dL, BUN 4.4 mg/dL (eGFR 139 ml/min/1.73 m^2), random blood glucose 99 mg/dL, c-reactive protein (CRP) 53.82 mg/L, activated partial thromboplastin time (APTT) 24.9 seconds (control 28.6 seconds), partial thromboplastin time (PPT) 11 seconds (control 11.4 seconds), triiodothyronine (T3) total 0.6 ng/dL, thyroxine (T4) total 12.8 mg/dL, thyroid stimulating hormone (TSH) 1.643, FT4 1.24 pmol/L, serum iron (SI) 33 mcg/dL, total iron binding capacity (TIBC) 207 mcg/dL, reticulocyte 22‰, mean corpuscular volume (MCV) 73.3 fl/dL, mean corpuscular hemoglobin (MCH) 23.1 pg/dL, mean corpuscular hemoglobin concentration (MCHC) 31.6 g/dL and from the blood gas analysis pH 7.608, $pCO_2$29.5, pO_2 119.4, bicarbonate 29.8 mmol/L, base excess +8.2, SaO_2 99.3%. The urinalysis revealed no proteinuria, white blood cell (WBC) 0-1/hpf, red blood cell (RBC) 10-14/hpf, epithelial cells 1-2/hpf, no casts seen.

The chest X-ray was within normal limits (**Figure**

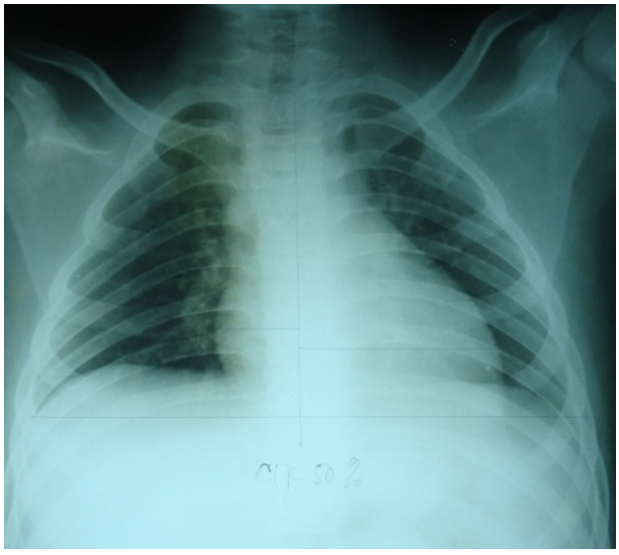

Figure 1. Chest X-ray of the patient at admission

tubulopathy disorder work-up that was done after 1 week of hospitalization showed serum hypokalemia (1.9 mmol/L), hypomagnesemia (1.6 mg/dL), and hypocalcemia (7.8 mg/dL) with hypocalciuria (24-hour urinary calcium was 16 mg). Other urinary (potassium, sodium, magnesium, and chloride) and serum electrolytes (sodium and chloride) were within normal limits. Renal ultrasonography revealed normal kidneys with no evidence of nephrocalcinosis (**Figure 2**).

Based on the history, clinical examination, laboratory and radiology investigations, the patient was diagnosed to have Gitelman syndrome. He received oral supplementation of potassium (500 mg tablet twice daily), and magnesium tablets 250 mg, both four times daily.

One week after treatment for Gitelman syndrome, his laboratory results normalized (serum potassium 3.8

