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Osmotic demyelination syndrome: a potentially avoidable disaster

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Summary

Osmotic demyelination of the brain (ODS) is a dreaded complication that typically occurs several days after aggressive therapy for chronic hyponatraemia, but is eminently avoidable. In this teaching exercise, Professor McCance, an imaginary consultant, is asked to explain how he would have treated a 28-year-old female who had hyperkalaemia, hypoglycaemia, hypotension and hyponatraemia (118 mM) to prevent the development of ODS. He begins with a review of the physiology, including his own landmark work on chronic hyponatraemia associated with a contracted extracellular fluid volume. Adding quantitative analysis, the cause of the excessive rise in plasma sodium concentration is revealed, and a better plan for therapy is proposed.

Introduction

The central figure in this teaching exercise is an imaginary consultant, Professor McCance, who practiced medicine almost 70 years ago. His emphasis is both on concepts and a quantitative analysis. The overall objective is to demonstrate how an application of simple principles of integrative physiology at the bedside can play an important role in clinical decision-making (Table 1). The discussion focuses on a patient who had a very unfortunate outcome. Her physicians believed they had made an appropriate diagnosis and had treated her according to current recommendations.[1] But might the catastrophe have been avoided? They agonized over the case and re-examined all their therapeutic decisions, eventually asking their learned mentor, Professor McCance, to share his thoughts with them.

Consultation

A 28-year-old woman complained of progressive weakness and fatigue over the past 6 months. Her appetite was poor and she had a 3-kg weight loss. She vomited on several occasions, but denied taking diuretics. On past medical history, she had long-standing myasthenia gravis. The most striking findings on physical examination were a very low blood pressure (60/40 mmHg) and tachycardia (126 bpm) while lying flat. Her jugular venous pressure was low, and she did not have oedema. Because there was no evidence of blood loss, they believed that she had a markedly contracted extracellular fluid (ECF) volume. The concentrations of sodium (P_{Na}), potassium (P_K), chloride (P_{Cl}), and glucose (P_{Glu}) in plasma were 118, 8.1, 90, and 2.5 mmol/l, respectively (Table 2). Three emergencies, hyperkalaemia, hypoglycaemia and a very low ECF volume, were identified.

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Table 1 Summary of physiology principles

Physiology principle	Comment
1. K^+ is held in cells by an inside negative voltage	A gain in ICF K^+ is usually balanced by a loss of ICF Na^+ and/or H^+
2. K^+ excretion is regulated primarily in the CCD	Assess both the $[K^+]_{CCD}$ and flow $rate_{CCD}$
3. Corticotrophin releasing hormone (CRH) is a non-osmotic stimulus for ADH release	Suppressing CRH with cortisol may initiate a water diuresis
4. In the absence of vasopressin, urine flow rate is determined by distal volume delivery	Distal filtrate delivery falls when GFR is low or with avid upstream Na^+ reabsorption
5. Na^+ excretion should be minimal when ECF volume is low	Any Na^+ excretion is excessive with a low effective circulating volume
6. There are different mechanisms for Na^+ absorption along the nephron	Look for the other important functions of each segment to determine the site of the lesion
7. About 500 mmol Na^+ is delivered daily to the CCD in adult humans	Na^+ excretions > 100 mmol/day cannot be explained solely by Addison's disease. Expect a FE_{Na} of < 3% with CCD dysfunction
8. Na^+ is the major ECF osmole and Na^+ content therefore determines ECF volume	The ECF volume should be contracted if hyponatraemia is due to a Na^+ deficit
9. Examine the mass balances for both water and Na^+ to predict the change in P_{Na}	This simple but very useful tool is also called a 'tonicity balance'
10. The major danger with chronic hyponatraemia is ODS	The risk of ODS is greater in patients with hypokalaemia or malnutrition

Table 2 Serial plasma and urine biochemistry in a patient with Addison's disease

Hours...	0	8	12	24	48	72	96
Plasma							
Na^+ (mmol/l)	118	120	129	123	130	135	139
K^+ (mmol/l)	8.1	6.0	5.1	5.8	5.6	5.0	4.7
Cl^- (mmol/l)	90	94	92	93	95	98	101
HCO_3^- (mmol/l)	12	13	15	18	25	27	24
Anion gap (mEq/l)	16	13	21	12	10	10	14
Glucose (mg/dl)	45	81	148	182	166	140	112
Glucose (mmol/l)	2.5	4.5	8.2	10.1	9.2	7.8	6.2
BUN (mg/dl)	94	86	78	68	67	63	57
Urea (mmol/l)	34	31	28	24	24	23	20
Creatinine (mg/dl)	5.3	4.7	4.0	2.2	2.0	2.0	1.6
Creatinine (μmol/l)	461	409	348	191	174	174	139
Hgb (g/l)	146	128	116	112	108	99	103
Urine							
pH	5.0	5.0	4.8	5.3	6.1	–	–
Na^+ (mmol/l)	136	70	81	39	21	19	13
K^+ (mmol/l)	14	11	13	37	25	44	63
Cl^- (mmol/l)	134	68	82	59	40	–	–
U_{osm} (mOsm/kg H_2O)	438	–	–	–	–	–	–
Infused fluid over 1st 12 h	4.6 l isotonic saline						
Urine output over 1st 12 h	4.5 l, $U_{Na+K} = 80$ mM						

Issues related to hyperkalaemia

With a P_K of 8.1 mmol/l, the major concern was the high risk of a lethal cardiac arrhythmia. Because the only findings on her EKG were sinus tachycardia and minor peaking of the T waves, attention could be directed toward lowering her P_K quickly and beginning a diagnostic work-up. The presumptive diagnosis was Addison's disease and, because of the history of myasthenia gravis, an autoimmune basis was its most likely aetiology. The high P_K was mainly due to a reduced rate of excretion of K^+,

the consequence of a lack of renal actions of aldosterone, resulting in a whole-body K^+ surplus. A shift of K^+ out of cells could also be present at that time due to low insulin levels (insulin release was inhibited by hypoglycaemia and high α-adrenergic levels[2] in response to the low blood pressure) and metabolic acidosis.[3] Professor McCance always insisted on a quantitative analysis, and asked, '*How much K^+ must be retained to cause such a high P_K?*'

Question 1. How much K^+ must be retained to cause such a high P_K?

