Severe hypokalaemia in a Chinese male


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Summary

A 34-year-old Chinese man developed acute, severe, generalized muscle weakness while mountaineering. In the Emergency Department that morning, the most striking abnormalities were flaccid paralysis of both upper and lower limbs and a plasma potassium (K⁺) concentration (P_k⁺) of 1.7 mmol/l. To explain the basis for this constellation of findings, an imaginary consultation was sought with Professor McCance, the legendary integrative physiologist. Using both a deductive and a quantitative analysis, he illustrated that a simple story of an acute shift of K⁺ into cells was not sufficient to explain the patient’s hypokalaemia. The clue he used to suspect a large total body deficit of K⁺ was a higher than expected rate of K⁺ excretion on the initial spot urine (higher than expected ratio of K⁺: creatinine in the urine). This interpretation was supported by the fact that the patient needed a large supplement of K⁺ to raise his P_k⁺ to just under 3 mmol/l. It was only after more detailed studies based on urine chemistry that an accurate diagnosis and effective treatment could be instituted. The final question was why one of the hallmarks of the diagnosis of hyperaldosteronism (hypertension) was absent, yet hypokalaemia was so severe.

Introduction

This is the fourth article in our series on the application of principles of integrative physiology at the bedside that begins with a problem in the fluid, electrolyte, acid-base, and/or energy-metabolism area. Once again, our consultant is Professor McCance, an integrative physiologist who practiced medicine more than 50 years ago. His focus is on concepts—additional data are sought only when necessary. He relies on a quantitative analysis based on whole-body physiology to formulate a broad-based differential diagnosis and a specific plan for therapy (Table 1). Although he uses information that was primarily present during his lifetime, McCance often seeks information from both consultants in his era and from today’s physicians who have a background in molecular medicine. Using all of this information, his goal is to make a more accurate diagnosis and to optimize therapy for the patient.

The consultation

Professor McCance was asked to help with the care of a 34-year-old Chinese man who had developed severe weakness while climbing a mountain that morning. The patient denied taking medications or drugs of any kind. In the Emergency Department,
there were no abnormal physical findings other than flaccid paralysis of both the lower and upper limbs. His blood pressure was consistently close to 120/80 mmHg, and his heart rate was approximately 80 bpm. The most striking laboratory finding was a very low plasma potassium ($K^+$) concentration (PK) (1.7 mmol/l). As shown in Table 2, all the other laboratory tests were within the normal range. Suspecting that the diagnosis would be hypokalaemia periodic paralysis (HPP), McCance asked, ‘What are the expected laboratory findings on admission in a patient with HPP?’

