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Gitelman's syndrome-associated hypokalemia: A case report

Areen A Mitaeb and Hasan Eideh*

Department of Pediatrics, Palestinian Medical Complex Hospital, Palestine

Abstract

We report a case of male with Gitelman's syndrome who presented to pediatric emergency department mainly due to hyperemesis, fever and hypoactivity. Thus, he was admitted to the pediatric ward and intravenous potassium supplementation was commenced to counter the observed hypokalemia (2.9 mmol/L). Hyperemesis receded, and the patient's symptoms improved. However, serum potassium was still low (range 3-3.8 mmol/L). After doing further investigation by pediatric endocrinologist, the patient plasma aldosterone level was elevated (468 pg/ml) and he was found to have a homozygous missense mutation on SLC12A3 gene chr1656,921,865A > T,p.N7361 in whole Exome sequencing.

Introduction

Potassium is critical for many vital cell functions. Ninety eight percent of total body potassium is intracellular, and kidney plays a dominant role in potassium homeostasis **[1].** Hypokalemia is a common clinical problem in endocrinologists and nephrologists' practice. There are many obvious causes of hypokalemia such as diarrhea, vomiting or diuretics abuse. Other causes such as tubulopathies are rarely observed and their diagnosis is more challenging [2].

Gitelman's syndrome is relatively common but overlooked cause of hypokalemia. It is an autosomal recessive inherited disease of renal tubules with a prevalence of 1-10/40,000 [3]. It is characterized by hypokalemia and hypomagnesemia caused by renal K+ and Mg2+ wasting. Other typical changes are metabolic alkalosis, hypocalciuria and hyperreninemic hyperaldosteronism [4].

First symptoms of GS occur in children or young adults with normal growth are history of salt-craving behaviors, muscular cramps and weakness, constipation, nocturia, polyuria, thirst, polydipsia, cardiac arrhythmias, paresthesias [4]. Arterial hypotension is common and in many cases the most prominent symptom, however, in aging GS population hypertension can occur [5]. GS does not interfere with children's moods and social relationships and have no negative impact on their quality of life [4].

Case report

A 3 years old boy presented to the Emergency Department of Pediatrics in Ramallah Governmental hospital, Palestine, with repeated vomiting, fever and mild to moderate dehydration. His mother reported he had vomited around four times; the vomitus was not bilious consisting of normal gastric content and associated with fever which was documented by the mother (axillary temp 37.6°C). On examination, patient was lethargic, moderately dehydrated, heart rate 118/min, respiratory rate 30/min, and blood pressure 114/79 mmHg (above 95th percentile for age and height 89-107/45-64). At the time of presentation, his weight was 13 kg (in 10th percentile), height was 95 cm (in 25th percentile) and head circumference was 51 cm (in 75th percentile).

Laboratory tests showed that his hemoglobin was 13 g/dl; the total leukocyte count was 4.4 × 1000 cells per mm^3 and blood and urine culture were sterile. His serum sodium was 136 meq/l, potassium 2.9 mmol/L, ca 9.71 mg/dl, and magnesium 1.99 mg/dl (normal 1.6-2.6 mg/dl) and creatinine 0.36 mg/dl. Following proper treatment, his hydration status improved; but hypokalemia was persisting. Arterial blood gas analysis showed mild metabolic acidosis (pH 7.39, HCO_3 21.3, $PaCO_2$ 34, and PaO_2 56).

On detailed history, Parents had first degree consanguineous marriage as they are cousins. Mother was 24 and father was 30 years old at marriage time and have four pregnancies, Our patient is 4th in order of pregnancies which was conceived at age 40. His mother had a history of behchet and asthma during gestational period for which she was taking colchicine in the first and second trimesters, prednisone 20 mg in the first and e second trimesters which was tapered to 5 mg in the third trimester. During pregnancy she also received potassium once due to an episode of hypokalemia, aspirin, plavix and clexane. Our patient was product of cesarean section which was done at 36+3 week indicated due to previous cesarean section, fetal bradycardia and maternal chronic diseases. The baby was born with weight of 3000 g, and Apgar measurements were 8 and 9 at 1 and 5 min, respectively. He had a small (around 1×2 cm) hyperpigmented area over his left hand (Figure 1). He was admitted to NICU for 7 days, kept on O_2 therapy due to RDS and then discharged. He had remained symptom free until the age of 5 months when the first episode of non-projectile vomiting and fever occurred.

After reviewing the past medical reports, we noticed that he experienced a long-term history of recurrent episodes of illnesses that resemble the current episode (Table 1). He was diagnosed approximately one year ago with reactive air way disease which require

Correspondence to: Hasan Eideh, Department of Pediatrics, Palestinian Medical Complex Hospital, Ramallah, Palestine, E-mail: hasan_eideh@yahoo.com

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albuterol administration. Hypokalemia was pointed out in the previous three months, but we were reluctant to do further investigation considering its relation to vomiting and albuterol use. however, in the recent one month we noticed that despite the intensive replacement of potassium, its level remained constantly low (range 3-3.8 mmol/L) (Table 2).