Physiology principle 1: To retain the usual amount of K^+ in cells, there must be a large, inside-negative voltage

For electroneutrality, the gain in ICF K^+ should be balanced primarily by the loss of intracellular cations (Na^+ and/or H^+).

Return to the bedside: Because the ICF Na^+ concentration is ~15 mmol/l and the ICF volume in this patient is ~20 l, she would normally have ~300 mmol of Na^+ in her ICF compartment. Loss of this entire ICF Na^+ content would permit entry of a maximum of 300 mmol of K^+ into her ICF compartment. Any additional K^+ retained would result in a large rise in the P_K if there were few H^+ exported from cells (Figure 1). From a therapeutic point of view, if she were to excrete ~50 mmol of K^+, her P_K might decline abruptly. Therefore, her attending physician attempted to raise the rate of K^+ excretion in this patient. Because there could also be a shift of K^+ out of cells due to a lack of insulin, they administered glucose, insulin, $NaHCO_3$, and isotonic saline (to re-expand her ECF volume) to reverse the putative K^+ shift. The next question was, '*What would be the fastest way to increase her rate of excretion of K^+?*'

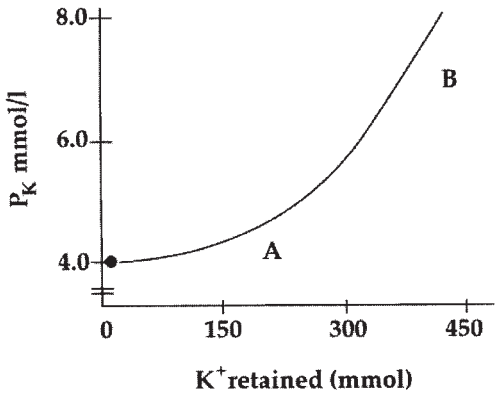

Figure 1. Relationship between K^+ retention and the P_K. For details, see text. In this schematic, the retention of close to 300 mmol of K^+ results in only a modest rise in the P_K (to close to 6.0 mmol/l) because cells still have abundant intracellular Na^+ (part A of the curve). A small additional rise in K^+ retention causes a sharp rise in the P_K (part B of the curve).

Question 2. What would be the fastest way to increase her rate of excretion of K^+?

Physiology principle 2: K^+ excretion is regulated in the CCD

Raising the urine K^+ concentration (U_K) and/or the urine flow rate can increase the excretion of K^+ (equation 1)

$$K^+_{excretion} = U_K \times \text{Flow rate}_{urine} \quad (1)$$

Return to the bedside: Because the actions of aldosterone to increase the net secretion of K^+ in the cortical collecting duct (CCD) require new protein synthesis (Figure 2),[4] the fastest way to increase the rate of excretion of K^+ is to increase the flow rate in this nephron segment. As discussed in a prior consultation in this series,[5] the flow rate in the terminal CCD is directly proportional to the rate of delivery of osmoles when vasopressin acts (equation 2).[6] Therefore, to achieve a high flow rate in the CCD, saline should be infused rapidly to re-expand her contracted ECF volume. Giving a loop diuretic along with the saline might speed up this effect.

$$\text{Flow rate}_{CCD} = \#\text{Osmoles excreted}/P_{osm} \quad (2)$$

The dangers of a water diuresis

The team was quick to point out that there had been no need to give a loop diuretic because of her 'good urine output' after saline was infused. They were somewhat surprised to notice that this 'good' response was a matter of considerable concern for their Professor, and wondered whether this might pose some danger to the patient.

Question 3. What major danger might be in store for the patient?

Physiology principle 3: One of the physiological stimuli for the release of vasopressin is a very low effective circulating volume

Return to the bedside: The stimulus for the release of vasopressin might disappear when her ECF volume was re-expanded. As a result, her urine

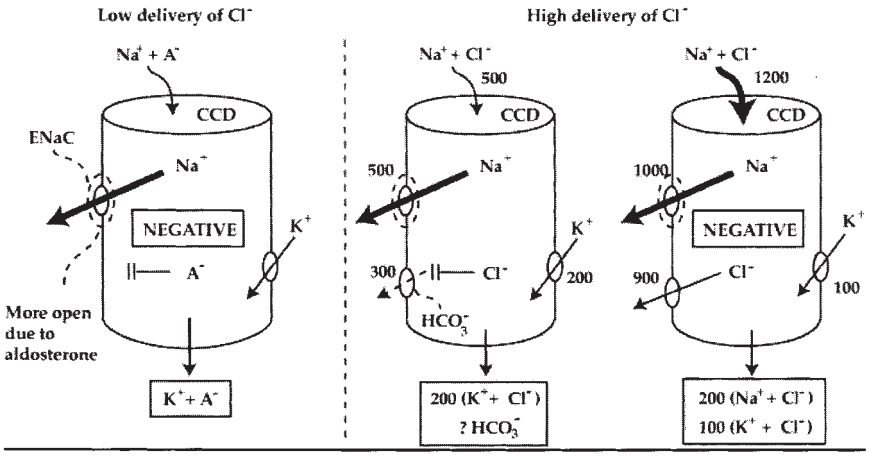

Figure 2. Secretion of K^+ in the cortical collecting duct. The barrel-shaped structure represents the CCD. A negative voltage is created in its lumen by reabsorbing Na^+ faster than Cl^-. Na^+ is reabsorbed when its specific ion channel (ENaC) is in an open configuration due to the presence of aldosterone. Cl^- reabsorption is slow if there is little delivery of Cl^- to the CCD (Na^+ is accompanied by another, non-absorbable anion, left of the dashed line), and Na^+ will be absorbed faster than Cl^- if Cl^- reabsorption is inhibited by HCO_3^- (centre), and/or if there is a very high delivery of Na^+ and Cl^- together with a larger capacity to reabsorb Na^+ as compared to Cl^- (far right).

volume could increase markedly and the urine Na^+ concentration (U_{Na}) plus U_K should fall to the 10–20 mmol/l range. As a result, there could be a rapid rise in her P_{Na}. However, there was another reason why the release of vasopressin could be suppressed in this patient when treatment was instituted (Table 3). '*What factor other than nausea and a low ECF volume might cause the release of vasopressin in a patient with adrenal insufficiency?*'

Question 4. What factors other than nausea and a low ECF volume might cause the release of vasopressin in a patient with adrenal insufficiency?'