Table 1  Principles of physiology in this case

<table>
<thead>
<tr>
<th>Physiology principle</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute hypokalaemia is usually caused by a shift of $K^+$ into cells</td>
<td>Renal or GI $K^+$ losses are very low. A caveat is that old urine may be in the bladder. The $[K^+]<em>{ECF}$ is 30–40×$[K^+]</em>{ICF}$. Cells have abundant open $K^+$ channels.</td>
</tr>
<tr>
<td>2. $K^+$ is held in cells by an inside negative voltage</td>
<td>Na-K-ATPase is upregulated by hyperthyroidism. Na-K-ATPase is activated by $\beta_2$-adrenergics or insulin. NHE is activated by insulin ± a high $[H^+]_{ICF}$.</td>
</tr>
<tr>
<td>3. Shift of $K^+$ can be caused by a large negative ICF voltage due to activation of the Na-K-ATPase or by providing a higher ICF Na$^+$ concentration</td>
<td>In chronic hypokalaemia, the urine should be virtually $K^+$-free (&lt;15 mmol/day).</td>
</tr>
<tr>
<td>4. There is no ‘normal’ urine composition</td>
<td>The usual urine K/Cr is 5 in mmol terms.</td>
</tr>
<tr>
<td>5. Creatinine is excreted at a constant rate</td>
<td>Both $[K^+]_{ECF}$ and flow rate in the CCD must be assessed. Aldosterone opens the ENaC to enhance this process.</td>
</tr>
<tr>
<td>6. $K^+$ excretion is regulated in the CCD</td>
<td>The $[K^+]<em>{CD} = [K^+]</em>{urine} U/P_{osm}$. TTKG should be &lt;2 with $K^+$ depletion.</td>
</tr>
<tr>
<td>7. The driving force for $K^+$ excretion is the negative lumen voltage caused by absorbing Na$^+$ more rapidly than Cl$^-$ in the CCD</td>
<td>Faster Na$^+$ absorption causes ↑ECFV and slower Cl$^-$ absorption causes ↓ECFV.</td>
</tr>
<tr>
<td>8. Separate fast Na$^+$ from slow Cl$^-$ absorption as a cause of renal $K^+$ loss by looking at ECF volume and the $U_{Na}$ and $U_{Cl}$</td>
<td>ECFV contraction causes low $U_{Na} \pm U_{Cl}$.</td>
</tr>
<tr>
<td>9. Aldosterone release is stimulated by ↑P$_K$ and ↓ECF volume (via ↑Aldo)</td>
<td>High P$_{Aldo}$ without a stimulus suggests primary aldosteronism.</td>
</tr>
<tr>
<td>10. Blood pressure = cardiac output × peripheral resistance</td>
<td>Increased NaCl intake (and ↑ECFV) can usually occur with minimal ↑in BP.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Units</th>
<th>Plasma</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium mmol/l</td>
<td>140</td>
<td>46</td>
</tr>
<tr>
<td>Potassium mmol/l</td>
<td>1.7</td>
<td>10</td>
</tr>
<tr>
<td>Chloride mmol/l</td>
<td>104</td>
<td>40</td>
</tr>
<tr>
<td>Bicarbonate mmol/l</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Inorganic phosphate mmol/l (mg/dl)</td>
<td>0.7 (2.2)</td>
<td>–</td>
</tr>
<tr>
<td>Magnesium mmol/l (mg/dl)</td>
<td>0.8 (1.0)</td>
<td>–</td>
</tr>
<tr>
<td>Glucose mmol/l (mg/dl)</td>
<td>6.5 (107)</td>
<td>–</td>
</tr>
<tr>
<td>Urea (BUN) mmol/l (mg/dl)</td>
<td>5 (14)</td>
<td>–</td>
</tr>
<tr>
<td>Creatinine μmol/l (mg/dl)</td>
<td>100 (1.15)</td>
<td>3600 (40)</td>
</tr>
<tr>
<td>$K^+$/Creatinine mmol/l/mmol/l</td>
<td>–</td>
<td>2.8</td>
</tr>
<tr>
<td>Osmolality mOsm/kg H$_2$O</td>
<td>–</td>
<td>156</td>
</tr>
</tbody>
</table>

**Question 1. What are the expected laboratory findings on admission in a patient with HPP?**

**Physiology principle 1: an internal shift of $K^+$ is the most likely cause of acute hypokalaemia**

Return to the bedside: An acute shift of $K^+$ into cells is even more likely if there is an absence of factors that usually accompany a large $K^+$ loss (e.g. profuse diarrhoea or a very large urine volume). The key supporting laboratory evidence for a diagnosis of HPP is a very low $K^+$ excretion rate and the absence of an acid-base disorder in plasma. If an acid-base disorder is present, one should suspect that renal $K^+$ wasting is a major component of the process leading to the very low $P_K$. Because the urine $K^+$ concentration ($U_K$) was 10 mmol/l and the plasma acid-base parameters were in the normal range in our patient (Table 2), the presumptive diagnosis was HPP.

While impressed with the reasoning of their Professor, the team wanted to know why it was so important to establish whether HPP was present. After all, HPP is an extremely rare disorder and one for which there is little known effective therapy. These reservations were not off-putting to Professor McCance. He pointed out that if the paralysis was due to HPP, the goal for therapy would be to reverse
this internal shift of $K^+$ into cells while avoiding giving a large exogenous $K^+$ load because the latter would place the patient at risk of rebound hyperkalaemia. To emphasize this point, he reminded them of the word ‘periodic’ in the name HPP. The renal fellow then added a pertinent comment. It was recently reported that in the specific case of HPP due to hyperthyroidism, initial therapy with non-specific blockers of $\beta$-adrenergic receptors caused the $P_K$ to return to normal levels within 2–3 h. After removing the acute threat of a cardiac or respiratory emergency in this way, therapy could then be directed at the hyperthyroidism. Therefore little exogenous $K^+$ should be given to a patient with HPP. In contrast, if the low $P_K$ were due to a large total body deficit of $K^+$, large amounts of $K^+$ should be given as long as the $P_K$ was in the dangerously low range.

