A case of hypokalemia

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Case

57 y.o. male

CC: Weakness

HPI: About 20 years ago, he developed bilateral lower extremity weakness. Laboratory evaluation showed hypokalemia. Since then, he has been receiving potassium supplement, but his serum potassium has remained low or low normal. He did not experience further episode of weakness. He denied vomiting, diarrhea, palpitation, tremor or excessive sweating. He also denied use of over the counter medications or supplements.

PMH: gall bladder polyp, colon polyp, hyperuricemia

FH: Father: hypertension, DM, emphysema, angina pectoris, Grandfather: liver cancer
    Mother: subarachnoid hemorrhage
Case

SH: occupation: high school teacher, smoking: 20 cigarettes/day (20 y.o. ~ 45 y.o.)
   alcohol: none

Medications:
Ursodeoxycol 100mg twice daily
Vitamin B 2
Sustained release potassium chloride 2400mg twice daily
Allopurinol 100mg once daily
Physical Examination

Height 163 cm, BW 76 kg
Well nourished, not in acute distress
BP 136/86 mmHg, HR 66/min, regular
Neck: no goiter
Lung: clear to auscultation
Heart; normal S1, S2 without murmur
Abdomen: soft and flat, normal bowel sound, no bruit
Extremity: no edema
Skin: moist, no rash
Question

What test is the first step in differential diagnoses of hypokalemia?

1. Plasma renin activity and plasma aldosterone concentration
2. Urine electrolytes
3. Arterial blood gas
4. Thyroid function tests
Answer

Rule out pseudohypokalemia.

“Pseudohypokalemia”

- Caused by potassium uptake by cells after venipuncture
- Usually seen in patients with many metabolically active blood cells, such as patients with acute myeloid leukemia
- Can be prevented by rapid separation of the plasma from the cells following venipuncture or storage of the blood at 4 °C before assay.
Answer

You eventually need to perform all the tests but the first step is to check urine electrolytes to determine if hypokalemia is from renal or extrarenal potassium loss.
<table>
<thead>
<tr>
<th>Laboratory Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABG</strong></td>
</tr>
<tr>
<td>pH 7.475</td>
</tr>
<tr>
<td>pCO2 42.8 mmHg</td>
</tr>
<tr>
<td>HCO3 31.1 mmol/L</td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>WBC 8400 /µl</td>
</tr>
<tr>
<td>Hb 16.8 g/dL</td>
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<tr>
<td>Hct 48.7 %</td>
</tr>
<tr>
<td>Plt 233 × 10³/µl</td>
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</tbody>
</table>
Laboratory Data

24 hour urine study
Na: 137 mEq/day
K: 137 mEq/day
Cl: 199 mEa/day
Ca: 26 mg/day
Cre: 1418 mg/day
Question

What are the possible causes of his hypokalemia?

1. Primary aldosteronism
2. Hypokalemic periodic paralysis
3. Diarrhea
4. Renal tubular acidosis
5. Diuretic abuse
6. Vomiting
7. Bartter syndrome
8. Gitelman syndrome
9. Liddle syndrome
Differential Diagnosis of Hypokalemia

Hypokalemia

$U_K < 10-20 \text{ mEq/L}$
$U_K < 15-30 \text{ mmol/day}$
$U_K:Ucr < 13 \text{ mEq/gCre}$
or $1.5 \text{ mEq/mmolCre}$

Intracellular shift

Metabolic alkalosis
Insulin
Periodic paralysis
Hyperadrenergic state

Extra-renal potassium loss

Diarrhea
Burn

Renal potassium loss

$U_K > 10-20 \text{ mEq/L}$
$U_K > 15-30 \text{ mmol/day}$
$U_K:Ucr > 13 \text{ mEq/gCre}$
or $1.5 \text{ mEq/mmolCre}$
Differential Diagnosis of Hypokalemia

Renal potassium loss

Metabolic alkalosis
- $U_{Cl} < 20$ mEq/L
- Vomiting
- Remote diuretic use

Metabolic acidosis
- Variable pH
- Mg deficiency
- Low~normal BP
- Bartter syndrome
- Gitelman syndrome
- Diuretics

Renal tubular acidosis
- $U_{Cl} > 20$ mEq/L
- Hypertension

Next page
Differential Diagnosis of Hypokalemia

$U_K>20$, metabolic alkalosis, $U_{Cl}>20$, hypertension

High PAC
- Low PRA
  - Primary hyperaldosteronism
- High PRA
  - Renovascular HTN
  - Malignant HTN
  - Renin-producing tumor

Low-normal PAC
- Glucocorticoid
- Cushing syndrome
- Liddle syndrome
**Answer**

Step1. His urine potassium was > 20 meq/L, 24 hour urine potassium 137mEq, urine K/Cre 139mEq/gCre →renal potassium loss

Step2. ABG showed metabolic alkalosis. →renal tubular acidosis is unlikely

Step3. His urine chloride was > 20 mEq/L. →vomiting is unlikely

Step4. He is not hypertensive. →Bartter syndrome, Gitelman syndrome, diuretic abuse are the consideration.
His PRA was 6.6 ng/ml/hr and PAC was 236.6 pg/ml. What is the most likely cause of elevated PRA and PAC?

