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Hypokalemic Periodic Paralysis in a 13-Year-Old Girl: Diagnostic Approach of Gitelman Syndrome

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Abstract: ***Background: Hypokalemic periodic paralysis is characterized by episodes of acute muscle weakness following decreased serum potassium levels due to primary or secondary cause. Identifying the cause of hypokalemia can be challenging and demands a thorough workup. Secondary hypokalemic periodic paralysis could be due to Gitelman syndrome, a rare autosomal recessive salt-losing renal tubulopathy. Laboratory abnormalities found in Gitelman syndrome are hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. The disease is usually detected during adolescence or adulthood and the prevalence is estimated to be 1 in 40,000 individuals. Due to its low prevalence, Gitelman syndrome is rarely considered in the initial differential diagnosis of hypokalemia. Objective: The aim of this case report is to describe the diagnostic approach of Gitelman syndrome based on clinical and laboratory findings. Case: A 13-year-old girl was presented with recurrent acute episodes of muscle weakness of upper and lower limbs, without signs of gastrointestinal loss, inadequate intake, or past history of any medical prescription. On physical examination, blood pressure was slightly decreased, she had decreased power in all extremities, but it was more severe in the lower extremities. Physiological reflexes were diminished without sensory deficits. Laboratory tests revealed severe hypokalemia, metabolic alkalosis, and hypocalciuria. Glomerular filtration rate was normal. Renal ultrasonography showed no abnormalities. Thus, a diagnosis of Gitelman syndrome was made. The patient was treated with intravenous potassium replacement and showed remarkable recovery after five days. Treatment was continued with daily oral potassium. Conclusion: Investigations for the etiology of hypokalemic periodic paralysis should be carried out and consider Gitelman syndrome as a differential diagnosis. Gitelman syndrome can be diagnosed based on clinical and laboratory findings.***

Keywords: hypokalemic periodic paralysis, Gitelman syndrome

1. Introduction

Hypokalemia is present when serum potassium levels are below 3.5 mmol/L due to various causes. It usually results from decreased total potassium body (reduced intake or increased excretion) or disturbance of potassium cellular shift [1]. Clinical presentation varies from asymptomatic to severe life-threatening conditions such as arrythmias. Diarrhea, vomiting, and diuretic medications are common causes of hypokalemia. More challenging causes are tubulopathies that needs further investigations [2].

Hypokalemic periodic paralysis (HPP) is one of the clinical spectrums due to decreased serum potassium levels, characterized by episodes of muscle weakness. It can be due to primary or secondary causes. Primary, it is autosomal dominant inherited and caused hypokalemia by intracellular shift of potassium in the skeletal muscle. Secondary HPP could be due to various disorders, such as renal tubular acidosis, thyrotoxicosis, primary hyperaldosteronism, diarrhea, barium intoxication, Liddle syndrome, Conn's syndrome, Bartter syndrome and Gitelman syndrome [3],[4].

Gitelman syndrome is a rare autosomal recessive salt-losing renal tubulopathy caused by mutations in the SLC12A3 gene encoding the thiazide-sensitive sodium-chloride cotransporter (NCCT) expressed in the distal convoluted tubule (DCT). Laboratory abnormalities found in Gitelman syndrome are hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. The disease is usually detected during adolescence or adulthood and the prevalence is estimated to be 1 in 40,000 individuals. Due to its low prevalence, Gitelman syndrome is rarely considered in the initial differential diagnosis of hypokalemia [5],[6].

Hypokalemia and paralysis are common clinical problems found in the emergency room. Identifying the cause of hypokalemia can be challenging and demands a thorough workup. It is important to investigate the underlying cause, because failure of treatment is usually caused by the incapability to identify the underlying disease. In this case, we present a patient with hypokalemic periodic paralysis caused by Gitelman symdrome. We will describe the diagnostic approach of Gitelman syndrome based on clinical and laboratory findings.

2. Case

A 13-year-old girl came to emergency department with muscle weakness on both legs and arms since a day before admission. Weakness felt heavier on the lower extremities. The symptom was accompanied by generalized muscle cramps. It began with fatigue and numbness in the extremities, and then progressively worsened until the patient was unable to walk and lift her arms. She experienced more than three episodes of muscle weakness in the past year, since it started. Each episode lasted a few days and resolved after intravenous potassium administration. The usual weakness was not precipitated by physical activities. Between attacks, she can still do daily activities. There were no history of vomiting, diarrhea, or unusual eating habit. Frequent urination at night and excessive urine volume were denied. She had no history for any medical prescription including diuretics. Prenatal history was unremarkable and experienced a normal delivery with birth weight of 3,500 g. She grew up normally with no childhood history of similar symptoms. No other family member had a similar illness and there was no history of parental close-family marriages.