**Physiology principle 2: the vast majority (98%) of $K^+$ in the body is inside cells, with a ratio of ICF:ECF $K^+$ that is close to 35:1**

*Return to the bedside:* It is widely held that a very large deficit of $K^+$ (≈500 mmol) is required to cause the $P_K$ to fall to <2.0 mmol/l in an adult. Because there was no history of polyuria or a very large volume of diarrhoea as may occur with cholera, our Professor felt that the low $P_K$ was due to an acute shift of $K^+$ into cells. He then asked the team if any additional information was obtained from the history that could support a diagnosis of HPP.

**Question 2:** What information from the history could help support a diagnosis of HPP?

HPP often affects young adults. In Asians, its basis is usually secondary to hyperthyroidism, whereas it is a familial disorder in most instances in Western countries. When the family history was explored, none of our patient’s family members had these disorders. On clinical grounds, hyperthyroidism is more likely to be the cause of HPP if there is tachycardia and a high-normal or slightly elevated systolic blood pressure. Our patient did not have clinical or laboratory evidence to support a diagnosis of hyperthyroidism. Complementing his team on their careful clinical assessment, our Professor turned again to basic principles of physiology and asked, ‘What might cause an acute shift of $K^+$ into cells?’

**Question 3:** What might cause an acute shift of $K^+$ into cells?

**Physiology principle 3:** to cause $K^+$ to move across a semipermeable membrane, there must be a driving force and permeability (an open channel for $K^+$ in this instance)

*Return to the bedside:* The driving force is a more negative voltage in the ICF compartment. This voltage is created by pumping positive voltage in the form of the cation, sodium ($Na^+$) out of cells via the Na-K-ATPase (Figure 1). This electrogenic pump exports 3 $Na^+$ for every 2 $K^+$ that enter cells. The main activator of this Na-K-ATPase is a $\beta_2$-adrenergic agonist. On the other hand, insulin, by activating the $Na^+/H^+$ exchanger (NHE) in cell membranes, causes a rise in the concentration of $Na^+$ in the ICF compartment without changing the voltage (the ICF compartment does become more alkaline). This higher $Na^+$ concentration causes more $Na^+$ to be pumped out of cells in exchange for $K^+$ by the Na-K-ATPase. This effect of insulin helps prevent hyperkalaemia when $K^+$-containing food is absorbed. Therefore conditions where catecholamine levels are high, hyperthyroidism is present, or insulin levels might be high (a high carbohydrate intake) could provoke an acute shift of $K^+$ into cells. A quantitative analysis is also helpful. To lower the $P_K$ from 4.0 to 1.7 mmol/l in a 70 kg adult who has 15 l of ECF, one need only shift 35 mmol of $K^+$ into cells (15 l×2.3 mmol/l).

An acute shift of $K^+$ into cells could have been precipitated by the adrenergic response related to vigorous exercise (mountain climbing) performed on the morning of admission. This shift could have been magnified if he consumed a large quantity of carbohydrates because a rise in the plasma glucose

![Figure 1.](image-url)

**Figure 1.** Creation of a more negative voltage in cells. The circle depicts the cell membrane. The Na-K-ATPase pumps positive voltage out of cells causing a large inside negative voltage (−60 to −90 mvolts). This ion pump is activated by $\beta_2$-adrenergics. Insulin, by activating NHE in cell membranes (shown on the left), causes the electroneutral entry of $Na^+$ into cells and thereby more positive voltage exit via the Na-K-ATPase. $K^+$ exits cells through ion channels until the electrochemical equilibrium for $K^+$ is approached.
concentration ($P_{\text{Glu}}$) causes the release of insulin from $\beta$-cells of the pancreas\(^7\) (Figure 1). All of the above features could be exaggerated if our patient had a genetic lesion such as HPP or if he had chronic K\(^+\) depletion. While our focus has been on generating a more negative ICF voltage, fewer open K\(^+\) channels could contribute to a greater proportion of K\(^+\) remaining inside cells.

Although the lack of clinical information to support a diagnosis of HPP was mildly disquieting, our Professor stated that he was not unhappy about a tentative diagnosis of HPP. Nevertheless, he warned, ‘Beware, the acute discovery of a chronic condition does not make this an acute illness!’ ‘What would persuade you that our patient might have a chronic condition that helped to cause his low $P_{K}$?’ he asked.