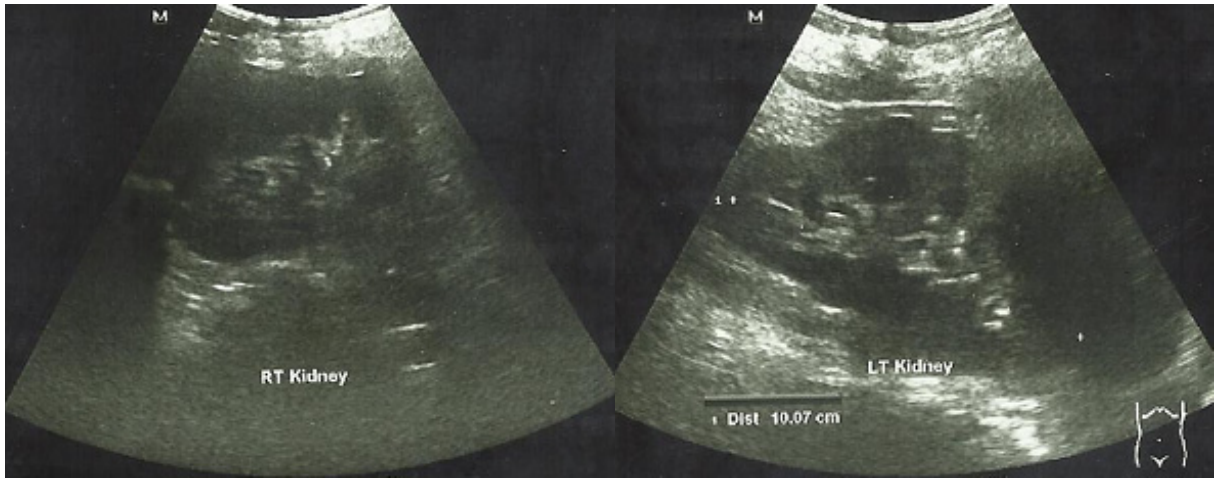

Figure 2. Renal ultrasonography of the patient at 2 weeks after admission

1), and the head CT scan was unremarkable.

Work-up for renal tubulopathy and psychiatric disorders was done; meanwhile, the patient still had recurrent episodes of hypokalemia despite multiple intravenous potassium corrections. A referral to the Department of Psychiatry was done to exclude the possibility of any psychological problems as the underlying disease for the recurrent vomiting. He was found to have psychological and attitude disorders caused by the underlying primary disease. He was treated with 5 mg clobazam tablets once daily. His urine production decreased to 2-3 mL/kg/hour.

Another laboratory examination for the renal

mmol/L, serum sodium 140 mmol/L, serum calcium 9.4 mg/dL, serum chloride 102 mg/dL, serum magnesium 2.2 mg/dL, hemoglobin level 10.2 g/dl, hematocrit 32.7%, leukocyte count 15,200/mm^3, platelet count 635,000/mm^3 and CRP 5 mg/L). The patient was in good condition, there was no complaint of vomiting and he was able to walk again. The patient was discharged and advised to come for follow-up at the Pediatric Nephrology and Psychiatric Outpatient Clinics. Two weeks after discharge, the patient visited both clinics and was found to be in good clinical condition. One month after that visit, he was still in good clinical condition with no complaints.

Discussion

In this case, a 13-year-old boy came with recurrent vomiting and weakness with refractory hypokalemia that required multiple hospital admissions for the 3 years prior. We noted that he had been drinking more than 5 liters of water per day with a high urine output (6-7 mL/kg/hour).

In this patient, the recurrent vomiting episodes were non-bilious, persistent and moderate in nature for previous 3 years. Therefore, further work-up for systemic disorders were carried out.

Acute onset of weakness in a child is a neurologic emergency and should be evaluated in a hospital setting where subspecialists are available. Acute weakness in childhood is divided into four categories: (1) unilateral or bilateral weakness with evidence of cortical involvement, (2) unilateral weakness without cortical involvement, (3) bilateral weakness without cortical involvement, and (4) weakness with signs of spinal cord involvement.[11]

This patient had bilateral weakness in his lower extremities. No symptoms of cortical involvements were seen. Neurological examination showed decreased motor strength of the lower limbs and normal physiological reflexes. We assessed him to have bilateral weakness without cortical involvement. Other etiologies needed to be further excluded, including hypo/hyperkalemia, periodic paralysis, congenital paramyotonia, congenital myotonia, metabolic myopathies, acute motor axonal neuropathy, tick paralysis, and diphtheria.

The patient was also hypokalemic. Hypokalemia is defined to be serum potassium <3.5 mmol/L. Hypokalemia can result from poor potassium intake, increased translocation into the cells, or most commonly, increased losses in the urine or the gastrointestinal tract. In situations of potassium wasting via the kidney or gastrointestinal tract, there is a genuine decrease in total body potassium. The most common mechanisms leading to hypokalemia are increased urinary losses due to increased sodium delivery to the distal nephron, as with diuretics, mineralocorticoid excess, nonabsorbable anions, and increased urine flow, as with osmotic diuresis. The presence of primary mineralocorticoid excess should be suspected in any patient with the triad of hypertension, hypokalemia, and metabolic alkalosis.[12,13]

Hypokalemia with low total body potassium occurs in renal potassium wasting (such as renal tubular acidosis, Bartter syndrome, Gitelman syndrome, hyperaldosteronism, hyperreninemia, congenital adrenal hyperplasia, Cushing, Liddle syndrome, and drugs), gastrointestinal potassium loss (such as vomiting, diarrhea, and laxative abuses), and decreased potassium intake (as in anorexia nervosa).[12] We should perform laboratory investigations including serum electrolyte panel, urea, creatinine, bicarbonate, pH, urine potassium excretion, and transtubular potassium gradient measurement. If the urine K^+ excretion is >20 mmol/L, the blood pressure is normal with normal/high plasma bicarbonate, and the urine chloride is >20 mmol/L, then these abnormalities can caused by diuretic therapy, non-diuretic therapy, and Bartter or Gitelman syndromes.[12-14]

