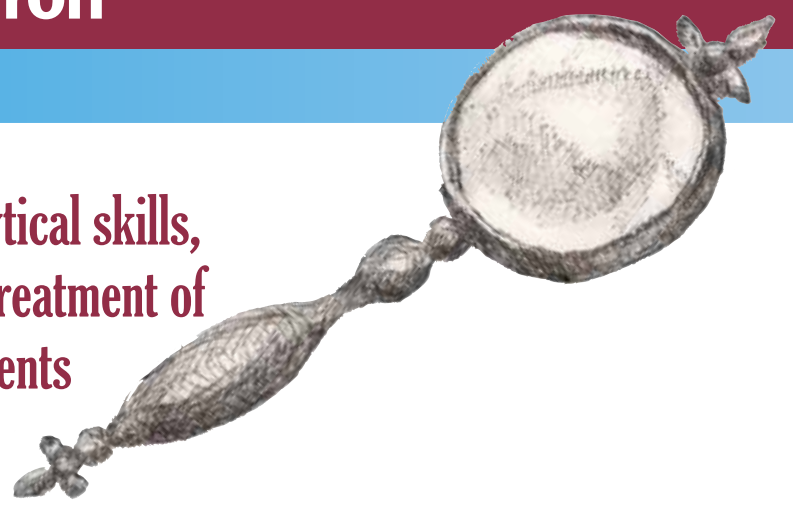
Detective Nephron



Detective Nephron, world-renowned for expertise in analytical skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the consultant.

Ms. Curious Tubule enters the room along with L.O. Henle to present a case.

Nephron My apprentice, what do you have for me? And we have our medical student back. Good!

Henle and Tubule look at each other.

Henle I have a patient with a potassium level of 1.8 mmol/L.

Nephron *(chuckling)* Hmm. That is really low. Can the patient walk?

Tubule *(confidently)* No, that is why this 43-year-old woman is here with profound lower extremity weakness leading to being bedridden for the past 2 days.

Nephron That's always the problem. Figuring out the cause is more important. I am assuming the medical team has started replacing her potassium. What do you think is causing all this?

Henle Broadly speaking, hypokalemia can result from potassium losses or translocation.

Nephron Good place to start.

Tubule *(curiously)* Can you elaborate on translocation?

Nephron Good! And?

Henle Well, translocation refers to shifting of potassium into cells. This can result from two major mechanisms. The first is from increased work of Na-K ATPase, which can be noticed in patients with hyperinsulinemia. This is also the reason why patients in refeeding syndrome can become hypokalemic. An increase in β-2 adrenergic activity also increases the activity of this pump, leading to hypokalemia. The second mechanism is stimulation of the cellular H+ and K+ exchange that can be sometimes seen in alkalemia leading to potassium being pumped into the cells and hypokalemia. Also, sometimes in leukocytosis (e.g., in acute myeloid leukemia), there may be uptake of potassium by the leukocytes, leading to pseudohypokalemia.

Tubule Also, I have heard that increased blood cell production, as seen in treatments with folate and vitamin B12 for anemia and GM-CSF for neutropenia, can result in hypokalemia.

Henle I doubt this patient has any of them, because the leukocyte count, hemoglobin, and platelets are completely normal. She has been eating a regular diet, has normal blood glucose levels, and has not recently been using β-2 adrenergic agents. She really didn't have many symptoms except for this weakness and perhaps some dry eyes and mouth for the past 3 months.

Nephron Good thought process. Since you've started, let us now complete the other side of the equation.

Tubule You mean potassium losses? Well potassium losses can be from extrarenal causes or renal causes.

Nephron Why don't we talk about her diarrhea?

Tubule She has none! She has no medical history for any such causes of nonrenal losses.

Henle I would consider moving to renal causes of losses, given that she has a non–anion gap metabolic acidosis, might I add.

Tubule Oh, I missed that part of her laboratory examination.

Nephron Did you confirm the metabolic acidosis with an arterial blood gas determination? A compensatory response *to* respiratory alkalosis can look exactly like metabolic acidosis, meaning a low serum bicarbonate. We need to see a low arterial pH to be sure.

Henle Yes, we did. Her pH was 7.21.

Tubule *(confidently)* In terms of renal losses, that's a long list.

Nephron Her 24-hour urine potassium must be more than 20 mmol.

Tubule Of course you can guess the number correctly. Actually, it was 41 mmol in 24 hours. Also, her urine pH is 6.5, and her random urine electrolytes are Na, 34 mmol/L; K, 21 mmol/L; and Cl, 35 mmol/L. Therefore, her urine anion gap is +20.

Henle Wait a second! Clearly, we know there are urinary losses here, and there is a positive anion gap, which suggests possibly a renal tubular acidosis (RTA), given that she had normal renal function. But there are other mechanisms we need to consider. Nephron: Please enlighten us, my friend.

Nephron Please enlighten us, my friend.