**Question 4:** What would persuade you that our patient might have a chronic condition that helped to cause his low $P_{K}$?

**Physiology principle 4:** there are no normal values for the composition of the urine—there are, however, expected renal responses to a specific stimulus such as a low $P_{K}$

*Return to the bedside:* In a patient who has a low $P_{K}$ that is due to a prolonged and very low K\(^+\) intake or to non-renal and/or prior renal K\(^+\) loss, the urine should be virtually free of K\(^+\). In Professor McCance’s experience, this meant that a 24-h urine should contain <15 mmol K\(^+\). This impression was later confirmed by Huth and coworkers.\(^{10}\) One of the junior housestaff asked whether one could assess the rate of excretion of K\(^+\) in the Emergency Department rather than wait for the 24-h urine result. Professor McCance thought that this was possible and put the question to the team, ‘What simple tests are needed to indicate that our patient suffered from a chronic, ongoing renal K\(^+\) loss?’

**Question 5.** What simple tests are needed to indicate that our patient suffered from a chronic, ongoing renal K\(^+\) loss?

**Physiology principle 5:** one can assess the 24-h K\(^+\) excretion rate if one relates the $U_{K}$ in a spot urine to the concentration of a constituent of that urine that is excreted at a constant rate (creatinine)

*Return to the bedside:* The simplest way to determine the rate of excretion of K\(^+\) is to measure the urine flow rate and the urine K\(^+\) concentration in a second-voided urine (equation 1). Another way to measure it is to compare the rate of excretion of K\(^+\) to the rate of excretion of a constituent of the urine such as creatinine (Cr) that is excreted at a constant rate\(^{11}\) (equation 2).

$$K_{\text{excretion}} = \text{Flow rate} \times [K]_{\text{urine}}$$

$$K_{\text{excretion}} = [K]_{\text{urine}} / [Cr]_{\text{urine}}$$

Subjects on a typical Western diet excrete close to 1 mmol of K\(^+\) per kg body weight per day,\(^{10}\) while their rate of excretion of creatinine is approximately 0.2 mmol/kg body weight/day. Therefore the $U_{K}/U_{\text{Creat}}$ ratio is 5 in mmol terms. The data reported back from the lab revealed a $U_{K}$ of 10 mmol/l and a $U_{K}/U_{\text{Creat}}$ ratio of close to 3 in mmol terms (Table 2)—this value is appreciably greater than 1, the expected value in simple K\(^+\) depletion,\(^{12}\) so the rate of K\(^+\) excretion was appropriately high given the severe degree of hypokalaemia. This analysis begged the question, ‘What is the reason for the high rate of excretion of K\(^+\)?’

**Question 6:** What is the reason for the high rate of excretion of K\(^+\)?

**Physiology principle 6:** control of the excretion of K\(^+\) is exerted in the last nephron site that secretes K\(^+\)—the cortical collecting duct\(^{13}\)

*Return to the bedside:* There are two components to analyse with respect to K\(^+\) excretion (equation 1).

First, one must assess the concentration of K\(^+\) in each litre of fluid exiting the CCD ($[K^{+}]_{\text{CCD}}$). This process is electrically driven, and therefore depends on electrogenic reabsorption of Na\(^+\) via the epithelial Na\(^+\) channel (ENaC) in the luminal membrane of principal cells in the CCD (Figure 2). Thus control of K\(^+\) secretion must occur at a site with enough delivery of Na\(^+\) to ensure the excretion of all the K\(^+\) that was ingested. Since control mechanisms were developed in prehistoric times when K\(^+\) intake (fruits, berries) could be as high as ~400 mmol/day, the site of control of K\(^+\) excretion needs to have a delivery of at least 500 mmol of Na\(^+\) daily. Hence this site should be prior to the medullary collecting duct (MCD) (i.e. the CCD).

