

Diagnostic Approach to the Patient with Hyponatremia and the Cause of Hyponatremia

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Diagnostic Approach

Diagnosis should proceed in a series of sequential steps to ensure that true hyponatremia is present and to establish the pathophysiologic mechanism and cause.

The **First** step in the approach of hyponatremia is to rule out *pseudo-hyponatremia* due to hyperlipidemia or severe hyperproteinemia. This can be done in one of two ways:

- By measuring the serum osmolality and demonstrating that it is approximately 2 x the serum sodium,
- Alternatively, the serum sodium can be measured with an ion-selective electrode (the usual method of measurement in many laboratories).

If neither method is available nor either severe hyperlipidemia (usually with lactescent serum) or severe hyperproteinemia are present, you can estimate the contribution of these abnormalities mathematically. In normal subjects, the plasma water is approximately 93 percent of the plasma volume, with fats and proteins accounting for the remaining 7 percent. Thus, a normal plasma sodium level of 142 mEq/L (measured per liter of plasma) represents a concentration in the physiologically important plasma water of 154 mEq/L ($142 / 0.93 = 154$).

However, the plasma water fraction may fall below 80 percent in patients with marked hyperlipidemia (as in uncontrolled diabetes mellitus) or hyperproteinemia (as in multiple myeloma). In these settings, the plasma water sodium concentration and plasma osmolality are unchanged, but the measured sodium concentration in the total plasma volume will be reduced (since the specimen contains less plasma water).

The **Second** step is to ensure that the *hyponatremia represents hypoosmolality* and is not due to dilution of the serum sodium by water pulled into the extra cellular fluid (ECF) volume by hypertonicity. The substances which can produce this include glucose and mannitol.

- You can measure the serum osmolality to ensure that it is low
- You can also calculate the contribution of the glucose concentration to the hyponatremia. Note that there are substances which can elevate the osmolality without producing dilutional hyponatremia (e.g., urea, ethanol) as they distribute equally intra and extracellularly and produce an osmolar gap.

The **Third** step is to assess the *ECF volume status* of the patient. Patients with hyponatremia are divided into 3 groups based upon the presence or absence of edema and signs of volume

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depletion (e.g., hypotension, urine sodium >10 mEq/L).

Cause of hyponatremia

Causes of hyponatremia can be grouped into three categories based upon the pathophysiologic mechanism.

Hyponatremia due to ECF volume loss (true hypovolemia): This is the group of patients with no edema and signs of volume depletion. The hyponatremia in this group is due to both increased proximal tubular reabsorption (limiting delivery to the diluting sites) and increased secretion of ADH. The causes of hypovolemia include: *Diarrhea, vomiting, hemorrhage, third spacing, burns, excessive sweating, and use of diuretics, Bartter's syndrome, osmotic diuresis (glycosuria, mannitol administration, protein load (tube feeding), adrenal insufficiency and cerebral salt wasting.*

Cerebral salt wasting is a rare syndrome and has been described in patients with cerebral disease (particularly subarachnoid hemorrhage). It mimics the findings in the SIADH, except that salt-wasting is the primary defect with the ensuing volume depletion leading to a secondary rise in ADH release. Patients also may have hypouricemia due to increased urinary uric acid excretion. The etiology is unclear but some studies support the possible role of a circulating factor that impairs renal tubular function.

The diagnosis of hyponatremia due to ECF volume depletion can be verified by assessing the response to expansion with normal saline. You can also measure the urine sodium. It is typically less than 10 mEq/L in nonrenal causes of sodium loss. The fractional excretion of sodium (FENa) should be less than 1%. Recognize that intrinsic renal disease or the administration of diuretics in the 24 hrs prior to the measurement can interfere with diluting ability and elevate the urine sodium concentration despite the presence of hypovolemia.