Physiology principle 3 restated: In the absence of cortisol, the level of corticotropin releasing hormone (CRH) rises and CRH stimulates the production of vasopressin, independent of the P_{Na}

Because a rise in glucocorticoids should decrease CRH levels, it will remove this stimulator of vasopressin release.

Return to the bedside: Once the glucocorticoid was administered and the ECF volume was re-expanded, a large water diuresis should be anticipated. As a result, her P_{Na} could rise excessively. Our Professor was not finished with his physiological analysis. He asked the group one more question, '*Once vasopressin levels fall, what determines the urine flow rate?*'

Question 5. Once vasopressin levels fall, what determines the urine flow rate?'

Physiology principle 4: In the absence of vasopressin, the urine flow rate is determined by the rate of delivery of fluid to the distal nephron (Figure 3)

Return to the bedside: The volume of filtrate delivered distally should be very low in a patient with a severely contracted ECF volume. In this setting, the urine could become hypertonic even if vasopressin is not detected in plasma—this has been called 'trickle-down hyponatraemia'.[7] If a very large water diuresis developed, Professor McCance asked, '*What would your therapy be to prevent too rapid a rise in her P_{Na}?*'

Question 6. What would your therapy be to prevent too rapid a rise in her P_{Na}?

Physiology principle 4 restated: Vasopressin makes the distal nephron permeable to water and thereby prevents the excretion of dilute urine

Return to the bedside: When the urine output begins to rise appreciably, and if the osmolality (U_{osm}) is less than the P_{osm}, vasopressin should be given to prevent an excessive rise in her P_{Na}.[8] However, she did not appear to have a water diuresis because her U_{Na+K} was 80 mmol/l (accounting for a U_{osm} of 160 mOsm/kg H_2O). In addition, there should also have been an appreciable excretion of urea when

Table 3 Factors contributing to the development of ODS

1. Failure to regain lost osmoles in brain cells at the usual rate
   (i) Deficit of K^+
   (ii) Low availability of organic solutes due to malnutrition*
2. Overly rapid rise in P_{Na}
   (i) Administering fluid with a higher Na^+ concentration than her P_{Na} or $U_{Na} + U_K$*
   (ii) Adding KCl to isotonic saline
   (iii) Excreting dilute urine due to:
      (a) Suppression of vasopressin release
         Re-expansion of the ECF volume*
         Removal of non-osmotic stimuli such as pain, anxiety, nausea, vomiting*
         Administration of cortisol* or thyroid hormone
         Removal of a drug causing the release of vasopressin
         Improvement of metabolic lesion causing release of vasopressin (e.g. porphyria)
      (b) Raising distal flow rate
         Re-expansion of ECF volume*
         Diminished NaCl reabsorption in upstream nephron segment*
   (iv) Having a lower U_{Na+K} because of an osmotic diuresis (e.g. urea) when vasopressin acts*

For details, see text. *Factors that could have contributed to the development of ODS in this patient.

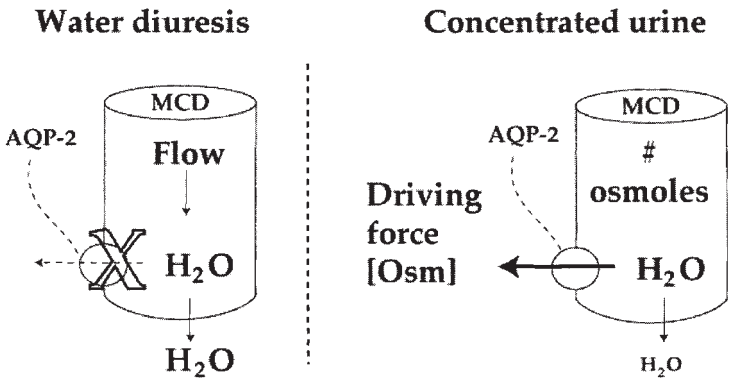

Figure 3. Determinants of the urine volume. The factors required for a water diuresis are shown on the left of the dashed line, and include closed aquaporin 2 (AQP) channels and a large distal flow rate. The factors required for concentrated urine are shown on the right of the dashed line, and include open aquaporin 2 (AQP-2) channels, a high medullary interstitial osmolality, and effective osmoles delivered to the collecting duct.

the GFR rose, making the U_{osm} be greater than her P_{osm}. The housestaff realized at this point that they should have measured the U_{osm}, but unfortunately, this was not done.

Satisfied that the team now fully appreciated the risks of a brisk water diuresis, Professor McCance shifted the focus to the unexpectedly high rate of excretion of Na^+.

Issues related to an excessive renal excretion of Na^+

Professor McCance took a moment to define what 'excessive' should mean with respect to the excretion of Na^+.

Physiology principle 5: The normal kidney can reduce Na^+ excretion to almost zero when there is marked ECF volume contraction

Return to the bedside: Important control mechanisms probably developed in Paleolithic times. The more important the function, the greater its control strength should be.[9] Moreover, multiple regulators might be needed for a high degree of control.[10] Because prehistoric diets were very low in Na^+ and because there are obligatory losses of Na^+ in sweat, almost no Na^+ should have been excreted in our ancestor's urine. This view is supported by current examples of isolated cultures who eat these diets.[11] In contrast, our current diets contain much more

Na^+.[12] This high intake of salt expands the ECF volume and reduces the renal reabsorption of Na^+. Therefore a specific rate of Na^+ excretion or a U_{Na} cannot define excessive excretion of Na^+.