On physical examination, she was alert and looked very weak. Her weight was 52 kg (50-75th percentile) and height was 149 cm (10-25th percentile). Her blood pressure was slightly decreased 90/60 mmHg (less than 50th percentile), pulse rate was 92 beats per minute, respiratory rate was 20 breaths per minute, and axillary temperature was 36.6^{o}C. Chest examination revealed normal heart sound and clear lungs. The abdomen was normal without any organomegaly. The extremities were warm without edema. Neurological examination showed decreased power in all extremities, more severe in the lower extremities, and physiological reflexes were diminished. There were no sensory deficits and negative pathologic reflexes. Her urine output was 2-3 ml/kg/hour.

Laboratory test showed serum sodium was 144 mmol/L, potassium 1.89 mmol/L, chloride 109.6 mmol/L, calcium 9.7 mg/dl, and magnesium 2.62 mg/dl. Arterial blood gas analysis revealed metabolic alkalosis with pH 7.50, pCO2 39.3 mmHg, pO2 138.4 mmHg, HCO3 30.20 mmol/L, base excess 7.1 mmol/L, SO2 99.0%. Twenty-four-hour urine electrolyte showed sodium 74.0 mmol/d, potassium 31.93 mmol/d, chloride 78.44 mmol/d, calcium 0.46 mmol/d. Glomerular filtration rate was normal (106.42 ml/min/1.73m^2), ureum 8.90 mg/dl, and creatinine 0.77 mg/dl. Thyroid function was normal with free T4 1.63 ng/dl and TSH 6.05 µIU/ml. Electrocardiogram result showed no signs of decreased T-wave amplitude or ST-segment depression. Renal ultrasonography revealed normal kidneys with no evidence of nephrocalcinosis.

Based on clinical and laboratory findings, a diagnosis of Gitelman syndrome was made. The patient was given intravenous potassium 0.75 mEq/kg equal to 40 mEq three times. Intravenous potassium was switch to oral KSR 600 mg daily after serum potassium was increased to 3.02 mmol/L with subsequent clinical improvement of muscle strength. She was discharged after five days of admission. A 3-month follow up revealed good clinical condition and no recurrence of muscle weakness.

3. Discussion

Hypokalemic periodic paralysis can be due to primary or secondary causes. Primary or familial HPP is autosomal dominant inherited, related to a defect in muscle ion channels that causes intracellular shift of potassium in the skeletal muscle [3],[4]. Diagnosis of familial HPP is accomplished if recurrent episodes of muscle weakness present with low potassium level despite a normal acid base status. However, other diseases associated with potassium wasting must be ruled out. A positive family history strongly favors a diagnosis of familial HPP. Secondary HPP or sporadic paralysis are related to the dysfunction of ion channels caused by electrolytic disturbances. The causes of sporadic forms could include renal tubular acidosis, thyrotoxicosis, primary hyperaldosteronism, diarrhea, barium intoxication, Liddle syndrome, Conn's syndrome, Bartter syndrome and Gitelman syndrome [7],[8]. In this case, the diagnosis of familial HPP seemed unlikely, because this patient had no positive family history of HPP. Hypokalemia was presented with acid base disorder, so that other causes of HPP should be investigated.

Four potential mechanisms were thought to be responsible for hypokalemia. These include poor potassium intake (anorexia nervosa, long-term hunger), increased translocation into the cells (insulin administration, thyrotoxicosis), increased gastrointestinal loss (vomiting, diarrhea, laxative abuses), and excess renal potassium losses [1],[9]. In this case, hypokalemia seemed not to be related to inadequate intake as anorexia nervosa and long-term hunger were not detected. A negative history of medication and normal thyroid hormone level ruled out potassium cellular shift. Gastrointestinal loss was also excluded since the patient had no symptoms of chronic vomiting ot diarrhea. Therefore, increased renal loss should be confirmed by findings of high urinary potassium excretion.