The patient had no history of gastrointestinal loss, taking diabetic or laxative medicines, malnutrition, surgery, or diuretic therapy. His laboratory findings revealed urinary K^+ excretion >20 mmol/L (29.7 mmol/L), with normal blood pressure. Blood gas analysis revealed metabolic alkalosis with normal plasma bicarbonate (bicarbonate 29.8), and urine chloride >20 mmol/L (252 mmol/24 hours). So, the hypokalemia in this patient could have been caused either by Bartter or Gitelman syndrome, because we had excluded other possibilites such as diuretic or non-diuretic therapy. [12,13,15]

In addition to hypokalemia, this patient also had hypomagnesemia. Magnesium (Mg^{2+}) is the second most abundant intracellular cation after potassium, and the fourth most abundant cation of the body after calcium, potassium, and sodium, which is involved in hundreds of enzymatic reactions and is essential for life. Magnesium is an important co-factor for many biological processes, most of which use ATP. As an essential mineral, Mg^{2+} is important for bone mineralization, muscular relaxation, neurotransmission, and other cellular functions. Extracellular Mg^{2+} concentration is tightly regulated by intestinal absorption and renal excretion. Magnesium plays a role in the regulation of parathyroid hormone (PTH) secretion. Hypermagnesemia suppresses the release of PTH. Acute hypomagnesemia has the opposite effect, however, as profound Mg^{2+} depletion decreases the release of PTH and induces skeletal resistance to PTH and hypocalcemia. Consequently,

profound Mg^{2+} deficiency causes tetany, cardiac arrhythmia, bone instability, and encourages renal stone formation. The kidney plays a crucial role in the maintenance of Mg^{2+} balance, with approximately 2 g of Mg^{2+} filtered daily by the human kidney, and approximately 100 mg appearing in the urine.[14,16,17] Serum Mg^{2+} concentration is not often measured in routine blood tests, therefore, it needs to be directly measured in clinical situations that are likely to be associated with disturbed Mg^{2+} homeostasis, such as chronic diarrhea, hypokalemia, cardiac arrhythmias, and hypocalcemia. Renal Mg^{2+} wasting has also been associated with Gitelman syndrome and in some cases, Bartter syndrome.[14,16,17]

This patient had no complaints of diarrhea, and he had a clinically normal nutritional condition. Laboratory results revealed that his thyroid and parathyroid functions were within normal limits. There was no history of consumption of tacrolimus or aminoglycosides, diuretics, or post-obstructive diuresis. Having excluded the other etiologies of magnesium deficiency, therefore, the hypomagnesemia in this patient was suspected to be due to Bartter syndrome (BS) or Gitelman syndrome (GS).

The patient also suffered from anemia. According to the laboratory results, the anemia was categorized to be iron deficiency anemia. It can be caused by the prolonged achlorhydria because of persistent vomiting and insufficient oral intake that occurs in people who need a lot of iron, such as small children, teens, and pregnant women. Gastric acid is required in order to maintain the common ferric form of inorganic soluble iron, and achlorhydria may be a significant cause of iron deficiency anemia.[18]

According to the laboratory results, we assumed the patient suffered from infection due to the presence of fever, his high CRP level, and the urinalysis results. Unfortunately, because of technical problems, blood and urine cultures were not done. But, after receiving antibiotics for 7 days, the CRP level decreased, and he had no recurrent fever.

The patient had vomiting, weakness, hypokalemia, hypomagnesemia, normal calcium, hypocalciuria, and metabolic alkalosis. As such, he was suspected to have Bartter syndrome, with a differential diagnosis of Gitelman syndrome.

