Diagnosis and Clinical Approach in Gitelman’s Syndrome

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ABSTRACT

Hypokalemia, defined as a plasma potassium concentration <3.5 mmol/l, is the most common electrolyte abnormality encountered in our clinical practice. Unfortunately, in many cases, the etiologies were unclear and resulted in a wrong treatment. Indeed, the true etiology could be such a ‘rare’ one and could be found by doing a comprehensive work up. One of this is Gitelman’s syndrome, a rare genetic disorder characterized by hypokalemic alkalosis, hypomagnesemia, hypocalciuria, and secondary aldosteronism without hypertension. Since this disorder is found in 1% Caucasian populations, this is one of the most frequently inherited renal tubular disorders.

A 27 year old man came to emergency room with weakness and generalised muscle cramps. He was investigated three months before for a similar electrolyte disturbance which was found to be inconclusive. The routine laboratory data in emergency room revealed a potassium concentration of 2.3 mmol/l. He had never used diuretics or hormonal therapy nor had history of vomiting or diarrhea. He had normal blood pressure and the blood gas analysis revealed metabolic alkalosis. On his ECG (electrocardiography), we found the prominent U wave. Despite his low concentration of serum potassium and chloride, the concentration of these electrolytes in urine were extremely high. We also found hipomagnesemia. The calcium concentration in serum was normal with slightly hypocalciuria. Even with aggressive oral and intravenous potassium suplementation, the patient remained hypokalemic.

In cases when the etiology of hypokalemia is unclear, we should perform some investigations to confirm the diagnosis and give the proper treatment. In Gitelman’s syndrome, where the defect in the distal tubule cannot be corrected, the treatment must be a life-long. Most patients require oral potassium and magnesium suplementation, since drug therapy is usually incompletely effective.

Key words: hypokalemia, Gitelman’s syndrome, potassium, magnesium suplementation.

INTRODUCTION

A low serum potassium concentration is perhaps the most common electrolyte abnormality encountered in clinical practice. When defined as a value of less than 3.6 mmol of potassium per liter, hypokalemia is found in over 20 percent of hospitalized patients. The majority of these patients have serum potassium concentration between 3.0 and 3.5 mmol per liter, but as many as one quarter have values below 3.0 mmol per liter. For outpatient, a low potassium concentration has been found in 10 to 40 percent of patients treated with thiazide diuretics.1-4

Hypokalemia is usually well tolerated in otherwise healthy people, but it can be lifethreatening when severe. As a result, when hypokalemia is identified, the underlying cause should be sought and then treated. Mostly, hypokalemia is caused by a simple diagnosis, such as diarrhoea, vomitting, or intake of diuretic, and needed only a simple investigation. However, in some situations when these ‘usual’ causes were unproven, we habitually diagnosed these patients with familial periodic paralysis hypokalemic or just left it inconclusive. Indeed, the true etiology could be such ‘rare’ ones like Conn’s, Bartter, or Gitelman’s syndromes, and We must do a little effort to find it by doing more comprehensive workup. Therefore we could treat our patients better according to the diagnosis.1-4

We report a case of a 25-year old man who coming to the emergency room with weakness and generalised muscle cramps. The routine laboratory data in emergency room revealed a potassium concentration of 2.3 mmol/l. He had never used diuretics or hormonal therapy nor he had history of vomitting or diarrhea. Blood gas analysis of this patient revealed metabolic alkalosis with normal blood pressure. He was investigated three months before for a similar electrolyte disturbance which was found to be inconclusive. With the comprehensive workup, we
suggested this patient has Gitelman’s syndrome. In this paper we will discuss about how the diagnosis was made up and how other ‘usual’ differential diagnoses were eliminated. Hopefully, this case will give us a better understanding about the etiology and the clinical approach to patients with hypokalemia in order to give a better management for our patients.

CASE ILLUSTRATION

A 25 year old man came to emergency unit with weakness and generalised muscle cramps since 4 days before. The weakness and cramps felt heavier in both legs and arms. The patient also complained about having frequent micturition. There was no history of taking diuretic or hormonal therapy. There were no history of diarrhoea, vomiting, or unusual eating habit. There was no family history of endocrine disease. He was investigated three months before with same complaints which was found inconclusive. He had never diagnosed of having diabetes, hypertension, or heart disease.