Hyponatremia in edema forming states: These are conditions in which the kidney holds onto sodium and water in response to a hemodynamic stimulus. The three major clinical conditions are:

- **Congestive heart failure (CHF):** In states of CHF, a decrease in cardiac output (effective volume depletion) initiates a baroreceptor response which triggers the renal response via secretion of the three "hypovolemic" hormones (renin-angiotensin, ADH, and norepinephrine). The severity of the defect in water excretion (due to the neurohormonal activation) and of the associated reduction in the plasma sodium concentration parallels the severity of the heart disease. Patient survival is significantly reduced (in comparison to normonatremic patients) once the plasma sodium level falls below 137 mEq/L. A plasma sodium concentration below 125 mEq/L represents near end-stage disease.
- **Cirrhosis:** Severe vasodilatation in the splanchnic, skeletal muscle and dermal vascular beds reduces the pressure at the baroreceptor which triggers the renal response.
- **Nephrotic Syndrome:** In many of these patients there is evidence of overfilling of the circulation and the renal sodium and water retention appears to be a primary event triggered by inflammation in the glomerulus and renal interstitium. In some, with very severe hypoalbuminuria, there is evidence of under filling with a tendency toward hypotension.

Hyponatremia associated with normal ECF volume: Hyponatremia in the absence of either an edema forming states or true ECF volume depletion is due to either massive water ingestion or more commonly a defect in the ability to excrete a water load. Deficiency in the ability to excrete water is typically due to increased activity of ADH but may be due to insufficient solute intake.

Massive water ingestion: If diluting ability is intact, and renal function is normal, the urine

osmolality should be below 75 mosmol/kg and water ingestion must exceed 15 liters per day in a 60 kg man, to produce sustained hyponatremia. Primary polydipsia is a disorder in which there is a primary stimulation of thirst. It is most often seen in individuals with psychiatric illnesses, particularly those taking antipsychotic drugs in whom the common side effect of a dry mouth leads to increased water intake. Most patients with psychologic polydipsia also have a concentrating defect due to SIADH from the psychosis and present with a urinary osmolality between 100 and 200 mosmol/kg.

Increased activity of ADH: If the urine osmolality is >75 mosmol/kg, the causes of increased ADH secretion including the SIADH are usually clinically apparent and include the following:

- **Pain and stress:** This is often seen following major surgery. ADH release may last for 2-5 days following major surgery and the duration and severity of the condition is directly correlated with increased patient's age.
- **Hormonal deficiencies:** Hypothyroidism and glucocorticoid deficiency as in hypopituitarism. Hyponatremia is also seen in adrenal insufficiency but volume contraction due to aldosterone deficiency plays the predominant role.
- **Thiazide diuretics**
- **Carcinoma:** Ectopic production of ADH by a tumor is most often due to a small cell carcinoma of the lung, but is also occasionally seen with other lung tumors such as those originating in the duodenum and pancreas.
- **Pulmonary disorders:** Pulmonary diseases, particularly pneumonia (viral bacterial, tuberculosis) can lead to the SIADH, as well as asthma, atelectasis, acute respiratory failure, and pneumothorax.
- **CNS disorders:** Encephalitis, meningitis, abscess, subdural hematoma, trauma, stroke,

tumor, Guillain-Barre syndrome, acute intermittent porphyria and acute psychosis.

- **Drugs:** Certain drugs can enhance ADH effect or release. Chlorpropamide, carbamazepine and oxcarbazepine appear to either have a direct effect on the renal collecting tubules or enhance the responsiveness to circulating ADH. Drugs which enhance ADH release and thereby cause the syndrome of inappropriate ADH include clofibrate, morphine, barbiturates, cyclophosphamide (IV), vincristine, thioridazine, tricyclic antidepressants, bromocriptine, haloperidol, thioridazine, fluoxetine, and sertraline.
- **Idiopathic SIADH:** This condition has been described in a few patients, typically in the elderly. At times, it appears to have been due to an occult tumor.
- **Reset osmostat:** Hyponatremia due to a reset osmostat can be seen with any of the causes of the SIADH, and accounts for 25 and 30 percent of overall cases. It is typically associated with chronic illness (cirrhosis, tuberculosis) and malnutrition. It is important to distinguish this variant as it is asymptomatic and does not require specific therapy to raise the serum sodium concentration.
- **HIV infection:** Hyponatremia in these patients may be due to volume depletion, adrenal insufficiency, drugs, pneumonia or SIADH.