The appropriate response to potassium depletion is to excrete <15 mmol/d of potassium in the urine, due to increased reabsorption and decreased distal secretion. Renal loss is suspected if the urinary potassium excretion is >15 mmol/d, so that further diagnosis is based on blood pressure and associated acid-base disorder [1],[10]. An important problem of hypokalemia presented with high blood pressure is primary hyperaldosteronism, in which there is an increased aldosterone level. Low aldosterone level is seen in primary mineralocorticoid excess with the triad of hypertension, hypokalemia, and metabolic alkalosis [11],[12]. If blood pressure is low or normal, the next step is to evaluate the acid-base status. Metabolic acidosis could be found in diabetic ketoacisosis and renal tubular acidosis (proximal or distal type), whereas metabolic alkalosis is associated with Gitelman or Bartter syndrome [1]. In this case, serum potassium was 1.89 mmol/L with manifestation of muscle weakness. Urinary potassium excretion was >15 mmol/d (31.93 mmol/d) with slightly decreased blood pressure (90/60 mmHg) and metabolic alkalosis (pH 7.50, HCO3 30.20 mmol/L, base excess 7.1 mmol/L). The potential diagnosis of this patient was Gitelman or Bartter syndrome, because we had excluded other possibilites.

Gitelman syndrome is a rare primary salt-losing renal tubular disorder, that is inherited as autosomal recessive traits. It is a more benign condition than Bartter syndrome that is often not diagnosed until late childhood or even adulthood. It is characterized by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria, high aldosterone and renin levels with normal blood pressure [2],[7]. The clinical manifestations are caused by loss-of-function mutations in the SLC12A3 gene, located on q3 of chromosome 16 which encodes the thiazide-sensitive NCCT in the DCT. Therefore, Gitelman syndrome resembles chronic treatment with thiazides [12],[13].

The natural history of Gitelman syndrome is variable in terms of age at clinical diagnosis, biologic phenotype, and clinical manifestations. Symptoms of Gitelman syndrome patients range from asymptomatic to severe manifestations, such as paralysis and cardiac arrest [2],[13]. Muscle weakness and cramps, which may be severe and usually

involve the arms and legs are observed in almost all patients, they are due in part to hypokalemia and hypomagnesemia. Affected patients may also present with tetany (approximately 10 percent of individuals), particularly in association with decreased intestinal absorption of magnesium (eg, vomiting, diarrhea). Beside the symptoms mentioned before, the cardinal neuromuscular symptoms related to hypokalemia and/or hypomagnesemia include salt craving, nocturia, 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 [7],[11]. In this case, the clinical presentations found on this patient were muscle weakness on both legs and arms accompanied by fatigue, numbness, and generalized muscle cramps. There was no history of vomiting, diarrhea, any medical prescription, and excessive urine volume.

The pathogenesis of Gitelman syndrome can explain the laboratory findings we found on this patient. The underlying potassium wasting is mediated by chronic renal salt-wasting and stimulation of the renin-angiotensin-aldosterone system (RAAS) as the consequence of relative hypovolemia. The defect in the NCC that leads to decreased sodium chloride reabsorption in DCT is thought to initiate the following sequence [7],[11]. Initial salt loss leads to mild volume depletion. The intravascular volume contraction stimulates sodium reabsorption in the collecting duct via upregulation of RAAS. The combination of hyperaldosteronism and increased distal flow (due to the reabsorptive defect) will cause enhanced potassium and hydrogen secretion at the secretory sites in the collecting tubules. This results in hypokalemia and metabolic alkalosis. The renal release of vasodilator prostaglandins (prostaglandin E2 and prostacyclin) is also increased in this condition and may partially explain why the blood pressure remains normal [2],[14].

The mechanisms leading to hypomagnesemia and hypocalciuria in Gitelman syndrome remain unclear. Hypomagnesemia is a common abnormality in Gitelman syndrome, although it is not observed in every case. In normomagnesemic patients, clinical manifestation and electrolyte abnormalities are milder. Several hypotheses have been proposed to explain the hypocalciuria in Gitelman syndrome. One hypothesis for the hypocalciuria focuses on increased calcium reabsorption in the DCT secondary to hyperpolarization of the luminal cell membrane. A second hypothesis suggests enhanced reabsorption of calcium in the proximal tubular segments in response to hypovolemia [11],[12].

