Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron It's been a while, Mac. What do you have for me?

Mac I have a 67-year-old man with a serum sodium (Na) of 120 mEq/L.

Nephron (*excited*) Whoa! Finally...electrolytes stuff!

Mac Trust me, you are going to love this one. You are like a child when it comes to hyponatremia.

Nephron Did you know that hyponatremia is the most searched item on UpToDate.com?

Mac Hmm…. I can totally relate to that.

Pause

Mac This man in his 60s has diabetes mellitus and a history of some form of autoimmune pancreatitis and…

Nephron Stop! Nice! What an amazing topic. Nephrologists love and hate hyponatremia. I think it is just fascinating. Is he symptomatic?

Mac (*laughing out loud*) No, not really. Interestingly, his kidney function is normal; his serum osmolality is 290 mOsm/kg.

Nephron (*angry*) Oh, come on! You are spoiling the fun! So, are you telling me this is not true hyponatremia?

Mac (*surprised*) I thought you love esoteric stuff! The way I categorize hyponatremia is based on serum osmolality. If the serum osmolality is <275 mOsm/kg, I would assume that this is true *hypotonic* hyponatremia. If it is >275 mOsm/kg, then we are dealing with three forms of *hyponatremias*: isotonic, hypertonic, or hypotonic hyponatremia.

Nephron (*bored, rolling his eyes*) Oh yes! You just nailed an important forgotten concept: Plasma tonicity does not equate to plasma osmolality. Excellent! Plasma osmolality refers to the concentration of the particles dissolved in plasma, whereas plasma tonicity refers to the concentration of particles that have an osmotic effect and are able to pull water (effective osmolality). These are solutes that cannot cross cell membranes and have predominantly extracellular fluid distribution.

Mac Well, let's get the easy side done first. If this was true hyponatremia—hence, hypotonic hyponatremia—then I would look at the urine, I think, in two buckets: urine osmolality high > 100 mOsm/kg or urine osmolality low ≤ 100 mOsm/kg.

Nephron (*winking*) I am glad you are thinking what the kidney is thinking! If you have hyponatremia with a low plasma tonicity, then the kidney is doing the appropriate thing when the urine osmolality is low or in the ≤100 bucket. In other words, the urine is appropriately diluted for the hypotonic plasma. The kidney is trying to rid the body of excess water to correct the hyponatremia by dumping it out into the urine. Is this vasopressin dependent or independent hyponatremia?

Mac Independent, of course…don't be ridiculous! In this case, vasopressin or the anti-diuretic hormone (ADH) is low. Thus, water is not reabsorbed in the tubules, leading to a dilute urine.

Nephron (*laughing*) This brings three diagnoses to mind: low solute intake, such as tea and toast; beer potomania and primary polydipsia; and in patients with reduced kidney function. Hyponatremia, due to low solute intake, seems to correct very fast, as most people tend not to recognize that diagnosis.

Mac Urine osmolality in this patient was 340 mOsm/kg; urine Na was...

Nephron But wait! Why? Why? Why? You don't need to go there yet. You had told me his serum osmolality was 290…

Mac (*trying to remember*) Oh yes. You are correct…

Nephron (*jumps in*) Let's go back to your categorizing the hypotonic hyponatremia and if the urine osmolality was >100 mOsm/kg. This is vasopressin dependent!

Mac (*surprised*) Obviously! The serum Na is low, indicating there is little excess water, and the kidney is retaining more water because vasopressin is signaling it to do so. Now, we need to figure out why.

Silence

Mac Hmm...you are exactly correct! What do you think about checking the urine Na?

Nephron (*shocked*) Yes! And if it is low (<20 mEq/L), then you are dealing with a condition where vasopressin secretion is physiologically appropriate and caused by low effective arterial blood volume. This could be in the setting of volume depletion, heart failure, or cirrhosis.

Mac (*jumps in*) And, if the urine Na is >30 mEq/L or so, then you have a vasopressin secretion that is physiologically inappropriate, and you are dealing with endocrine disorders, such as cortisol deficiency and everyone's favorite: syndrome of inappropriate anti-diuresis (SIAD). They keep changing names in nephrology! Oh well, no more syndrome of inappropriate ADH (SIADH). Some use it still, and some don't. What's in a name?

Nephron So, let's get back to our case. That was a nice discussion so far.

Mac (*confidently*) The patient in our case has a serum osmolality of 290. I would think this is pseudohyponatremia.

Nephron Hmmm…. Not all the time. Remember, you had mentioned earlier that this depends on the tonicity. You can still have hypotonic hyponatremia even when the serum osmolality is >275 mOsm/kg, caused by the presence of ineffective osmoles, such as ethanol or urea, which distribute freely across the cell membrane and increase the osmolality but not the tonicity. Therefore, sometimes, a person with alcohol use disorder can be hyponatremic and have a normal serum osmolality (remember tonicity is not equal to osmolality).

Mac (*confused*) Good point. But when you have high serum osmolality, it is possible that the tonicity is also high, as seen in hyperglycemia or mannitol.

Nephron (*interrupting*) Excellent point! But when the serum osmolality and the tonicity are normal, then you have this entire category of iso-osmolar isotonic hyponatremia that is seen with paraproteinemia and hyperlipidemias.

Mac Although our patient has diabetes, his serum glucose is not high. He has no history of hyperlipidemia or hypertriglyceridemia, and a recent paraprotein workup was negative. There are no elevated serum-free light chains.

Nephron Is this serum Na real? Did you repeat the lipids and serum-free light chains?