This patient had an excessive excretion of Na^+, because it occurred when her ECF volume was contracted.[13] Professor McCance turned his attention to the rate of excretion of Na^+ prior to treatment, a time when her ECF volume was contracted. Although the baseline U_{Na} was 136 mmol/l, he needed an index of her urine or flow rate to calculate the Na^+ excretion rate. In the absence of a timed urine collection or a urine creatinine concentration,[14] the U_{osm} can be useful for this purpose. Because the U_{osm} was 438 mOsm/l, and because she could be expected to excrete 400–500 mOsm/day because of a poor dietary intake, he deduced that her Na^+ excretion rate on admission could have been 100–150 mmol/day if these assumptions are valid. This rate of Na^+ excretion was too large to represent a steady state value. In addition, in the first 12 h of therapy, she excreted 4.5 l of urine with a U_{Na} plus U_K of 80 mmol/l when saline was infused (Table 2). It was now clear to the team that this was more than could be expected from aldosterone deficiency alone, so they turned to McCance and asked, '*Why was the infused saline excreted so rapidly?*'

Question 7. Why was the infused saline excreted so rapidly?

Physiology principle 6: When the kidneys are normal, they reabsorb 99.5% of the filtered Na^+ on a typical Western diet

Failure to do so can be caused by the presence of an inhibitor of renal Na^+ reabsorption (e.g. ECF volume expansion or a diuretic), the lack of an anion accompanying Na^+ that the kidney is able to reabsorb (usually this anion is Cl^-), tubular damage, and/or a lack of a stimulator of renal Na^+ reabsorption (e.g. aldosterone deficiency).

Return to the bedside: Her rate of excretion of Na^+ after therapy began was close to 360 mmol in 12 h (80 mmol/l × 4.5 l). This can be extrapolated to 720 mmol/day, a value that is almost five-fold higher than the usual Na^+ excretion rate.[12] An explanation was needed for this enormous excretion of Na^+.

The patient denied the intake of drugs that inhibit the renal reabsorption of Na^+ (diuretics) and because the urine contained both Na^+ and Cl^- (Table 2), the patient seemed to lack a stimulator of renal Na^+ reabsorption, or had an endogenous inhibitor of renal Na^+ reabsorption. Urine and plasma samples had been sent for analysis and a therapeutic trial with intravenous cortisol begun. Although Professor McCance agreed with their strategy, he still felt strongly that there must be more to the case than just a lesion in the CCD, and asked the nephrology consultant to tell him about the modern natriuretic agents available today.

McCane was told that there are different mechanisms for the reabsorption of Na^+ in the major segments of the nephron (Table 4). Examining the urine for evidence of failure to perform essential functions of each nephron segment could reveal a basis for the excessive natriuresis.

Lesion in the proximal convoluted tubule (PCT)

Aside from reabsorbing 18 000 of the 27 000 mmol of filtered Na^+ each day, the PCT reabsorbs essential nutrients and ions that are filtered. The absence of a high rate of excretion of bicarbonate (HCO_3^-), glucose, phosphate, and amino acids in later urine samples suggested that she did not have an important defect in her PCT.

Table 4 Findings to define nephron site responsible for renal NaCl wasting

Nephron segment	Other major function	Findings if defect		Acid-base disorder
		Urine	Plasma	
PCT	Reabsorb valuable solutes	Glucosuria, phosphaturia, Aminoaciduria	Low P_{HCO3}, normal or low P_K	Metabolic acidosis
LOH	Concentrate the urine	U_{osm} Max = P_{osm}, high K^+ excretion	Low P_K	Metabolic alkalosis
DCT	Reabsorb Mg	High U_{osm} Max, high K^+ excretion	Low P_K, low P_{Mg}	Metabolic alkalosis
CCD	Excrete K^+ if aldosterone acts	Low excretion of K^+	High P_K	Metabolic acidosis

For details, see text. Max, maximum.

Lesion in the thick ascending limb (TAL) of the loop of Henle (LOH)

The LOH reabsorbs 8000 of the 9000 mmol of Na^+ delivered to it each day. The commonest agents that cause decreased reabsorption of Na^+ and Cl^- in the LOH are loop diuretics. Inborn errors involving key ion transporters in the mTAL give rise to a family of diseases called Bartter's syndrome (Figure 4). Cationic agents that bind to the calcium-sensing receptor (CaSR) on the basolateral aspect of cells of the TAL can also reduce the reabsorption of Na^+ and Cl^- in the LOH.[15]

Because this patient had a lower than expected U_{osm} when vasopressin was likely to be present, dysfunction of the TAL was a possible contributor to renal salt wasting (Appendix). However, the typical electrolyte abnormalities with lesions in the LOH include hypokalaemia with an excessive excretion of K^+ (Table 4) and this patient had an extremely high P_K with a low rate of excretion of K^+ (Table 2). Therefore, a defect in Na^+ reabsorption in the LOH could contribute to, but not be the sole reason for, her large Na^+ excretion rate.

Lesion in the distal convoluted tubule (DCT)

More than 96% of filtered Na^+ is reabsorbed upstream to the DCT. Approximately 1000 mmol of Na^+ are delivered to the DCT each day, and close to half of this is reabsorbed in the DCT in a normal adult. In addition, this nephron segment is the last major site for Mg^{2+} reabsorption. A defect in DCT function therefore presents with renal Na^+, K^+ and Mg^{2+} wasting causing hypokalaemia and hypomagnesaemia, features that were not present in this patient.