Gitelman and Bartter syndrome are congenital renal tubular disorders characterized by hypokalemia and metabolic alkalosis. A hallmark of both syndromes is activation of RAAS and hypokalemia, but with normal or low blood pressure. We can differentiate Gitelman syndrome from Bartter syndrome by investigating calcium and magnesium concentration in serum and urine. In Gitelman syndrome, the defect can account both the magnesium wasting and the often marked decrease in urinary calcium excretion, in contrast to hypercalciuria seen in classic Bartter syndrome [11],[13]. Gitelman and Bartter syndrome have similarities with regards to the changes in plasma composition and urinary electrolyte excretion produced by chronic diuretic administration. Bartter syndrome resembles the effect of furosemide, a loop diuretic that induces hypercalciuria and impairs urinary-concentrating ability. In contrast, Gitelman syndrome resembles hydrochlorothiazide, a thiazide diuretic that induces hypocalciuria. Another way of distinguishing this two conditions is the impaired natriuretic response to a thiazide diuretic in Gitelman syndrome. In general, Gitelman syndrome patients usually presents at an older age with milder clinical manifestations and normal growth [11],[16].

In this case, the initial symptoms appeared at the age of 12 years old (adolescent) with normal growth. Prenatal history was unremarkable. Laboratory examination revealed normal serum magnesium (2.62 mg/dl), but urinary calcium excretion was low (0.46 mmol/d). Renal ultrasonography showed no evidence of nephrocalcinosis. Based on clinical and biochemical features, the patient was diagnosed to have Gitelman syndrome.

Recent studies have identify more than 170 mutations throughout the SLC12A3 gene in patients with Gitelman syndrome. A genetical study would confirm the diagnosis of Gitelman syndrome. However, genetical study remains confined to a few research laboratories because of the large size of most responsible genes, the multitude of recognized mutations and absence of “hot spots” along the gene, intrafamilial heterogeneity, and high cost [8],[18]. In this case, we didn’t perform the genetic analysis due to unavailability of genetic testing in our country. Nevertheless, even without a genetic report, clinicians should be able to make a diagnosis based on clinical and laboratory findings.

The aims of treatment in Gitelman syndrome are to improve patient symptoms, quality of life, and to ensure cardiac rhythm stability. All patients with Gitelman syndrome are encouraged to maintain a high-salt diet. A cardiac workup is recommended to screen for the risk factors of cardiac arrhythmias. Treatment is mainly symptomatic by supplementation of potassium chloride and magnesium chloride. Potassium and magnesium homeostasis are related to each other, and potassium depletion cannot be corrected until the correction of hypomagnesemia. On average patients should receive up to 500 mEq of potassium and 4-5 mg/kg/day of 5-10 mg of magnesium chloride [11],[12].

If symptomatic hypokalemia is not corrected by potassium chloride, 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 m2/day) with KCl (1-3 mmol/kg/day divided in 3-4 doses). Amiloride should be started with caution in order to avoid hypotension. The combination of a nonsteroidal antiinflammatory drug (NSAID) and a potassium-sparing diuretic (such as spironolactone or amiloride, often in higher than usual doses of up to 300 and 40 mg/day, respectively, to more completely block distal potassium secretion) can raise the plasma potassium concentration toward normal, largely reverse the metabolic alkalosis, and partially correct the hypomagnesemia [7],[11]. In this case, the patient was given intravenous potassium 0.75 mEq/kg equal to 40 mEq three

times. After clinical improvement, treatment was switch to oral KSR 600 mg daily. She was discharged after five days of admission and continued taking oral potassium. She was recommended to maintain high-salt diet.

Genetic counseling is important. Since Gitelman syndrome 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 Gitelman syndrome, 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 [11],[19].

In general, the long-term prognosis of Gitelman syndrome, in terms of growth and life expectancy is favorable. Progression to renal insufficiency is extremely rare in Gitelman syndrome. Follow-up of patients with Gitelman syndrome should be carried out with regular serum and urine electrolyte measurements done at least monthly [2],[11].

4. Conclusion

Investigation for the etiology of hypokalemic periodic paralysis should be carried out and consider Gitelman syndrome as a differential diagnosis. Gitelman syndrome can be diagnosed based on clinical and laboratory findings. The long-term prognosis of Gitelman syndrome is favorable.

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