Disclosure of Interest

No interest conflicts to declare
Thank you very much Mr Chairmen and I would like to thank the organisation for the invitation to present on the differential diagnosis of hyponatremia.

So first off, I wanted to ask why the differential diagnosis of hyponatremia is important. I think as you've also seen in the previous presentation, it's an extremely heterogeneous disorder, it can be acute, chronic symptomatic, asymptomatic, transient, drug-induced or reflect an underlying disease. It's often a difficult diagnosis and therefore, error prone and there are diverse and sometimes opposite therapeutic options for example, fluid resuscitation versus fluid restriction. We've seen, and this is also supported by the literature including our own studies, that inadequate management often translates into poor outcomes. Remember these patients are not only admitted in your ward where I'm sure the management is good but they are throughout the hospital.
So, let's look at an imaginary patient. You can clearly see that this patient is hyponatremic because there's a relative excess of water in his extracellular fluid volume.

Phone rings: Serum sodium 115 mmol/l

1. Could it be an artefact? **Yes!**
2. Is it hypotonic? **Need additional lab**
3. Time course? **≤ or > 48h (if known)**
4. Symptoms? **Seizures or coma?**
5. History? **H2O? Heart/liver? Drugs?**
6. Urine biochemistry? **Urine osmolality & sodium**
7. Volume status? **Esp. if hypervolemic**

So, this is the way Mitch Halperin, one of my mentors, used to present his cases. The phone
rings, serum sodium 115 mmol/L, what are you going to do? What I would like to do is review the questions that I would ask in such a patient. First of all, remember that hyponatremia is not a disease, it's a laboratory diagnosis and therefore, you have to scrutinize each number that a lab gives you and ask yourself could it be and artefact? The answer is yes. Pseudohyponatremia still exists because all the samples you send off to the laboratory are being diluted and this dilution step assumes a normal distribution of the water and solid phase in blood and this assumption is no longer true in cases of hypertriglyceridemia, high protein levels or even high cholesterol levels. The second question to ask I think is, is this truly hypotonic hyponatremia? But to answer this question you would need additional labs. The time course is important, of course, and the arbitrary cut-off is 48 hours to distinguish acute from chronic hyponatremia but as you know, patients do not walk into the emergency room with their lab results of the previous 48 hours. So this in practice is often difficult to establish. So therefore, as professor Gross also told you, we often have to rely on symptoms but the difficulty with symptoms is that we've come to realize over the last few years more and more that the symptoms of acute and chronic hyponatremia largely overlap. So, my focus here would be on the really severe symptoms such as seizures and coma because in these incidences you're relatively sure that it would be acute hyponatremia. The history is important, of course. You would have to know if this patient has had excessive water intake, for example in primary polydipsia, underlying disease such as heart failure or liver failure and I believe it's very important to carefully analyse the drug history because there are so many drugs that can induce hyponatremia. Well, most of you will be nephrologists so the urine biochemistry is important, of course, and the two parameters that are helpful here are urine osmolality and urine sodium. Last but not least, I would assess volume status. Some of you may ask why not put this first? Well, I do believe it is important to assess volume status in all patients with hyponatremia. But we know from the literature that the sensitivity and specificity of this is very low, especially when you have to differentiate hypovolemic from euvoletic causes of hyponatremia. So, here, my focus would be especially on hypervolemia because this is easily distinguishable due to the presence of peripheral oedema.

So what is out there? What are the causes of hyponatremia that need to be differentiated? Well, the first distinction is to look at non-hypotonic causes of hyponatremia because there can be so-called effective osmoles that can either be endogenous or exogenous and the most common by far endogenous effective osmole is glucose. So hyperglycaemia is always important to exclude as a cause of non-hypotonic hyponatremia. But these effective osmoles can also be exogenous, for example, some of you may be familiar with the TURP Syndrome where during urological surgery irrigant enters the intervascular space and these irrigants are often effective osmoles and can attract water from the intracellular fluid compartment. There are other examples including mannitol, ethylene, glycol and sorbitol and also some radio contrast media. But by far the vast majority of causes are hypotonic causes and I won't go
through this list but you will recognise the most common causes of hyponatremia here.

So what would the requirement be for a diagnostic algorithm for hyponatremia? Well, first and foremost I believe it's important not to get lost, to be perplexed, disoriented or bewildered by the diagnostic algorithm.