On physical examination the patient appeared well, his body mass index was 21 kg/m². On vital sign we found his blood pressure was 100/70 mmHg and his pulse was 90 per minute. The respiratory rate was 20 per minute and the temperature was 36.5°C. He was euvolemic clinically with normal skin turgor. He had no evidence of postural hypotension nor did he have any peripheral edema. Our neurologic examination found there were tetraparesis with normal physiologic reflexes and negative pathologic reflexes.

His biochemical investigation revealed a potassium concentration of 2.3 mmol/l. His full blood count and liver function test were within normal limit. There was no abnormality on his chest X-ray. On his ECG (electrocardiography), we found sinus rhytm with QRS frequency 100/minute and the prominent U wave. (Figure 1)

Based on anamnesis, physical examination, and basic laboratory findings, initially we doubly diagnosed this patient as having familial hypokalemic periodic paralysis. To confirm the correct aetiology, we planned to perform serum electrolyte, including sodium, potassium, chloride, magnesium, and calcium, and also urine electrolyte, urine osmolality, and blood gas analysis.

The following biochemical investigation revealed hypokalemic metabolic alkalosis. (Table 1) Despite his low concentration of serum potassium and chloride, the concentration of these electrolytes in urine were extremely high. We also found hipomagnesemia. The calcium concentration in serum and urine were within normal limit. The GFR of this patient was normal and the blood glucose was also within normal value.

Despite aggressive oral and intravenous potassium suplementation, the patient remained hypokalemic (highest potassium concentration was 3.3 mmol/l. (Figure 2)

Based on anamnesis, physical examination, and comprehensive investigation of urine electrolyte and blood gas analysis, we suggested this patient has Gitelman’s syndrome. The reasons and clinical approach of this diagnosis will be discussed.

| Table 1. Biochemical investigation on day 3 of admission |
|-----------------|-----------------|
| Investigation   | Serum           | Urine             |
| Electrolytes    |                 |                   |
| Sodium          | 139 (135-145 mmol/l) | 998 (27-287 mmol/d) |
| Potassium       | 2.2 (3.5-5.3 mmol/l) | 117 (25-123 mmol/d) |
| Chloride        | 93 (97-107mmol/l)  | 997 (110-250 mmol/d) |
| Magnesium       | 1.6 (1.7-2.5 mmol/l) |                   |
| Calcium         | 2.40 (2.25-2.70 mmol/l) | 0.4 (0-0.75 mmol/d) |
| Osmolality      | 287.15 (285-295 mOsm/kg) | 466 (250-900 mOsm/kg) |
| Blood Gas Analysis |              |                   |
| pH              | 7.513 (7.37-7.45)  |                   |
| pCO₂            | 38.2 (32-46 mmHg)  |                   |
| pO₂             | 92.8 (71-104 mmHg) |                   |
| HCO₃⁻           | 30.9 (21-29 mmHg)  |                   |
| Base excess      | +6.7 (-2 +2)      |                   |
| O₂ saturation   | 97.7 (94-98 %)     |                   |
| Urea            | 25 (20-60 mg/dL)   |                   |
| Creatinine      | 1.2 (0.5-1.6 mg/dL) |                   |
| Blood glucose   | 94 (<140 mg/dL)    |                   |

DISCUSSION

Hypokalemia, defined as a plasma potassium concentration <3.5 mmol/l, may result from one (or more) of the following: decreased intake, increased translocation into the cells, or, most often, increased losses in the urine (or gastrointestinal tract or sweat). 2,3,5
This patient came with hypokalemia and paralysis. At first, since this patient never had history of using drugs or hormones nor had vomiting or diarrhea that could make potassium shifted acutely into the cell, we suspected he suffered from hypokalemic periodic paralysis (HPP). This disorder traditionally is suspected in most of hypokalemia with muscle weakness. However, the diagnosis of HPP must accomplish these 4 elements. First, if there were a positive family history, recurrent clinical pattern, or evidence of hyperthyroidism. Second, if there was no indication of other diseases known to be associated with potassium wasting. Third, if the patients required less than 1.5 mmol of potassium chloride per kilogram of body weight to return their plasma potassium concentration to the normal range. Fourth, the absence of an acid-base disorder. Because this patient had no positive family history, had no evidence of hyperthyroidism, had metabolic alkalosis, and didn’t get normal plasma potassium concentration despite aggressive potassium chloride supplementation, the diagnosis of HPP seemed unlikely on him. Therefore, we thought there must be a problem associated with potassium wasting.

To find out this problem, we followed this algorithm on Figure 3.