Lesion in the CCD

Physiology principle 7: Approximately 500 mmol of Na^+ are delivered daily to the CCD

The CCD is the nephron segment where aldosterone has its major physiological action, opening epithelial Na^+ channels (ENaC), and thereby causing accelerated reabsorption of Na^+.[16] Because electroneutrality must prevail, there are two major effects of Na^+ reabsorption by ENaC that depend on whether or not Cl^- is reabsorbed via its ion conductive pathway.[17] On the one hand, if little Cl^- is delivered to, or if Cl^- is reabsorbed more slowly than Na^+ in, the CCD, its lumen acquires a larger net negative voltage and this drives the net secretion of K^+ (Figure 2).[18] Two potential mechanisms contribute to this kaliuretic effect. First, the presence of an inhibitor of Cl^- reabsorption (HCO_3^- and/or an alkaline luminal pH[19]) in its lumen. Second, an alkaline luminal pH could increase the conductance of luminal K^+ channels in the CCD.

On the other hand, aldosterone will promote the electroneutral reabsorption of Na^+ and Cl^- in the CCD, if both Na^+ and Cl^- are delivered to the CCD, and the reabsorption of Cl^- is not limited by its permeability. Because only 500 mmol of Na^+ are delivered to the CCD each day, if there were no

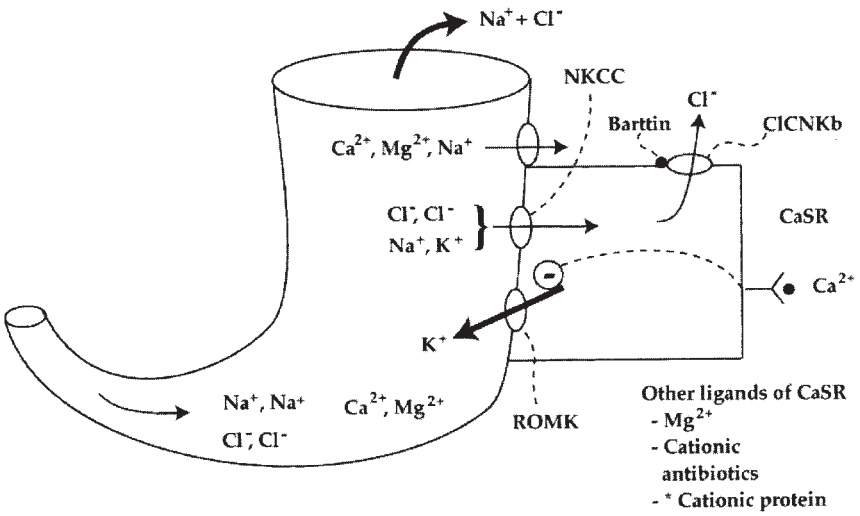

Figure 4. Transporter systems in the loop of Henle (LOH). The structure represents the LOH and its mTAL (thick ascending loop). There are three major ion transporters: the Na, K, 2 Cl-cotransporter (NKCC); a luminal K^+ channel (ROM-K); and a basolateral Cl^- channel (ClCNKb) with its Barttin modifier protein. The calcium-sensing receptor (CaSR) on the basolateral surface of the mTAL cell, when occupied, will lead to inhibition of the ROM-K. A possible site of action in this case is activation of the CaSR by one of the proteins associated with her autoimmune disease (shown by the *).

reabsorption of Na^+ in the CCD and downstream nephron segments, all 500 mmol would be excreted in the urine. This is less than 2% of the filtered load of Na^+ (27 000 mmol of Na^+/day)—called the fractional excretion of Na^+ (FE_{Na}).

Because the GFR should be reduced when the blood pressure is low, the filtered load of Na^+ will be much lower than normal in our patient with Addison's disease. Moreover, Na^+ reabsorption in the kidney should be stimulated when the ECF volume is low. In quantitative terms, because her P_{Creat} is elevated 6-fold (Table 2), her GFR should be roughly 1/6 of normal (20 vs. 120 ml/min) if there were a steady state. Therefore, her filtered load of Na^+ should be 118 μmol/ml × 20 ml/min or 2360 μmol/min when her P_{Creat} was so high. If each of the three following assumptions were true—the upstream nephron sites continued to reabsorb Na^+ in their usual proportions, there is no Na^+ reabsorption in the CCD, and a FE_{Na} of 2%—the expected Na^+ excretion rate would be 47 μmol/min. This is 1/10 of her observed rate of excretion of Na^+ (500 μmol/min, Figure 5) and suggests that she had an important defect in Na^+ reabsorption in an upstream nephron site as well as having a lack of mineralocorticoid actions in her CCD.

Return to the bedside: Professor McCance thanked the nephrology consultant for this illuminating update—it made his task extremely easy. He summarized his thoughts as to why so much of the infused Na^+ and Cl^- was excreted so rapidly. One reason was a lack of aldosterone-induced stimulation of Na^+ and Cl^- reabsorption in the CCD. Nevertheless, the rate of excretion of Na^+ and Cl^- was higher than anticipated due to a simple lack of aldosterone. Professor McCance homed in on the lower-than-expected U_{osm} in this patient in whom vasopressin was acting, and speculated whether one component of the renal Na^+ wasting might be due to partial inhibition of Na^+ and Cl^- reabsorption in the LOH. Because the patient had an autoimmune disease, it might be associated with abnormal plasma proteins. In addition, the concentration of these proteins should be higher when the plasma volume is very low. Moreover, if one of these circulating proteins was cationic, it could occupy the CaSR on the blood side of cells in the medullary TAL (Figure 4). He hastened to add that there were other reasons for the reduced concentrating ability (medullary interstitial damage and hyponatraemia itself[20]). At this point the medical team stated that the plasma concentration of the usual ligands for the CaSR, calcium (2.3 mmol/l) and magnesium (0.76 mmol/l) were in the normal range.