Bartter syndrome and Gitelman syndrome are congenital renal tubular disorders characterized by

Table 1. Summary of the clinical and biochemical features of the different subtypes of Bartter's syndrome[22]

	Type I, II BS (neonatal/antenatal)	Type III BS (classic)	Type IV BS	Type V BS	Gitelman S
Clinical features					
Age at presentation	Prenatal	Childhoold	Prenatal	Prenatal/neonatal	Adolescence, adult
Polyhidramnion	+	+/-	+	?	-
Growth retardation	+	+/-	+	?	-
Delayed cognitive development	+	+/-	+	?	-
Dysmorphia					
Polyuria	+	+	+	+	+/-
Polydipsia	+	+	+	+	+/-
Muscle weakness	-	-	+	?	+/-
Muscle crapms to tetany	-	-	-	+	+/-
Nephrocalcinosis	+	+/-	-	+	-
Sensorineural deafness	-	-	+	-	-
Biochemical features					
Serum K^+	↓	↓	↓	↓	↓
Serum Cl^-	↓	↓	↓	↓	↓
Metabolic alcalosis	+	+	+	+	+
Serum Mg^{2+}	Low-normal or normal	↓ in 20%	Normal	↓	↓ in 100%
Serum Ca^{2+}	Normal	Normal	Normal	↓	Normal
Urinary Ca^{2+}	↑↑↑	↑	Normal	↑	↓
Urinary prostaglandin E	↑↑↑	↑	↑↑↑	↑	Normal
Renin, aldosterone	↑	↑	↑	↑	=/↑

hypokalemia and metabolic alkalosis. A hallmark of both syndromes is activation of the renin-aldosterone-angiotensin system (RAAS) and hypokalemia, but with normal or low blood pressure. Once these two syndromes were recognized as distinct clinical entities, their similarities with regards to the changes in plasma composition and urinary electrolyte excretion produced by chronic diuretic administration became apparent: Bartter's and Gitelman's syndrome resembled the effects of furosemide, a loop diuretic that induces hypercalciuria and impairs urinary-concentrating ability, and hydrochlorothiazide, a thiazide diuretic that induces hypocalciuria. Indeed, apart from hypocalciuria, another way of distinguishing Gitelman's from Bartter's syndrome is the impaired natriuretic response to a thiazide diuretic.[21,22]

Table 1 shows a summary of the clinical and biochemical features of the different subtypes of Bartter's syndrome. In our case, the patient was a 13-year-old boy (adolescent), with complaints of vomiting and weakness, with laboratory examinations that revealed hypokalemia, hypomagnesemia, normal calcium, hypocalciuria, and metabolic alkalosis. Radiologic examination showed no evidence of nephrocalcinosis in the abdominal ultrasonography. Based on the data and the clinical and biochemical features shown in the table, the patient was diagnosed to have Gitelman syndrome.

Gitelman syndrome is characterized by hypokalemic, metabolic alkalosis in combination with significant hypomagnesemia and hypocalciuria in concordance to being a renal tubular salt-wasting disorder. In contrast to Bartter's syndrome (a genetically distinct and clinically more severe tubular transport disorder, which shares the hypokalemic metabolic alkalosis with GS), Gitelman syndrome presents at an older age with milder clinical manifestations and hypocalciuria with hypomagnesemia being consistent features.[1-3,23]

Most patients with Gitelman syndrome will only show the symptoms after the age of six years, therefore the disease is usually diagnosed during adolescence or adulthood. The general symptoms include muscle weakness and cramps, fatigue, febrile illness, tetany, vomiting, diarrhea, and abdominal pain. The cardinal neuromuscular symptoms related to hypokalemia and/or profound magnesemia include salt craving, nocturia, muscle weakness, tetanic episodes, and facial paresthesias. Fatigue is not completely related to the degree of hypokalemia; it can be severe in some patients, while others never complain of tiredness. In general, GS patients usually have normal growth and blood pressure with only mild polyuria. Some GS patients are completely asymptomatic except for the appearance at adult age of chondrocalcinosis that causes swelling, local heat, and tenderness over the affected joints. Growth delay can be seen in patients with severe hypokalemia and hypomagnesemia.[2,7]

The defect in the NCC in GS leads to decreased Na^+ and Cl^- reabsorption in the distal convoluted tubule (DCT) and increased solute delivery to the collecting tubule, with consequent volume conctraction. Hypovolemia stimulates the renin-angiotensin-aldosterone system and causes an increase in apical Na^+ reabsorption and stimulation of the basolateral Na^+/K^+-ATPase. The increased aldosterone levels stimulate cortical and medullary collecting duct H^+ pumps leading to increased apical H^+ ion secretion. K^+ and H^+ ion secretion increases as K^+ enters from the basolateral membrane via Na^+/K^+-ATPase, resulting in hypokalemia and metabolic alkalosis. The mechanisms leading to hypomagnesemia and hypocalciuria in GS remain unclear.[7,8]

Several hypotheses have been proposed to explain the hypocalciuria in Gitelman syndrome. One hypothesis for the hypocalciuria in GS focuses on increased calcium reabsorption in the DCT secondary to hyperpolarization of the luminal cell membrane. This explanation seems to be incomplete because calcium excretion is not reduced by the acute administration of thiazide, even though these agents cause the expected natriuresis and thereby the required electrical changes. A second hypothesis suggests enhanced reabsorption of calcium in the proximal tubular segments in response to hypovolemia.[8]