The patient was referred to follow up with pediatric endocrinologist. After doing further investigation, his pediatric endocrinologist found that the aldosterone level was elevated (468pg/ml) while the renin activity was normal. Renal CT was ordered to rule out an adrenal related problem but was surprisingly free. Finally, Genetic testing and whole exome sequencing was ordered while the patient was continued on 2.5 mg *2 daily of spironolactone and 20 mg *2 SOPA –K and potassium levels were followed at a regular basis.

Table 1. Past complains

Age	Complains	Diagnosis/ Work up
11 days	RDS (congenital pneumonia)	----------
5 months	Non-projectile Vomiting + fever	----------
6 months	Constipation	Rule out hirschsprungs (delay meconium)
7 months	Non-projectile Vomiting + fever	----------
8 months	Non-projectile Vomiting + fever	----------
8 months	Constipation + fever	Rule out intussusceptions
1 y & 1 m	Non-projectile Vomiting 3 times	----------
1 y & 6 m	Non-projectile Vomiting + fever+ tonsillitis	----------
1 y & 9 m	fever+ diarrhoea	Gastroenteritis
2 years	cough & wheezy chest	Reactive airway on Albuterol
2 y& 1 m	Non-projectile	Vomiting + fever
2y & 10 m	Non-projectile Vomiting + fever	Hypokalaemia
2y & 11 m	fever + Abdominal pain + hypokalaemia	Hyperaldosteronism
3 years	Non-projectile Vomiting + fever	Hypokalaemia

Table 2. Trends in serum potassium over the patient's ten days of hospitalization

Day of admission	Serum potassium
1	2.0 mmol/L
2	2.9 mmol/L
3	3.0 mmol/L
4	3.1 mmol/L
5	3.4 mmol/L
6	3.2 mmol/L
7	3.6 mmol/L
8	4.0 mmol/L
9	3.8 mmol/L
10	3.1 mmol/L

Figure 1. Hyperpigmented area over the left hand

We analyzed his genetic mutation by direct DNA sequencing. As a result, he was found to have homozygous missense mutation on SLC12A3 gene chr1656,921,865A> T,p.N7361 which encoded the thiazide-sensitive NaCl cotransporter. These genetic mutations are found in the majority of GS patients. We established a final diagnosis of GS based on his history and their genetic mutations.

Discussion

Gitelman's syndrome, also known as familial hypokalaemia-hypomagnesaemia, is a rare primary salt-losing renal tubular disorder first reported by Gitelman in1966. It is inherited as autosomal recessive traits. The prevalence is estimated approximately at 1 in 40000 inhabitants. No gender difference is observed.

The clinical manifestations are caused by loss-of-function mutations in the solute carrier family, member 3 (SLC12A3) gene, which encodes thiazide sensitive NaCl co-transporter (NCCT) in the distal convoluted tubules. Normally homozygous and combined heterozygous mutations are expected in Gitelman's syndrome as it is inherited in autosomal recessive trait. The intravascular volume contraction stimulates sodium reabsorption in the collecting duct via upregulation of renin-angiotensin-aldosterone system, maintaining sodium homeostasis at the expense of increased potassium and hydrogen ion secretion. This results in hypokalemia and metabolic alkalosis.

Clinical symptoms of Gitelman's syndrome include fatigue, cramps, muscle weakness, carpopedal spasms, salt craving and rarely serious symptoms such as paralysis and cardiac arrest. Growth retardation may also be seen in Gitelman's syndrome but not as frequent as in Bartter's syndrome. Most symptomatic patients present during periods of fever or when extra magnesium is lost during vomiting or diarrhea. However, many of the patients with Gitelman's syndrome remain asymptomatic during neonatal, infancy and preschool years. Often hypokalemia is only detected during routine blood taking for other reasons, as in our patient. The diagnosis of Gitelman's syndrome in this patient was made from laboratory investigation findings including hypokalemia, and hyperaldosteronism. Molecular analysis further confirmed the diagnosis.

Treatment of Gitelman's syndrome is mainly symptomatic by supplementation of potassium chloride and magnesium chloride. Observation of chondrocalcinosis. Sometimes aldosterone antagonists are required to correct and maintain serum potassium level. Patients are encouraged to maintain a high-salt diet. The long-term prognosis of Gitelman's syndrome, in terms of growth and life expectancy is favorable.

Conclusion

This case demonstrated a non-classical case of Gitelman's syndrome. He hadn't fulfilled most of the diagnostic criteria for Gitelman's syndrome including normotensive hypokalemic metabolic alkalosis, hypomagnesaemia and hypocalciuria. Once vomiting, diuretic and drug abuse are excluded from the differential diagnosis of a patient presenting with hypokalemia, rare conditions such as renal tubular acidosis, Gittelman's syndrome need to be considered which is feasible by genetic analysis.

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