One other point needed to be clarified for the housestaff. They were unsure why the blood pressure failed to rise with the initial rapid infusion of isotonic saline. Professor McCance then reviewed some of his own work that had shown that a very large deficit of Na^+ (close to 1000 mmol or half of the ECF Na^+ content) did not result in hypotension in normal subjects. In contrast, hypotension was present in patients with adrenal insufficiency with similar or smaller deficits of Na^+.[21] Moreover, he pointed out that the rise in blood pressure in their patient was more closely related to the administration of cortisol rather than the saline infusion, suggesting that cortisol might have had a permissive role in increasing her blood pressure.

Issues related to hyponatraemia and its rate of correction

Because this patient developed the osmotic demyelination syndrome (ODS), attention was directed at whether her P_{Na} had risen too far, or too fast. The housestaff had set a maximum target for the rate of rise in her P_{Na}—12 mmol/l/day (0.5 mmol/l/h).[1] Although the patient's P_{Na} was monitored closely, its rise exceeded the target of 0.5 mmol/l/h in the

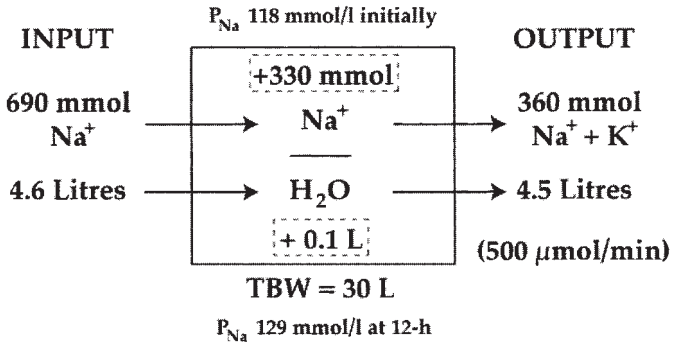

Figure 5. Basis for hyponatraemia as revealed by a tonicity balance. The rectangle represents the body with its P_{Na}. The inputs of $Na^+ + K^+$ and of water are shown on the left, while the outputs of $Na^+ + K^+$ and of water are shown on the right of this rectangle. Balances are shown in dashed boxes inside the rectangle.

first 12 h (Table 2). To reduce the risk of developing ODS, they decreased her P_{Na} over a period of hours by infusing hypotonic fluid to limit the rise in P_{Na} to 5 mmol/l in the first 24 h.[22,23] Nevertheless, she developed ODS. It seemed, therefore, that prevention of rapid correction is better than inducing a reduction in her P_{Na} once the therapeutic error was recognized. Based on the unfortunate outcome, they wished to know how Professor McCance would have proceeded.

Background for the plan of therapy suggested by Professor McCance

Our Professor briefly reviewed the concepts relevant to his strategy.

Concept 1: The P_{Na} is a ratio of the total quantity of Na^+ in the ECF compartment and the ECF volume (Figure 6). Therefore, hyponatraemia can be due to a Na^+ deficit and/or a surplus of water in the ECF compartment. When a deficit of Na^+ is the major cause for hyponatraemia, the ECF volume will be very contracted. In contrast, when there is a positive *balance* for water, there must have been both an input *and* a reason to minimize the renal excretion of water (actions of vasopressin).[8]

Concept 2: A fall in ECF tonicity causes water to move into cells, expanding the ICF volume (assuming that the number of effective osmoles does not decline, Figure 6). This is because cell membranes have aquaporin channels that permit rapid passage of water until osmotic equilibrium between the ECF and ICF compartments is restored.[24] An osmotic difference of just 5 mOsm/kg H_2O exerts a hydraulic pressure equal to the normal mean arterial blood pressure (i.e., one milliosmole exerts 19.2 mm Hg osmotic pressure).

Physiology principle 8: Na^+ is the major effective osmole and the Na content therefore determines the ECF volume

Corollary to concepts 1 and 2: There are two dangers to consider when a deficit of Na^+ is a major cause of hyponatraemia: a contracted ECF volume and an expanded ICF volume. For brain cells to retain their normal volume as the P_{Na} falls, they must export effective osmoles (Figure 6). Close to half of the effective osmoles that are lost in this setting are K^+ plus ICF anions, and the remainder are a family of small organic compounds.[25] When hyponatraemia is being corrected, to avoid shrinking brain cells excessively, these cells must reaccumulate the effective osmoles that were lost. Usually, it takes time to restore these ICF effective osmoles, so correction of chronic hyponatraemia should proceed slowly enough in *every* patient to prevent brain cell shrinkage and ODS.[1]

Concept 3: The acute discovery of a chronic condition does not make it an acute condition. Moreover, even with a chronic condition, a single set of laboratory data cannot tell you if the patient is in steady state.

Corollary to concept 3: If a lower initial P_{Na} were suspected prior to admission, it would be prudent to select a very slow rate of correction of hyponatraemia during the first day of therapy.

A simple plan

Several steps must be taken to construct a rational plan to treat a patient with hyponatraemia.

Step 1. Establish the duration over which hyponatraemia developed. Because this appeared to be a chronic process, the danger is too rapid a rise in the P_{Na}. Nevertheless, there was uncertainty in knowing that her initial P_{Na} represents a steady-state value because of the unexpectedly high rate of excretion of Na^+ on admission. This could be due to the intake of hypertonic salt prior to arriving at the hospital. Accordingly, the strategy of McCance was to select a much lower target for the rise in P_{Na}. He dispensed another 'clinical pearl'—a given rise in the P_{Na} is not a target to achieve; rather it is a *maximum* allowable value.

Step 2. A quantitative analysis of the basis of hyponatraemia is helpful to establish the mode of therapy. Decide whether to create a positive balance for Na^+ and/or a negative balance for water, based on estimates of the Na^+ content in the ECF compartment.

Step 3. Anticipate major threats that can develop during therapy and identify the earliest warning signs of their presence. In this respect, detecting a too rapid rise in the P_{Na} was of utmost importance. A pertinent question with respect to therapy was therefore, '*Can an infusion of isotonic saline cause her P_{Na} to rise very rapidly?*'

Question 8. Can an infusion of isotonic saline cause her P_{Na} to rise very rapidly?