The second component of the K\(^+\) excretion formula is the volume of fluid traversing the terminal CCD.\(^{14}\) The best way to approximate this flow rate is to deduce it using the following assumptions (Figure 2). First, if the $U_{\text{osm}}$ is greater than the plasma osmolality ($P_{\text{osm}}$), vasopressin actions were sufficient to cause the CCD to be permeable to water. Therefore the luminal osmolality in the CCD equals that of the interstitial compartment around the CCD (or equal to the $P_{\text{osm}}$). Hence for every 300 mosmol excreted, 1 l traversed the terminal CCD.\(^{14}\)
change occurs when ENaC is in a more open configuration. The \([K^+]_{\text{CCD}}\) can be deduced as follows (equation 3). Because the CCD is the last nephron segment where the majority of K⁺ secretion is regulated, the only reason for a major change in the luminal K⁺ concentration between the terminal CCD and the urine will be as a result of water reabsorption in the MCD. The degree of this water reabsorption is reflected by the urine:CCD osmolality ratio, where the osmolality in the lumen of the CCD is assumed to be equal to the \(P_{\text{osm}}\) when vasopressin acts (Figure 2). The \([K^+]_{\text{CCD}}: [K^+]_{\text{plasma}}\) ratio is called the transtubular K⁺ concentration ratio (TTKG). Although his \(U_{\text{osm}}\) was not higher than his \(P_{\text{osm}}\), his \([K^+]_{\text{CCD}}\) should be similar to the \(U_{\text{osm}}\) or close to 10 mmol/l; 6-fold higher than his \(P_K\). Moreover, in a K⁺-deficient subject without a stimulus for Na⁺ reabsorption in the CCD, this \([K^+]_{\text{CCD}}\) should be as low as the \(P_K\), because there should be no driving force to secrete K⁺ in the CCD. An inappropriately high \([K^+]_{\text{CCD}}\) will be found when Na⁺ is reabsorbed faster than Cl⁻ in his CCD.

**Summary to this point:** Given all this information, Professor McCance now believed that there were two separate processes that caused the severe degree of hypokalaemia with paralysis. There was an acute component of the picture, a K⁺ shift into cells. This was probably due to the actions of hormones rather than the genetic lesion of HPP: an adrenergic surge with exercise and insulin-induced activation of NHE. The second part of the picture was the abnormally high K⁺ secretion rate. Its basis required further definition. The housestaff were swayed by the logic of their Professor’s approach. They focused on the renal lesion and asked, ‘How could you separate faster reabsorption of Na⁺ from slower reabsorption of Cl⁻ as contributors to the lumen-negative voltage?’

**Question 7:** Is the K⁺ concentration inappropriately high in the lumen of our patient’s CCD?

**Physiology principle 7:** the driving force for K⁺ secretion in the CCD is a lumen-negative voltage and open K⁺ channels in the luminal membrane are needed for K⁺ permeability

*Return to the bedside:* When Na⁺ is reabsorbed faster than Cl⁻, the lumen of the CCD becomes more negatively charged (Figure 2). This voltage

**Question 8:** How could you separate faster reabsorption of Na⁺ from slower reabsorption of Cl⁻ as contributors to the lumen-negative voltage?

**Physiology principle 8:** when Na⁺ is reabsorbed faster than Cl⁻ in the CCD, the ECF volume should be expanded; furthermore, the urine can be free of Na⁺ and Cl⁻ when there is a deficit of NaCl

*Return to the bedside:* Because the physical examination cannot detect subtle changes in the ECF
decisions about this volume depend on more specialized tests such as measurements of the plasma renin activity. In general, with an expanded ECF volume, plasma renin activity should be low (Table 3). When the subject has a contracted ECF volume, the \( U_{Na} \) and/or \( U_{Cl} \) should be very low (Table 4). In contrast, with relatively slower reabsorption of Cl\(^-\) the ECF volume will be contracted and the urine will have abundant Na\(^+\) + Cl\(^-\) at this time.\(^{15}\)