More specifically, I believe the parameters should be evidence based and the laboratory parameters included should be readily available. I believe it is important to have an early triage of both non-hypotonic hyponatremia and acute hyponatremia and as mentioned, it should be easily digestible.
So I’m happy to be part of the European Guideline Development Group, which is a joint effort of the ERA-EDTA and the European Societies of Intensive Care Medicine and Endocrinology, and one of the products is a new diagnostic algorithm for hyponatremia. It looks like this. When you have a patient with hyponatremia, the first step we propose would be to exclude the non-hypotonic causes of hyponatremia. The next question we think is important to ask is if this patient is sure to have acute hyponatremia or has very severe symptoms that would make immediate treatment with hypertonic saline obvious and preclude waiting for further diagnostic work-up. If this is not the case, then the next parameter to assess we propose would be urine osmolality. If this below 100, you are sure that vasopressin, the water retaining hormone also called anti-diuretic hormone, is completely suppressed. This is an adequate response and if this is the case, you will enter a separate category of courses including primary polydipsia, low solute intake and beer potomania. If this is not the case, we propose to proceed with measuring urine sodium. If this is low and low is, of course, arbitrary but we set the cut-off at 30 mmol/l, your patient is likely to have a low effective arterial blood volume. This may mean two things, your patient could either be truly hypovolemic with a contracted intravascular and extracellular fluid volume. For example, if there is extra-renal loss of sodium for example in severe diarrhoea or your patient could have a contracted intravascular fluid volume but an expanded extracellular fluid volume as is the case in liver cirrhosis, heart failure or nephrotic syndrome. An important confounder here is a low sodium diet. If the urine sodium exceeds 30 mmol/L we believe the next question to ask would be is your patient on diuretics because these are such common drugs and they interfere with the interpretation with urine sodium. If not, then you’re lucky, you again have two possibilities, the patient could be truly hypovolemic for example, in primary adrenal insufficiency or the so-called cerebral salt wasting syndrome or if your patient is euvoletic, this is likely to be the syndrome of inappropriate anti-diuretic hormone secretion, which has its own set of diagnostic criteria. If not, then you’re not so lucky because then you should consider the diuretic as the cause of hyponatremia but, because it is a confounder, we believe you should still consider all the other causes as well.
So in summary, what to order? We believe it's important to order serum osmolality to exclude the non-hypotonic causes, glucose and potassium for example, hypokalaemia will point in the direction of diuretic use. Hyperkalaemia will point into the direction of adrenal insufficiency and urine sodium and osmolality as mentioned. Very important, sometimes you just don't know and then you could use the response to the instituted therapy as a diagnostic test. Other parameters are sometimes useful including the fractional sodium excretion in AKI, and uric acid as I will show in the next slide. Urine chloride is important if your patient has severe vomiting because this will generate an alkalosis with a natriuresis. So, in this situation, urine sodium can no longer be used to assess volume status but urine chloride can. Acid-base status to detect alkalosis in diuretic use or acidosis in diarrhea or adrenal insufficiency and I would have a low threshold for measuring cortisol or even doing a Synacthen test if adrenal insufficiency is considered. I'm not so convinced about the association between hypothyroidism and hyponatremia. So it's arguable if you would need to assess thyroid status.

"Roadtesting" on 121 cases

Utility and Limitations of the Traditional Diagnostic Approach to Hyponatremia: A Diagnostic Study

- Junior physicians with algorithm vs. senior physicians without algorithm vs. reference standard
- Diagnostic agreement: 71% (junior) vs. 32% (senior)
- Therapeutic consequences: 86% for junior (or 95% when volume status > FE\(\text{d}_{\text{UA}}\)) vs. 48% for senior
So, this algorithm that I just showed you, or a very similar one, was road tested by the group of Bruno Allolio and his colleagues on 121 cases. They actually had a quite elegant approach or you could also call it sadistic. They gave to junior physicians this algorithm but they did not give it to the senior physicians and they compared their diagnostic performances. As anticipated, the junior physicians did much better than the senior physicians did. They also looked if this had therapeutic consequences and therapy that was correct according to the reference standard was 86% for the junior physicians compared to 84% for the senior physicians. This performance even increased further when they replaced the assessment of volume status with calculating the fractional uric acid excretion. So, just simply following an algorithm gave a better diagnostic performance than the senior physicians who did not have the algorithm.

So, what about uric acid? This based also on a study by the group of Bruno Allolio from Germany where they tested the sensitivity and specificity of various parameters in patients with hyponatremia either on or off diuretics.
So, the plus sign indicates diuretic use and as you can see here, the urine sodium had especially a low specificity whereas the fractional uric acid excretion had a good sensitivity and specificity for differentiating hyponatremia. Serum uric acid is easier of course, and more readily available and still had a reasonable sensitivity and specificity and the characteristics for the patients who were not on diuretics are shown here.
So one slide on hyponatremia and CKD since this is a renal symposium. We know that in haemodialysis patients who do not have residual kidney function hyponatremia predicts mortality and this is independent of their cardiovascular underlying diseases.

Slide 16

This has also been shown now for CKD stages 3-5 and this association was also independent of underlying cardiac disease.