From this algorithm we can see that after eliminating decreased intake and intracellular shift as potential causes of hypokalemia, examination of the renal response can help to clarify the source of potassium loss. 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. Hypokalemia with minimal renal potassium excretion suggests that potassium was lost via the skin or gastrointestinal tract or that there is a remote history of vomiting or diuretic use.

The ECF volume status, blood pressure, and associated acid-base disorder may help to differentiate the causes of excessive renal potassium loss. A rapid and simple test designed to evaluate the driving force for net potassium secretion is the transtubular $K^+$ concentration gradient (TTKG).

The TTKG is the ratio of the potassium concentration in the lumen of the CCD ([K$^+$]$_{CCD}$) to that in peritubular capillaries or plasma ([K$^+$]$_p$). The validity of this measurement depends on three assumptions: (1) few solutes are reabsorbed in the medullary collecting duct (MCD), (2) potassium is neither secreted nor reabsorbed in the MCD, and (3) the osmolality of the fluid in the terminal CCD is known.

We can count the TTKG by using this formula.

$$\text{TTKG} = \frac{\text{K}^+ \text{ urine}}{\text{K}^+ \text{ plasma}} \times \frac{\text{OSM urine}}{\text{OSM plasma}}$$

According to the algorithm, the urine potassium concentration of this patient was high (117 mmol/l), so there must be potassium loss from the kidney. From TTKG formula above, we’ve counted that the TTKG of this patient was 30.67. Given that he had metabolic alkalosis without evidence of hypertension, vomiting, or diuretic abuse, the potential diagnosis of this patient was Bartter’s or Gitelman’s syndrome.

Alternatively, a urine chloride estimation may help to contribute to the aetiology of this patient. Urinary chloride is normally very low in patients who have been vomiting and have a metabolic alkalosis. The value of urinary chloride with surreptitious diuretic use is variable—high if the diuretic effect is still acting, but low when the diuretic effect has worn off. A high urine chloride concentration, on the other hand, suggests to continue either diuretic therapy or Bartter’s or Gitelman’s syndrome. The urine chloride concentration in this patient was inappropriately raised for the low
plasma chloride concentration. (Table 1) Due to the high urine chloride concentration and normal diuretic screen, again this suggested that the patient may have either Bartter’s or Gitelman’s syndrome.4,9

We can differentiate Gitelman’s from Bartter syndrome by investigating calcium and magnesium concentration in serum and urine. In Gitelman’s syndrome, the defect can account both the magnesium wasting and the often marked decrease in calcium excretion, in contrast to hypercalciuria seen in classic Bartter’s syndrome. Consistent with Gitelman’s syndrome, this patient had normal value of serum calcium concentration and had slightly reduced urine calcium concentration.6 (Table 1)

Because this patient presented in adulthood, he was able to concentrate his urine, and had a low serum magnesium and urine calcium, he best fits the diagnosis of Gitelman’s syndrome. (Table 2)

Even at this time it was possible, we didn’t perform the genetic analysis. Mostly because of the limitation of facility and financial problem. However, such analysis 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.10-11

The pathogenesis of Gitelman’s syndrome can explain the clinical and laboratory findings we found on this patient. As mentioned above, the primary defect in this disorder is an impairment in sodium reabsorption in distal tubule.9,10,12 The tubular defect in sodium chloride transport is thought to initiate the following sequence. Initial salt loss leads to mild volume depletion, resulting in activation of the renin-angiotensin-aldosterone system. The combination of hyperaldosteronism and increased distal flow (due to the reabsorptive defect) enhances potassium and hydrogen secretion at the secretory sites in the collecting tubules, leading to hypokalemia and metabolic alkalosis. The renal release of vasodilator

Figure 3. Algorithm depicting clinical approach to hypokalemia. TTKG, transtubular K⁺ concentration gradient; RTA, renal tubular acidosis.2
prostaglandins (prostaglandin E2 and prostacyclin) is also increased in this condition and may partially explain why the blood pressure remains normal. Consequently, this patient presented with hipokalemia with metabolic alkalosis and normal blood pressure.10

The clinical presentation found on this patient was also consistent with the Gitelman’s syndrome. This patient presented in adulthood with clinical manifestations of fatigue and muscle cramps in his whole body and also polyuria. Gitelman’s syndrome, an autosomal recessive disorder, is a more benign condition than Bartter’s syndrome that is often not diagnosed until late childhood or even adulthood. However, the syndrome is usually symptomatic and can be associated with serious clinical manifestations: 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). Severe fatigue may also be observed in some patients and a lower than average blood pressure may be seen, consistent with the tendency to salt wasting. Polyuria and nocturia are found in 50 and 80 percent, respectively. The polyuria may be accompanied by salt craving, suggesting that it is due to salt and water loss. Concentrating ability should be maintained, since function in the medullary thick ascending limb is relatively intact. A few patients may present with early onset disease as well as growth retardation.13-15