Nevertheless, there is a time delay before the plasma renin activity will be known. Accordingly, Professor McCance looked for evidence of conditions that would cause hypokalaemia with renal K\(^+\) wasting. The major categories in the groups that would have high plasma renin activity include diuretic abuse, renal artery stenosis, and the inborn errors of metabolism that produce endogenous diuretic-like actions (Bartter’s or Gitelman’s syndrome). There is also a possibility of a rare renin-producing tumour. The housestaff had done much of the preliminary testing to eliminate some of these possibilities. For example, his urine was negative for diuretics, the plasma magnesium concentration was normal, his maximum \( U_{osm} \) was 850 mOsm/kg H\(\text{2}\)O, and his urine calcium/creatinine ratio was in the normal range. Similarly, to look for evidence to suggest conditions that cause hypokalaemia with a high K\(^+\) excretion and a low plasma renin activity, they had asked about the likelihood of developing an ACTH-producing tumour (e.g. a history of smoking, etc.) and the ingestion of licorice. Again, there was no evidence from the history or physical examination to support these diagnostic possibilities. The absence of hypertension or a positive family history made inborn errors such as Liddle’s syndrome, apparent mineralocorticoid excess syndromes (AME) or glucocorticoid-responsive hypertension (GRA) rather unlikely. At this point, McCance departed, asking to be notified when the laboratory results of the hormone tests were known.

Some time later: The team called Professor McCance with the results of the laboratory tests. The patient had a normal plasma cortisol level, a very low plasma renin activity, and a surprisingly high plasma aldosterone level. The very low plasma renin activity suggested that faster reabsorption of Na\(^+\) rather than slower reabsorption of Cl\(^-\) was the likely basis for his excessive excretion of K\(^+\). Because the plasma aldosterone level was elevated, he deduced that the renal K\(^+\) wasting was caused by open ENaC in the luminal membrane of principal cells of the CCD\(^{18}\) (Figure 2).

**Physiology principle 9:** if aldosterone levels in plasma are elevated despite the absence of stimulators for its release (a high \( P_K \) or angiotensin II), this suggests an adrenal adenoma or hyperplasia of the adrenal gland.

**Return to the bedside:** Professor McCance now needed help from his modern day colleagues to provide the details of how best to image the adrenal gland. They advised him that if the adrenal adenoma was large, a CT scan could usually visualize the tumour, but a negative CT scan should

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**Table 3** Plasma renin and aldosterone in syndromes of mineralocorticoid excess

<table>
<thead>
<tr>
<th>Condition</th>
<th>Renin</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal gland lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>or tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH causes aldosterone synthesis (GRA)</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Kidney lesions: vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Kidney lesions: juxtaglomerular cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renin-secreting tumor</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Kidney lesions: principal cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liddle’s syndrome</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hereditary defect (AME)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>11(\beta)-HSDH fails to remove all cortisol Inhibition (e.g. licorice ingestion)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Saturated because of ectopic ACTH</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

For details, see text. AME, apparent mineralocorticoid excess syndrome; 11\(\beta\)-HSDH, 11\(\beta\)-hydroxysteroid dehydrogenase; GRA, glucocorticoid-responsive aldosteronism.

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**Table 4** Use of urine electrolytes in a patient with a contracted ECF volume

<table>
<thead>
<tr>
<th>Condition</th>
<th>Urine electrolyte</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na(^+)</td>
</tr>
<tr>
<td>Recent vomiting</td>
<td>High*</td>
</tr>
<tr>
<td>Remote vomiting</td>
<td>Low</td>
</tr>
<tr>
<td>Recent diuretics</td>
<td>High</td>
</tr>
<tr>
<td>Remote diuretics</td>
<td>Low</td>
</tr>
<tr>
<td>Diarrhoea or laxative abuse</td>
<td>Low</td>
</tr>
<tr>
<td>Bartter’s or Gitelman’s syndrome</td>
<td>High</td>
</tr>
</tbody>
</table>

*Urine concentration > 15 mmol/l; **urine concentration <15 mmol/l. In a patient with polyuria, the values for the concentrations of electrolytes in the urine will be much lower; the converse applies for a patient with oliguria. Use the urine to plasma creatinine ratio as a marker for water reabsorption throughout the nephron.
be followed-up by a more sensitive test such as magnetic resonance imaging (MRI). Our team proceeded directly to MRI, which revealed a 3-cm mass in the patient’s right adrenal gland, but this did not necessarily mean that the source of aldosterone was the adenoma. To prove this required the measurement of aldosterone levels in the blood draining each adrenal gland, or demonstration by immunohistochemistry that the tumour consisted of aldosterone-producing cells. Although somewhat controversial given the size of the adenoma, an adrenalectomy was performed using a laparoscopic approach. Two days after the surgery the team of physicians looked in on their patient in the surgical ward. They were standing around the bed, pleased with their management and the excellent response to surgery. Just then, they were joined by the surgical registrar and his intern who asked, ‘But why was this patient not hypertensive like all the others you’ve sent us?’