The mechanism of hypomagnesemia in GS remains unclear. Although the major site of passive reabsorption is the thick ascending limb of the loop of Henle through the paracellular pathway, active reabsorption of magnesium takes place in the DCT and accounts for 5-10% of the total filtered load. Because there is little magnesium reabsorption beyond the DCT, the DCT plays an pivotal role to determining the final urinary magnesium excretion. While hypomagnesemia in GS has been attributed to the associated hypokalemia, this hypothesis was not supported by studies in NCC-knock-out mice that developed hypo-

magnesemia and hypocalciuria without hypokalemia and by the observation of normomagnesemia-associated hypokalemia in patients with BS.[8]

Diagnosis of GS is based on the clinical symptoms (transient episodes of muscle weakness and cramps, occasional episodes of tetany, abdominal pain, vomiting, constipation, and fever) and biochemical abnormalities (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).[1-3,7]

Several extrarenal and renal disorders with similar laboratory findings and clinical presentation may be misdiagnosed as GS, leading to inproper management and inappropriate genetic testing. To further solidify a diagnosis of GS, a single or several random urine specimens can usually separate disorders of hypokalemia and metabolic alkalosis associated with extracellular fluid (ECF) depletion. Urine with high Na^+ and Cl^- excretion in the presence of ECF volume depletion is indicative of intrinsic renal disease or the lack of signaling to stimulate NaCl reabsorption. Gitelman syndrome, Barter syndrome, and other BS-like symptoms are often the diagnosis.[7]

Treatment of GS consists of oral supplementation of magnesium and potassium. Magnesium therapy not only corrects the hypomagnesemia, but also improves the hypokalemia. The recommended drug is oral magnesium chloride to compensate for renal Mg^{2+} and Cl^- losses. The daily dose for magnesium deficiency is 65-130 mg/kg/24 hours. This dose should be divided in 3-4 administrations to avoid diarrhea and has to be adjusted according to magnesium levels. The dose usually has to be increased during periods of infection, especially those accompanied by vomiting and diarrhea. Intravenous magnesium replacement with 50% magnesium sulphate at 0.2 mL/kg/dose (maximum 10 mL) over 2 hours is given twice per day. We should watch for signs of hypermagnesemia, such as facial flushing, loss of deep tendon reflexes, hypotension and atrioventricular block. Bolus doses of magnesium are rapidly excreted by kidneys, hence, smaller doses with continuous infusion are the better choice. Intracellular magnesium stores take longer to replete, hence, repletion should continue for at least 1 to 2 days after serum normalization.[1,2,5-8,24]

If symptomatic hypokalemia is not corrected by $MgCl_2$ administration, it can be treated by drugs that antagonize aldosterone activity or block the sodium channel in the collecting ducts. The preferred combination is amiloride (5-10 mg/1.73 m^2/day) with KCl (1-3 mmol/kg/day divided in 3-4 doses). Amiloride should be started with caution in order to avoid hypotension.[2,7]

Growth and puberty delay in some patients with severe GS can be corrected by adequate magnesium and potassium supplementation; also a growth-promoting effect of indomethacin has been reported in GS patients. All patients with GS are encouraged to maintain a high sodium and high potassium diet.[1,2,5,7] In general, growth is normal but can be delayed in Gitelman syndrome patients with severe hypokalemia and hypomagnesemia. A cardiac workup is recommended to screen for the risk factors of cardiac arrhythmias.[2,7,8]

Genetic counseling is important. Since GS is an autosomal recessive trait, the recurrence risk for parents with an affected child is 25%. If the parents already have other children who are not obviously affected, we cannot be absolutely sure that they do not have GS, because clinical symptoms can appear later in life. If the parents are eager to know the status of the other children and in case the molecular defect in their affected child has been elucidated, DNA analysis in the other children may be performed. Although technically feasible, antenatal diagnosis for GS is not advised and as yet has never been asked for, because of the good prognosis in the majority of patients.[2,3,23]

In general, the long term prognosis of Gitelman syndrome patients is excellent. Progression to renal insufficiency is extremely rare in GS. Follow up of patients with GS should be carried out with regular serum and urine electrolyte measurements done at least monthly.[2,5,7,23]

We report a rare case of Gitelman syndrome in a child. The treatment for the patient is lifelong supplementation of magnesium.

Conflict of interest

None declared.

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