Physiology principle 9. Mass balances for both Na^+ and water must be examined to determine whether the P_{Na} will rise

Professor McCance called this a tonicity balance (Figure 5).[8]

Return to the bedside: When a patient loses very little Na^+ and water, one need only compare the tonicity of the intravenous fluid to that of the patient to estimate its effects on body fluid tonicities and volume. Because this patient had a large urine

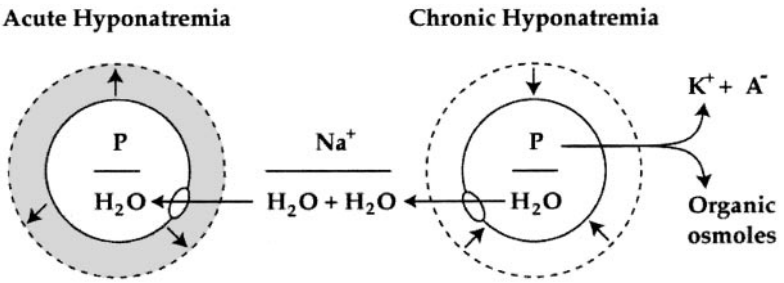

Figure 6. Defense of the ICF volume of the brain in chronic hyponatraemia. The solid circle represents the normal size of brain cells. Water can cross brain cell membranes through water channels and achieve osmotic equilibrium. The effective osmoles in the ECF compartment are Na^+ and its attendant anions Cl^- and HCO_3^-, whereas K^+ and organic osmoles are the particles (P) that are the major effective osmoles in cells. In acute hyponatraemia, shown on the left, brain cells swell, as shown by the shaded area and the dashed line. In chronic hyponatremia (shown on the right), most cells in the brain have decreased in size by exporting some of their effective osmoles, K^+ salts and small organic compounds.

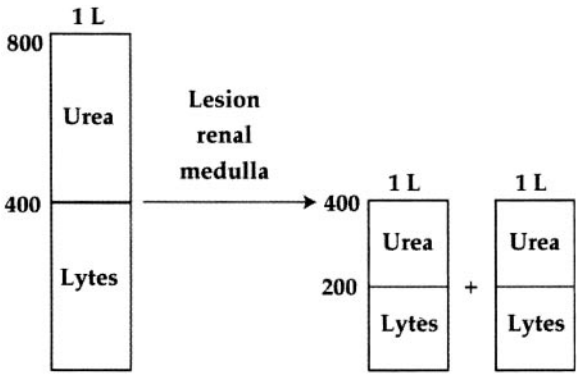

Figure 7. Exacerbation of polyuria by a lesion in the loop of Henle. The rectangle on the left represents 1 l of urine excreted when vasopressin acts and the medullary interstitial osmolality is in the 800 mOsm/kg H_2O range. Approximately half of the urine solutes are urea, and the other half are electrolytes (lytes). With a major concentrating defect limiting the maximum U_{osm} to 400 mOsm/kg H_2O as the only change, the urine volume will now be two-fold higher, with a U_{Na+K} in the hypotonic range as shown to the right of the arrow.

output, one must compare the tonicity and volume of the infusate to that of the urine. Although one would not expect an infusion of fluid with a Na^+ concentration only somewhat higher than the P_{Na} (in this case, isotonic saline) to change the P_{Na} by a large amount, nevertheless it did. The reason why the infusion of isotonic saline caused such a large rise in P_{Na} was revealed by examining both the volumes infused and excreted (differed by only 0.1 l) and the differences in the concentrations of $Na^+ + K^+$ in the infusate and the urine (difference of 70 mmol/l, Figure 5). There were two reasons why her U_{Na+K} was only 80 mmol/l after the saline infusion began, said Professor McCance (Table 2). First, the U_{osm} was much lower than expected in a patient who presumably had high vasopressin levels (Table 2), possibly because of non-specific damage to the medullary interstitium or because of occupancy of the CaSR by a cationic protein in a patient with a dysproteinaemia (Figure 4). Second, with a high plasma urea level (Table 2), there could be a large urea excretion rate when the GFR rises due to improved haemodynamic parameters. Thus with the same total U_{osm}, the greater the concentration of urea in the urine, the lower its U_{Na+K} must be (Figure 7).

In summary, this patient rapidly developed a positive balance of 330 mmol of $Na^+ + K^+$ and a positive balance of 0.1 l of water (Figure 5)—the former accounted for the 11 mmol/l rise in her P_{Na}.

Selecting the best rate of correction of the P_{Na} in this patient

The obvious goal is to prevent the development of ODS. '*What rate of correction of the P_{Na} should have been selected in this patient to minimize the risk of ODS?*' asked Professor McCance.

Question 9. What rate of correction of the P_{Na} should have been selected in this patient to minimize the risk of ODS?

Physiology principle 10. The major danger during the treatment of chronic hyponatraemia is the development of ODS

The maximum rate of rise in P_{Na} should be lower in this patient than in *every* patient who had ever developed ODS. The danger of ODS is probably much greater in patients who are malnourished and/or K^+ depleted.[26,27]

Return to the bedside: Since our patient had lost weight over the preceding months, she was likely to be malnourished. Because there was probably little danger associated with a P_{Na} of 118 mmol/l in an asymptomatic patient and because he was not

certain that her P_{Na} was not lower in the past 24-h, Professor McCance believed that she would be better off with little or no rise in her P_{Na}. His suggestion was simply to expand her ECF volume by having the net retention of 2–3 l of a solution that was isotonic to the patient on the first day in hospital, with no change in her P_{Na}. To achieve this latter aim, the tonicity of the intravenous solution should be equal to that of the urine (create a tonicity balance by infusing almost half-isotonic saline, Figure 5). From day 2, the goal would be to raise the P_{Na} by only 4 mmol/l per day because of her malnourished state. He would create a positive Na^+ balance of 120 mmol of $Na^+ + K^+$ (4 mmol/l × 30 l TBW) to achieve this daily rise in P_{Na}.