Slide 17
This begs a number of questions: what is the role of vasopressin in these patients? Because if you do not have residual kidney function, you cannot argue that vasopressin is responsible for hyponatremia. The question there is, is non-adherence to fluid restriction then the only cause of hyponatremia or are other mechanisms involved? What is the typical urine biochemistry in these patients? Because a kidney that is chronically diseased may not be able to retain sodium as well or concentrate or dilute as well and maybe we should consider hyponatremia and CKD as a separate entity.

I wanted to finish just by giving you a few examples of cases to illustrate the challenges of the differential diagnoses of hyponatremia. This was a patient with clear psychogenic polydipsia who came in with acute hyponatremia, had cerebral oedema but as you can see from the urine sodium and urine osmolality, this was not completely suppressed so there was no water diuresis and we believe that the anti-psychotic medication this patient was receiving
also gave him an SIADH as a combination of factors leading to the hyponatremia.

Slide 19

\[ S_{Na} 127, U_{Na} 15, U_{Osm} 438 \]

This was a patient with hyponatremia in a low urine sodium who had active hepatitis C. We all believed it would be liver cirrhosis.

Slide 20

\[ S_{Na} 127, U_{Na} 15, U_{Osm} 438 \]

Hoorn et al., Nephron Physiol 2011
but when we looked further, it turned out to be SIADH due to aspergelosis. The confounder here was the low urine sodium but this patient was on a low sodium diet.

Slide 21

Another patient with severe hyponatremia and high urine sodium, high urine osmolality, we all believed it would be SADH and the patient was also treated with water restriction, no response and eventually the patient turned out to have bilateral adrenal metastasis from a previous melanoma and this patient was not frankly hyperkalaemic or had orthostatic hypotension but he had primary adrenal insufficiency.

Slide 22
Another one a 44-year old woman who was a smoker but also on an anti-depressant. We did a chest x-ray, no abnormalities, believed the anti-depressant caused the hyponatremia even though she had been 10 years on the drug.

Then stopped the anti-depressant hyponatremia recurred and the CT scan showed small cell lung cancer anyway.
Finally a young 29-year old female who was pregnant and hyponatremia was discovered during pregnancy and it was first thought that maybe Reset Osmostat was responsible for the hyponatremia but then hyponatremia persisted after her pregnancy, she turned out to have SIADH and after a long search we found an olfactory neuroblastoma as the cause of her SIADH.

Slide 25

What should you do different starting tomorrow?

- Time for a new diagnostic algorithm
- European guideline 2013
- Remaining areas of uncertainty
  - Diuretics
  - Uric acid
  - Copeptin
  - Chronic kidney disease

So in summary, what should you do different starting from tomorrow? We believe it is time for a new diagnostic algorithm for hyponatremia and there will be a European guideline in the next half of 2013 but there are remaining areas of uncertainty: diuretics, uric acid and I didn’t get a chance to talk about co-peptin and also CKD.
I thank you for your attention and I'll be happy to answer any questions.

Chairman: Thank you Doctor Hoorn for your excellent presentation in which you suggested that if we all became a lot younger and used your algorithm, we would be correct with the differential diagnosis did you say 99% of the time?

Dr. Hoorn: 95%.
Chairman: So, questions please go ahead.

Question: Good morning I'm Eva Nagler from European Renal Best Practice. This is more a remark and a warm invitation rather than a question. I've got this beautiful algorithm on this very useful postcard. I would like to send out a warm invitation to our booth, which is located at the entrance of the exhibition hall downstairs in the other building where you can get a free copy of this one. I'll try to be at the exit at the end of this session and hand out some.

Chairman: Thank you and all of you please try to participate in this activity. Other questions please?

Question: Doctor Hoorn, I often encounter the situation where the pathology of hyponatremia seems to be mixed. The patient has small cell carcinoma of the lung and SIADH because he smoked but he also has heart disease and congestive cardiac failure. How am I, according to you and your algorithm, to distinguish what the leading pathology is which might guide my treatment?

Dr. Hoorn: Excellent question. So the point is that hyponatremia is often multifactorial and I believe it is. Well the diagnostic algorithm is meant for 90% of the majority of cases where there would be a single cause and for the remaining 10% I think it's very important to follow-up the response to treatment and keep an eye on whether this hyponatremia completely disappears or if there are other accompanying factors that still need addressing. There are, as reflected by the case I presented, sometimes mixtures of polydipsia and SIADH and you have to carefully review the history to be able to review both causes.

Chairman: Do you ever measure? You don't seem to measure ADH in your algorithm.

Dr. Hoorn: No, actually, I think urine osmolality is an excellent reflection of the activity of vasopressin and as you know, it's a very difficult assay. There is some promise in the form of copeptin, which is a surrogate marker of vasopressin and a very stable one. It may be promising in the future for help in differential diagnosis.

Chairman: With there being no further questions we thank you very much again.

Dr. Hoorn: Thank you.