Mac (*nodding*) Yes, the serum-free kappa light was 4.3 mg/dL, and lambda was 3.5 mg/dL with a normal ratio for the serum creatinine of 0.9 mg/dL. Total cholesterol came back at 1900 mg/dL. His lipid panel, however, demonstrated a high-density lipoprotein (HDL) level of 39 mg/dL and triglycerides of 299 mg/dL. Electrolytes on a repeat blood sample were checked simultaneously using the indirect ion-selective electrode (ISE) method and the direct ISE method. The serum Na was 136 mEq/L in the direct ISE method and 119 in the indirect ISE method.

Nephron (*puzzled*) Fancy stuff you did there! I am glad you did not start the patient on oral urea or hypertonic saline. By the way, urea has become a new favorite for nephrologists, more than vaptans. But I see a rise in the sodium glucose co-transporter 2 inhibitor in this field soon. Let's wait. I have only seen the trailer…waiting for the movie!

Mac So dramatic, you are!

Nephron Hahaha! On a serious note, does this patient have jaundice?

Mac and Nephron exit to visit the patient bedside.

Nephron Mac, bedside rounds are the best! Brilliant! You don't even have to touch the patient anymore (only see that he is yellow and jaundiced). Physical examination reminders needed in electronic health records, please!

Mac (*confused*) Yes, apparently, he has a biliary stricture.

Nephron Fascinating information. Please order a lipoprotein electrophoresis stat.

Mac You know, that's probably a send-out test and likely not going to be stat.

Nephron (*jumps in*) Yes, of course. Tell your team to stop checking serum Na levels, and if low, ignore them.

A few days later

Mac (*surprised*) Well, his total cholesterol was in the 1900-mg/dL range. Triglycerides were 239, very low-density lipoprotein (VLDL) was 140s, and HDL was very low, at a 5 range. The LDL X came back at a 1700 range. That was a very high value.

Nephron Fantastic! Lipoprotein X...makes sense. That is an LDL with a presence in the serum that is extremely specific for cholestasis. Phospholipids and unesterified cholesterol constitute the bulk of this molecule. Its lipid composition is like lipids found in normal bile but differs significantly from normal plasma lipoproteins. In cholestasis, bile lipoprotein refluxes into the plasma pool and binds to albumin to form this lipoprotein X.

Mac Does resolution of cholestasis coincide with improvement in hypercholesterolemia in most cases?

Nephron Yes, of course! Remember, this was your classic "pseudohyponatremia." Truly not real.

Low plasma Na in the context of normal tonicity is an analytical measurement artifact observed with increases in the solid fraction of plasma. Osmolality, measured by freezing-point depression, is not affected by such changes. Indirect ISE methods use diluted specimens and calculate electrolyte concentrations using a fixed factor based on normal plasma water content. In specimens with an increased solid fraction, the measured result is accurate. However, because the fixed factor used is not appropriate, an error is introduced, causing falsely low calculated results. Because direct ISE measures electrolyte concentrations in undiluted specimens, results measured by this method are not subject to the same artifact.

Silence

Nephron The presence of lipoprotein X should be considered in patients with obstructive jaundice and hyponatremia, particularly when results from routine lipid panels are confusing. Some gastrointestinal cancers affecting the gallbladder, causing obstruction and jaundice, can also do this.

A few days later

Mac (*winking*)

Nephron Yes, clearance of the obstruction and cholestasis resolved the serum Na.

Mac (*with excitement*) Yes! Yes!

Nephron (*laughing*) There you go again! Fascinating diagnosis, and treatment was to do nothing. Do no harm first, my friend. Do no harm. Let's have some NY style coffee today…. ■

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Coffee Drinkers May Have Lower Acute Kidney Injury Risk

Drinking at least two cups of coffee per day has a protective effect against acute kidney injury (AKI), reports a study in *Kidney International Reports*.

The analysis included 14,207 adults, aged 45 to 64 years, from the population-based Atherosclerosis Risk in Communities (ARIC) study. Coffee consumption was assessed at a single study visit using a semiquantitative food-frequency questionnaire and was evaluated for association with incident AKI.

Of the participants, 27% never drank coffee, 14% drank less than one cup per day, 19% drank one cup per day, 23% drank two or three cups per day, and 17% drank more than three cups per day. Several of the following health factors were associated with higher coffee consumption: absence of diabetes, lower body mass index (BMI), lower systolic and diastolic blood pressure, and higher daily energy intake. Estimated glomerular filtration rate (eGFR) was slightly lower for participants who drank more coffee.

Associations of coffee consumption with lower risk of AKI were significant for two to three cups and for three or more cups per day. The trends remained significant after adjustment for age, sex, race, education, daily energy intake, physical activity, smoking, alcohol use, diet quality, systolic blood pressure, diabetes status, anti-hypertensive therapy, eGFR, and BMI.

Coffee is widely consumed worldwide and has been linked to a wide range of health benefits. In a previous ARIC analysis, higher coffee consumption was associated with a lower incidence of chronic kidney disease.

Although emphasizing the need for more research, the investigators conclude, "Our data support chronic coffee consumption as an opportunity for cardiorenal protection through diet, particularly for the prevention of AKI hospitalizations or procedures" [Tommerdahl KL, et al. Coffee consumption may mitigate the risk for acute kidney injury: Results from the Atherosclerosis Risk in Communities (ARIC) study. *Kidney Int Rep*, published online ahead of print May 5, 2022. https://www.sciencedirect.com/science/article/pii/S2468024922013699]. ■