Concluding remarks

It should be clear from this case that carefully designed therapy is required if ODS is to be prevented. While all the physicians involved agreed that this patient had Addison's disease, on further analysis it appeared that the function of at least two nephron sites had been compromised. The first warning sign of this additional problem was a lower than expected U_{osm} and the second was a larger than expected natriuresis early in the course of treatment. Professor McCance suspected that there was a reduced reabsorption of Na^+ and Cl^- in the LOH. This LOH defect, along with a very high P_{urea}, would result in the excretion of urine with a lower tonicity than plasma (Figure 7). Because the composition of the intravenous fluid was not modified once her blood pressure and urine flow rate improved, her P_{Na} rose faster than expected. This could have been prevented by matching the tonicity and volume of the infusate to that of the urine (infusing close to half-isotonic saline).

The next major problem was to anticipate that once the ECF volume is expanded, nausea subsides, and cortisol is replaced, vasopressin might be suppressed and a rapid water diuresis may ensue. Moreover, re-expansion of the ECF volume will result in an increased distal delivery of fluid. If a water diuresis were to begin, the patient should be given vasopressin to prevent a rapid excretion of EFW.

The final point concerned selecting a target for the rise in P_{Na}. In a catabolic patient with malnutrition and chronic hyponatraemia, the maximum rate of rise of the P_{Na} should be close to 4 mmol/l/day (if the initial P_{Na} is truly a steady-state value). Based on the unfavourable outcome in this patient, Professor McCance said that he would now prefer to cause minimal or no rise in P_{Na} for the first 24 h in the absence of major symptoms related to hyponatraemia.

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Appendix

Case synopsis

A 28-year-old Chinese female was admitted to hospital because of generalized weakness, dizziness, multiple bouts of vomiting, progressive drowsiness and shortness of breath. She had lost at least 3 kg of weight. The past medical history included myasthenia gravis for 8 years that was treated with physostigmine. Pertinent negatives were the absence of psychiatric illness, the intake of other drugs, hyperlipidaemia or diabetes. Her family history was non-contributory.

On physical examination, she was drowsy but rousable. Her body weight was 50 kg. Blood pressure while lying flat was 60/40 mmHg, heart rate 126 beats/min, respiratory rate 24/min, and body temperature 37°C. The jugular veins were flat, and there was no oedema or ascites. Her skin was darkly pigmented, her mucous membranes were dry and her eyeballs sunken.

On laboratory examination (Table 2), she had evidence consistent with a low plasma volume (higher than expected haemoglobin and albumin levels: 4.4 g/l on admission and 3.3 g/l on day 3). Hyponatraemia (118 mmol/l) and hyperkalaemia (8.1 mmol/l), and a modest degree of metabolic acidosis (P_{HCO3} 12 mmol/l) were present. Her P_{Glu} was low (2.5 mmol/l). Urinalysis was normal, but her GFR was appreciably reduced, as reflected by high values for plasma urea and creatinine concentration. U_{osm} was 438 mOsm/Kg H_2O, U_{Na} was 138 mmol/l, U_K was 14 mmol/l, and her U_{Cl} was 134 mmol/l. Chest X-ray and abdominal sonography revealed no significant abnormalities.

Based on these findings, a clinical diagnosis of Addison's disease was made. This impression was confirmed later by the very low plasma aldosterone (15 pg/ml, normal 36–240 pg/ml), cortisol (4.2 g/dl, normal 6.9–25 g/dl) and markedly elevated adrenocorticotrophic hormone (ATCH) (150 pg/ml, normal 9–52 pg/ml).

She was treated with 4.6 l of isotonic saline along with glucose plus insulin in the first 12 h. Despite this treatment, the patient remained hypotensive for the first 4 h, until hydrocortisone (200 mg i.v.) was administered (blood pressure rose to 100/70 mmHg accompanied by a rapid rise in urine output). She excreted 4.5 l of urine during this 12 h period. Of note, her P_{Na} rose to 129 mmol/l (0.92 mmol/l/h) and her P_K decreased to 5.1 mmol/l (Table 2). Dextrose in water was substituted for normal

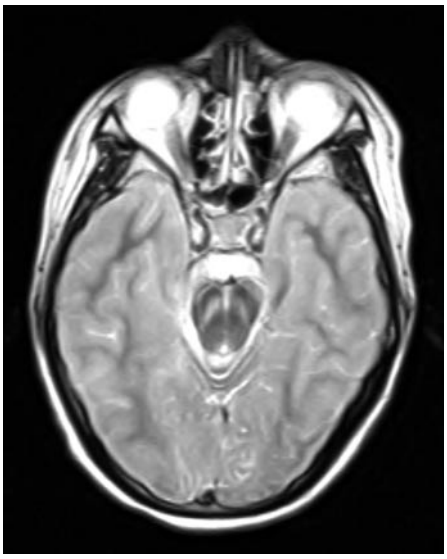

Figure 8. T2-weighted MRI of the brain. Notice the symmetrical areas of increased signal intensity in the pons, indicative of osmotic demyelination.

saline to lower her P_{Na} to 123 mmol/l in the next 12 h period. In subsequent days, the correction rate for hyponatraemia was set at 6–8 mmol/l per day.

Course in hospital

The clinical symptoms improved initially with this therapy. Alarmingly, on day 4, the neuro- logical status of the patient deteriorated. She became confused, irritable, and was hypertalkative. That night she became unresponsive. Acute respiratory failure and hypoxia were evident on day 5. ODS was confirmed by T2-weighted magnetic resonance imaging (MRI) of the brain which showed areas of increased signal intensity in the anteriolateral portions of both thalami, pontine, midbrain, basal ganglion, and external capsule areas (Figure 8). Currently, the patient remains in a vegetative state with frequent attacks of myoclonus.