1. He also has primary aldosteronism.
2. He also has renal artery stenosis.
3. He also has renin producing tumor.
4. Secondary aldosteronism from intravascular volume depletion.
Answer

4. Secondary aldosteronism from intravascular volume depletion.
Plasma renin activity (PRA) and plasma aldosterone concentration (PAC)

- Hypokalemia has to be corrected before measurements (hypokalemia suppress aldosterone).
- Many medications can affect the results.

<table>
<thead>
<tr>
<th></th>
<th>PAC</th>
<th>PRA</th>
<th>PAC/PRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I/ARB</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>β- blockers</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>Diuretics</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Plasma renin activity (PRA) and plasma aldosterone concentration (PAC)

- Mineralcorticoid antagonists (spironolactone, eplerenone) has to be stopped 4-6 weeks before the test
- ACE, ARB, diuretics, beta-blockers may be acceptable. (See next slide.)
Initial aldosterone/renin ratio on antihypertensives among patient with proven aldosterone-producing adenoma

Table 2. Plasma Aldosterone, PRA, ARR, Potassium, and Medications for Each Patient With Adrenal Adenoma

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (y)/Sex</th>
<th>PA (ng/dL)</th>
<th>PRA (ng/dL/3 h)</th>
<th>Calculated PRA (ng/mL/h)</th>
<th>ARR (ng/mL/L+ng/mL/h)</th>
<th>K+ (mEq/L)</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48/F</td>
<td>17</td>
<td>&lt;50</td>
<td>0.16</td>
<td>102</td>
<td>4.3</td>
<td>HCTZ, 25 mg/d</td>
</tr>
<tr>
<td>2</td>
<td>60/F</td>
<td>19</td>
<td>&lt;50</td>
<td>0.16</td>
<td>114</td>
<td>3.9</td>
<td>Enalapril, 10 mg/d</td>
</tr>
<tr>
<td>3</td>
<td>65/F</td>
<td>19</td>
<td>&lt;50</td>
<td>0.16</td>
<td>174</td>
<td>4.0 (3.3)</td>
<td>Lisinopril, 20 mg/d, HCTZ/triamterene, 75/50 daily, Verapamil, 120 mg/d</td>
</tr>
<tr>
<td>4</td>
<td>60/F</td>
<td>67</td>
<td>106</td>
<td>0.35</td>
<td>190</td>
<td>3.5 (2.9)</td>
<td>Nifedipine, 30 mg/d, KCl, 30 mEq/d</td>
</tr>
<tr>
<td>5</td>
<td>40/F</td>
<td>36</td>
<td>&lt;50</td>
<td>0.16</td>
<td>216</td>
<td>3.3</td>
<td>Labetalol, 400 mg/d</td>
</tr>
<tr>
<td>6</td>
<td>47/M</td>
<td>40</td>
<td>&lt;50</td>
<td>0.16</td>
<td>240</td>
<td>3.9 (2.7)</td>
<td>Enalapril, 20 mg/d, Atenolol, 100 mg/d, HCTZ/triamterene, 75/50 daily</td>
</tr>
<tr>
<td>7</td>
<td>42/F</td>
<td>41</td>
<td>&lt;50</td>
<td>0.16</td>
<td>246</td>
<td>3.6</td>
<td>Furosemide, 40 mg/d, Nifedipine, 60 mg/d, Quinapril, 20 mg/d, Metoprolol, 200 mg/d, KCl, 20 mEq/d</td>
</tr>
<tr>
<td>8</td>
<td>50/M</td>
<td>41</td>
<td>&lt;50</td>
<td>0.16</td>
<td>246</td>
<td>3.3</td>
<td>Nicardipine, 60 mg 3 × d</td>
</tr>
<tr>
<td>9</td>
<td>49/M</td>
<td>42</td>
<td>&lt;50</td>
<td>0.16</td>
<td>252</td>
<td>3.5</td>
<td>Labetalol, 200 mg 2 × d, Verapamil, 240 mg 2 × d, Phenoxybenzamine, 10 mg 3 × d (spironolactone, 50 mg 2 × d)</td>
</tr>
<tr>
<td>10</td>
<td>54/F</td>
<td>53</td>
<td>&lt;50</td>
<td>0.16</td>
<td>318</td>
<td>2.8</td>
<td>Enalapril, 10 mg 2 × d, KCl, 40 mEq every 4 h</td>
</tr>
</tbody>
</table>
Sensitivity/Specificity

Aldosterone/renin ratio of 40 (ng/dL/ng/ml/hr) gives the sensitivity of 100 % and specificity of 85 %

(off diuretics, ACE-I/ARB, beta-blocker)

Be careful of unit for aldosterone.
10pg/ml=1ng/dL

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Plasma renin activity (PRA) and plasma aldosterone concentration (PAC)

- The values need to be interpreted in the clinical context.
Case

The patient denied any use of diuretics. He is a school teacher and does not seem to have access to diuretics.