Our team lapsed into a slightly embarrassed silence as they realized that they had not even considered this excellent question. In retrospect, it was clear that most cases of primary aldosteronism were diagnosed in hypertensive patients with or without hypokalaemia, but to present with such a severe degree of hypokalaemia and not have hypertension was most unusual. In fact, no one could recall a single patient that had presented in this way! Never one to rely on anecdotal comments, Professor McCance asked the renal fellow to search the literature for similar case reports to our patient.

Result of the literature search: The renal fellow reported that primary hyperaldosteronism is the most common endocrine form of hypertension. The clinical and biochemical spectrum of primary hyperaldosteronism varies. Its most important clinical and biochemical features include hypertension, hypokalaemia, suppressed plasma renin activity, and an increase in aldosterone levels in plasma. Nevertheless, a normal Pk was found in 7–38% of reported cases, whereas a normal blood pressure was far less frequent. He found only 14 cases of primary hyperaldosteronism with a marked degree of hypokalaemia (Pk 2.4 ± 0.15 mmol/l, range 1.4–3.1 mmol/l) and absence of hypertension. Approximately 60% of these cases were described in Asians (primarily in Japanese patients). Their age range was 23–55 years, and 60% were female. No family history was noted. The presenting symptoms in most patients included hypokalaemia-induced neuromuscular manifestations. Of note, paraplegia or paralysis occurred in 50% of the cases. A typical biochemical and hormone profile of primary hyperaldosteronism was demonstrated in all patients.

Close to two-thirds of these patients had hypernatraemia (PNa 147 ± 1.7, n = 10). All but one had a unilateral adrenal adenoma. Almost all cases had a good response to spironolactone therapy prior to surgical removal of the adenoma. After surgery, the biochemical abnormalities were corrected and the blood pressure remained normal except for the development of hypotension in two cases.

Question 9. Why was this patient with primary hyperaldosteronism not hypertensive?

Physiology principle 10: blood pressure regulation is often discussed in the context of the formula depicted in equation 4

\[
\text{Mean arterial pressure} = \text{Cardiac output} \times \text{Total peripheral resistance}
\]

Return to the bedside: Perhaps, speculated McCance, our patient was fortunate in having low levels of vasoconstrictors and/or high levels of vasodilators so that NaCl retention led to ECF volume expansion (and he reminded them of the low plasma renin activity) which then suppressed angiotensin II (AII) while augmenting vasodilatory factors at the cost of no or only a marginally elevated blood pressure. He pointed out that many factors affect both the cardiac output and the peripheral resistance, and often in opposite directions. Therefore their effects on long-term control of blood pressure are, in general, small. In more detail, when aldosterone enhances the reabsorption of Na\(^+\) and Cl\(^-\) in the CCD, the ECF volume will increase until a new steady state is reached (this is called renal escape from the continuing NaCl retention of aldosterone). In effect, the expanded ECF volume depresses the reabsorption of Na\(^+\) and Cl\(^-\) at upstream sites in the nephron. A higher ECF volume would increase cardiac output and thereby blood pressure, if this were the only effect of an expanded ECF volume, but an expanded ECF volume suppresses the release of renin and thereby leads to the lower levels of the vasoconstrictor AII. This allows large increases in Na\(^+\) intake to be accommodated with minimal increases in blood pressure. Nevertheless, Professor McCance was not completely satisfied with this explanation, because virtually all patients with primary hyperaldosteronism have an expanded ECF volume and low AII levels, whereas only few have consistently normal blood pressure values. He reminded the group of the wide range of blood pressures within
the normal population, emphasizing that some people have much lower yet normal blood pressures. Moreover, a high salt intake, which expands the ECF volume, does not commonly cause the blood pressure to rise to hypertensive levels. In summary, McCance really could not explain this observation to his satisfaction. There is much more to learn about why certain patients are sensitive with respect to blood pressure response to an expanded ECF volume whereas others are not.