Henle I look at renal causes in physiology-based mechanisms. Increased distal sodium delivery as a cause of the K+ losses is one category (diuretics, vomiting, Bartter and Gitelman syndromes), but in those cases mostly there is some degree of alkalosis, which this patient lacks. I doubt this is Liddle syndrome, with increased epithelial sodium channel activity.

Nephron Do you want to know the magnesium level?

Henle Of course I do. That is another mechanism via decreased renal outer medullary potassium inward rectification.

Tubule And the magnesium was 1.02 mmol/L (2.5 mg/dL).

Nephron Is hypertension present?

Tubule No, which rules out increased mineralocorticoid activity increase (again mostly with some metabolic alkalosis).

Nephron It seems that a much more practical way to think might be to divide your causes with acidosis versus alkalosis. Isn't it? Let's stop listing all non–acidosis related causes, please!

Henle I think this is a distal RTA.

Tubule I think it is a proximal RTA.

Nephron Oh well, you will both have to defend your diagnoses.

Tubule The pathophysiology of hypokalemia in RTA is not well known, but given the degree of hypokalemia, I think this is too low for just a distal RTA.

Henle How do you explain the alkaline urinary pH then, in the absence of active treatment of a proximal RTA with bicarbonate? If you had proximal RTA in steady state, the distal component is still working, and you should be able to acidify the urine, but here your urine pH is high. Hence, I think this is a classic case of distal RTA.

Nephron In distal RTA, you are unable to excrete the daily acid load. In the absence of bicarbonate therapy, this results in progressive hydrogen ion retention. The serum bicarbonate levels are rarely below 10 meq/L. To enable you to make a diagnosis of distal RTA, the urine pH should be 5.5 or higher, the urine sodium concentration should be above 25 mmol/L, and the urine anion gap should be consistent with low rates of ammonium excretion (hence positive). The urine osmolal gap has been shown to be more useful, but I assume that wasn't done in this case.

Henle That is correct, and the serum bicarbonate was 15 mmol/L, which suggests against proximal RTA in this individual.

Nephron In proximal RTA, there is a reduced capacity to reclaim filtered bicarbonate in the proximal tubule. The serum bicarbonate concentration in untreated patients with proximal RTA is usually between 12 and 20 mmol/L. When the serum bicarbonate is low, virtually all of the filtered bicarbonate can be reabsorbed, and distal acidification proceeds normally, with a urine pH that is appropriate for the patient's diet.

Tubule Hmm... I guess this is distal RTA.

Henle Great. Let's go and treat her with repletion.

Nephron Stop by in a few days and tell me the cause of her distal RTA. It doesn't occur in isolation.

Tubule The major causes of distal RTA include autoimmune diseases, malignancy, and hypercalciuria. Perhaps we should look for those causes.

Henle Hmm…she did describe having dry eyes and mouth. What autoimmune diseases cause distal RTA?

Tubule I think she might have Sjogren syndrome (SS), which might complete the entire presentation: dry eyes, dry mouth, distal RTA.

Nephron Come back in 2 weeks, please.

Two weeks later

Henle Aggressive potassium repletion was initiated with combined oral potassium tablets and intravenous fluids. By day 2 of hospitalization, the patient reported marked improvement in overall strength, and her potassium had risen to 3.5 mmol/L. She was discharged on hospital day 6, receiving potassium replacement with potassium citrate.

Nephron Tubule, I am curious; what did you do next?

Henle (*jumping in*) We ordered a 24 hour urinary calcium concentration, and it was not elevated.

Henle We determined that the antinuclear antibody was speckled, and the antinuclear factor titer was 1:2560.

Nephron I see.

Tubule Perhaps this is lupus, so we got a double-strand DNA determination, and it was negative. Her normal lactate dehydrogenase level suggested against a malignancy. Her levels of Sjogren syndrome A at 518 AU/mL and Sjogren syndrome B at 530 AU/mL clinched the diagnosis of SS. A follow-up revealed a potassium level of 3.8 mmol/L and complete resolution of her previous symptoms.

Nephron Nice work, team!

Henle While it is common for patients with an established diagnosis of SS to have distal RTA, it is rare for patients to present with severe hypokalemia and acidosis as their initial presentation, especially in such a dramatic and severe manner.

Tubule Would we treat the underlying SS?

Nephron Good question; unlikely, if kidney function is normal. The indications for treatment of SS with steroids include symptoms (i.e., joint pain, dry mouth and eyes). There is evidence that steroids may resolve the distal RTA because it may be an antibody-mediated process that steroids can curtail, perhaps targeting the hydrogen ATPase pump in the distal nephron. It's a tough decision. Usually these patients do relatively well with potassium and alkali preparations like potassium citrate.

Nephron (*lecturing mode*) Again, from a single entity of hypokalemia you diagnosed a systemic illness. Remember, besides laboratory data and clinical acumen, you need a good history and physical examination because that will never be replaced! No online tool or laboratory test is going to give you the most information as well as the patient can!

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