Bartter syndrome and Gitelman syndrome are considered. How can you differentiate these two syndromes?
Genetic defect in Bartter syndrome

Genetic defect in Gitelman syndrome
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene affected</th>
<th>Gene product</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartter syndrome type I</td>
<td>SLC12A1</td>
<td>NKCC2</td>
<td>Antenatal Bartter syndrome (hyperprostaglandin E syndrome)</td>
</tr>
<tr>
<td>Bartter syndrome type II</td>
<td>KCNJ1</td>
<td>ROMK</td>
<td>Antenatal Bartter syndrome</td>
</tr>
<tr>
<td>Bartter syndrome type III</td>
<td>CIC-Kb</td>
<td>CLC-Kb</td>
<td>Hypochloremia, mild hypomagnesemia, failure to thrive in infancy</td>
</tr>
<tr>
<td>Bartter syndrome type IVA</td>
<td>BSND</td>
<td>Barttin (B-subunit of CLC-Ka and CLC-Kb)</td>
<td>Antenatal Bartter syndrome (hyperprostaglandin E syndrome) and sensorineural deafness</td>
</tr>
<tr>
<td>Bartter syndrome type IVB</td>
<td>CIC-Ka and CIC-Kb</td>
<td>CLC-Ka and CLC-Kb</td>
<td>Antenatal Bartter syndrome (hyperprostaglandin E syndrome) and sensorineural deafness</td>
</tr>
<tr>
<td>Bartter syndrome type V</td>
<td>CaSR gene</td>
<td>CaSR</td>
<td>Bartter syndrome with hypocalcemia</td>
</tr>
<tr>
<td>Giteiman syndrome</td>
<td>SLC12A3</td>
<td>NCC</td>
<td>Hypomagnesemia, hypocalcemia, growth retardation</td>
</tr>
</tbody>
</table>

Bartter and Gitelman syndrome

- Patients with Bartter syndrome would not respond to loop diuretics.
- Patients with Gitelman syndrome would not respond to thiazide diuretics.
## Furosemide loading tests

Furosemide 20mg iv

<table>
<thead>
<tr>
<th>Time</th>
<th>Before</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
<th>80 min</th>
<th>100 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume (L)</td>
<td>0</td>
<td>0.15</td>
<td>0.14</td>
<td>0.14</td>
<td>0.5</td>
<td>0.45</td>
<td>0.35</td>
</tr>
<tr>
<td>Urine Na (mEq/L)</td>
<td>80</td>
<td>27</td>
<td>31</td>
<td>32</td>
<td>107</td>
<td>106</td>
<td>102</td>
</tr>
<tr>
<td>Urine K (mEq/L)</td>
<td>26</td>
<td>14</td>
<td>11</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Urine Cl (mEq/L)</td>
<td>90</td>
<td>32</td>
<td>34</td>
<td>34</td>
<td>102</td>
<td>101</td>
<td>95</td>
</tr>
<tr>
<td>Urine Cre (mg/dL)</td>
<td>34.4</td>
<td>20.6</td>
<td>14.2</td>
<td>14.5</td>
<td>5.4</td>
<td>4.5</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Thiazide loading test

Trichlormethiazide 8mg po

<table>
<thead>
<tr>
<th>Time</th>
<th>Before</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
<th>150 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Volume (L)</td>
<td>0.13</td>
<td>0.15</td>
<td>0.14</td>
<td>0.2</td>
<td>0.15</td>
<td>0.23</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Urine Na (mEq/L)</td>
<td>29</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Urine K (mEq/L)</td>
<td>43</td>
<td>18</td>
<td>15</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Urine Cl (mEq/L)</td>
<td>51</td>
<td>23</td>
<td>20</td>
<td>18</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Urine Cre (mg/dL)</td>
<td>54.2</td>
<td>19.2</td>
<td>13.4</td>
<td>12.8</td>
<td>13.6</td>
<td>14.6</td>
<td>14.4</td>
<td>14.3</td>
</tr>
</tbody>
</table>
Diagnosis

Gitelman Syndrome