Course of his illness after adrenal surgery: After an adrenalec-tomy using a laparoscopic approach, the tumour was confirmed to be an aldosterone-producing adenoma. When seen in follow-up several months later, he was still normokalaemic without any KCl supplementation. The final diagnosis of Professor McCance was that our patient had primary hyperaldosteronism. His hypokalaemia and total body K⁺ deficit were due to the kaliuretic actions of aldosterone. More recent studies provided possible mechanisms that include a role for bicarbonaturia, the result of very low AII-stimulated reabsorption of NaHCO₃ in the proximal convoluted tubule. His extreme degree of hypokalaemia was probably the result of an acute shift of K⁺ into cells during vigorous exercise, a β-adrenergic effect that could have been augmented if he had eaten carbohydrates prior to that exercise (insulin release). Our Professor did not think that he had HPP, but this possibility could be revisited again if he developed another acute episode of weakness accompanied by a very low P₅.

Concluding remarks

The combination of a knowledge of integrative physiology, an awareness of the modern molecular information, and an ability to review the medical literature provided our modern-day physicians with a powerful set of tools to understand the basis of the disease in our patient and provided goals for its therapy. Nevertheless, this was not enough. As illustrated by our Professor, clinical experience, deductive reasoning, common sense, and a quantitative analysis were very valuable assets to be used at the bedside (Figure 3). Not only did this arsenal of tools lead to an accurate diagnosis, but it also pointed out some of the potential hazards of well-meaning therapy.

References


Appendix I: Case report

A 34-year-old Chinese male presented to the emergency department with the sudden onset of muscular weakness that progressed to paralysis involving all extremities. It started during vigorous exercise while he was climbing a mountain that morning. He was unable to walk for 4 h preceding admission. He did not have a history of similar episodes, and denied weight loss, change in bowel habits, palpitations, heat intolerance or excessive perspiration. Polyuria and nocturia had been noted for 1 week. On physical examination, he was found to have hypotension, tachycardia, and tremor. Laboratory investigations revealed a marked elevation in serum aldosterone levels, consistent with primary aldosteronism.

The patient was diagnosed with normotensive primary aldosteronism, a condition characterized by increased aldosterone production without hypertension. The underlying mechanism involves an adrenal adenoma that secretes aldosterone independently of renin-angiotensin system activation. The case highlights the importance of recognizing and treating this condition promptly to prevent progression to severe complications such as paralytic ileus and respiratory failure.
On physical examination, his initial blood pressure was 126/84 mmHg; heart rate 76 bpm; respiratory rate 14 breaths/min; and body temperature 36.9 °C. Head and neck examination was normal; his thyroid gland was not enlarged. Cardiopulmonary and abdominal examinations were unremarkable. There was a symmetric flaccid paralysis with areflexia in all extremities. Fasciculations, myoclonus, and muscular atrophy were not observed. The remainder of the physical examination was normal.

Hypokalaemia (1.7 mmol/l) was the most striking biochemical abnormality (Table 2). Although his U_K was low (10 mmol/l), his U_osm was 152 mOsm/kg H_2O. His U_K/U_creat was close to 3 mmol/mmol with the expected value being close to 1.\(^{12}\) Thyroid function studies, liver and lipid profiles were normal. His EKG revealed sinus rhythm (76 bpm) with prominent U waves. Abdominal sonography did not show any abnormality of the kidneys or the adrenal glands.

Intravenous administration of potassium chloride (KCl) at a rate of 10 mmol/h was given to treat his hypokalaemia and paralysis. His muscle strength increased, and he could walk when his P_K reached 2.7 mmol/l 16 h after starting KCl supplements. The total positive K balance was approximately 140 mmol at this time. He was then treated with oral KCl supplements (48 mmol/day) and spironolactone (75 mg/day). His systolic blood pressure ranged from 110 to 138 mmHg, and diastolic blood pressure from 70 to 86 mmHg. A Bartter’s-like syndrome was suspected initially based on the normal blood pressure, high urinary Na\(^+\), K\(^+\) and Cl\(^-\) excretion rates, and the absence of diuretic abuse or vomiting, but this diagnosis was abandoned when his P_K normalized (4.2 mmol/l) within two weeks and the result of his plasma renin activity became known.

Hormone studies revealed that plasma aldosterone was markedly elevated, with depressed renin activity and a normal cortisol concentration (Table 3), data suggestive of primary aldosteronism. Magnetic resonance imaging (MRI) of the adrenal glands delineated a mass lesion, about 3 cm in diameter, in his right adrenal gland. After adrenalectomy, the pathology confirmed an aldosterone-producing adenoma. He has been normokalemic for several months without KCl supplementation or spironolactone therapy.