The tubular defect in Bartter’s or Gitelman’s syndrome cannot be corrected. As a result, treatment (which must be life-long) is aimed at minimizing the effects of the secondary increases in prostaglandin and aldosterone production.10

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.16,17

A similar improvement in the plasma electrolyte picture can be achieved by the use of an angiotensin converting enzyme (ACE) inhibitor which diminishes the production of angiotensin II and aldosterone. However, the acute reduction in angiotensin II levels can lead to symptomatic hypotension in some cases; this problem is often transient and can be minimized by the initial use of low doses.18,19

Most patients require oral potassium and magnesium supplementation, since drug therapy is usually incompletely effective. However, the restoration of normal magnesium and potassium balance is often difficult to achieve. Diarrhea frequently limits the dose of magnesium given and the magnesium that is absorbed tends to be excreted in the urine. In addition, patients with impaired transport in the loop of Henle have diminished potassium as well as sodium and chloride reabsorption at that site. In this setting, blocking distal potassium secretion with amiloride and/or an ACE inhibitor will not reverse the absorptive problem in the loop, resulting in persistent potassium wasting.20

From the first day of admission, this patient had been treated with aggressive potassium chloride. He was given three slow release tablets of potassium chloride (equal to 60 mmol) a day in conjunction with intravenous potassium chloride. Initially, we gave 25 mmol intravenous potassium chloride eight hourly then we increased the doses up to 37.5 mmol six hourly on day 4 of admission. But, the potassium concentration still didn’t achieve normal range. (Table 1) From the literature we found that when potassium is given intravenously, the rate should be no more than 20 mmol perhour, and the patient electrolyte and cardiac rhythm

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**Table 2. Characteristics of Bartter’s and Gitelman’s syndrome**

<table>
<thead>
<tr>
<th></th>
<th>Bartter’s syndrome</th>
<th>Gitelman’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization of defect</td>
<td>Ascending limb of Henle</td>
<td>Distal tubule</td>
</tr>
<tr>
<td>Age of presentation</td>
<td>Prenatal, during infancy, early childhood</td>
<td>Mostly late childhood or at adult age</td>
</tr>
<tr>
<td>Biochemical differences</td>
<td>Serum magnesium may be decreased</td>
<td>Serum magnesium decreased</td>
</tr>
<tr>
<td></td>
<td>Urinary excretion of calcium increased or normal</td>
<td>Urinary excretion of calcium reduced</td>
</tr>
<tr>
<td>Molecular differences</td>
<td>Na-K-2Cl cotransporter (NKCC2) or apical K channel (ROMK) or basolateral C1 channel (CICNK) in thick ascending limb of Henle</td>
<td>Na-CI cotransporter in the distal tubule</td>
</tr>
<tr>
<td>Functional studies</td>
<td>Concentrating capacity severely impaired</td>
<td>Concentrating capacity normal or slightly impaired</td>
</tr>
<tr>
<td></td>
<td>GFR may be normal, decreasing or declining</td>
<td>GFR is normal</td>
</tr>
</tbody>
</table>

should be monitored. Other text stated that maximum rate of infusion is 0.3-0.5 mmol/kg/h. Frequently, this doses may be inadequate for severe hypokalemia.1

CONCLUSION

The first step to diagnose the aetiology of hypokalemia is to explore drugs or other causes that could make the acute shift of potassium into the cell. Mostly, this can be determined only by a careful anamnesis.

If the aetiology is still unclear, we should perform some physical examination and investigation to confirm the diagnosis. We might have to perform serum and urine electrolyte, blood gas analysis, and serum and urine osmolality. The transtubular K+ concentration gradient (TTKG) and urine chloride can bring us to the final diagnosis.

The diagnosis of Gitelman’s syndrome of this patient was based on these facts: no evidence of decreased intake nor intracellular shift of potassium, high TTKG, hypokalemia with metabolic acidosis, no evidence of hypertension, high urine chloride, normal serum and urine calcium concentration, presented in adulthood with hypomagnesemia and good renal function.

REFERENCES