Insufficient dietary solute intake: Beer drinkers or other malnourished patients, including those with low-protein, high water intake diets, may have a marked reduction in water excretory capacity that is directly mediated by poor dietary intake.

If the etiology of hyponatremia is not immediately obvious, one should consider the possibility of anterior pituitary insufficiency with glucocorticoid deficiency. If there is no contraindication to steroid administration, a useful diagnostic test (after drawing a serum cortisol level) is to give the equivalent of 50 to 100 mg cortisone. If the

patient is glucocorticoid deficient, a water diuresis will ensue in 30 to 45 minutes.

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Hyponatremia

Clinical Quizzes

Case 1: An 18-years old female (60 kg) presents to the ER with severe pain in her mouth. She had dental work done five days ago and now had developed a tooth abscess. She has been taking a variety of pain pills and has been unable to eat solid food for several days. Past medical history was significant for a postpartum hemorrhage complicated with hypotension 2 years ago. Laboratory data revealed sodium 111 mEq/L, chloride 74 mEq/L, potassium 3.9 mEq/L, CO₂ 28 mEq/L, BUN 12 mg/dL, creatinine 0.9 mg/dL, calcium 9.5 mg/dL, phosphate 3.6 mg/dL, magnesium 1.9 mg/dL, and albumin 3.9 g/dL. Hematocrit 41%, WBC 5100 cells/uL. Urinalysis showed trace protein, glucose negative, no blood, and no casts, RBC or WBC. Urine sodium was 11 mEq/L and urine osmolality 400 mosmol/kg.

Question: What orders would you like to write?

- A. Restrict free water to <1500 ml/day
- B. Oral surgery consult
- C. Intravenous saline, 3 liters/24 hours
- D. Hypertonic saline

Question feedback: (A, B and C).

It appears that the hyponatremia is due to a combination of reduced intake and ADH secretion in response to ECF volume contraction, pain, and medications.

Treatments therefore include restoration of ECF volume with isotonic saline, restriction of free water intake until the other issues are resolved, and drainage of the abscess.

Case 2: She is treated with IV fluids, water restriction and removal of the abscessed tooth. Ten days later, she is off all medication and her pain is gone. With restoration of free access to water, however her serum sodium falls to 129 mEq/L with a plasma osmolality of 265 mosmol/kg and a urine osmolality of 685 mosmol/kg. A diagnostic procedure is performed.

Question: What was the diagnostic procedure?

- A. Administration of 100 mg cortisol IV
- B. Administration of thyroid hormone
- C. Measurement of plasma vasopressin level
- D. Administration of thyroid hormone
- E. Measurement of the plasma glucose level

Question feedback: (A)

Infarction of the pituitary gland after substantial blood loss during childbirth has long been recognized as a cause of hypopituitarism and is called Sheehan's syndrome. It occurs as the length of the pituitary gland during pregnancy outstrips the increase in blood supply rendering the gland susceptible to infarction with hypovolemia such as that occurring with hemorrhage during delivery.

Severe hypopituitarism can be recognized during the first days or weeks after delivery by the development of lethargy, anorexia, weight loss, and inability to lactate. Less severe hypopituitarism may be manifested by fatigue, amenorrhea, and loss of sexual hair, or hyponatremia but may not be recognized for many years after the inciting event until there is a period of stress.

The hyponatremia is due to hypocortisolemia. Normal cortisol levels are necessary to allow suppression of ADH release by hypo-osmolality.

Administration of 100 mg cortisone in this situation is safe and has no side effects. Water diuresis will occur within 15-30 minutes and the response is diagnostic of hypocortisolism.

In this case, the patient recalled that she had had postpartum hemorrhage complicated by hypotension. She responded to IV cortisone with a brisk water diuresis and correction of hyponatremia.

Case 3: You are asked to see a 17-years old Caucasian female with acute post-operative hyponatremia. The patient had been in a good health until yesterday when she fell and sustained a compound wrist fracture. It was recommended that surgery be performed immediately. She was started upon low dose unfractionated heparin, a urinary tract catheter was placed and she received prophylactic antibiotics and was taken to the OR. Current medications include oxcarbazepine for trigeminal neuralgia, and inderal for hypertension. On examination she appears restless and confused and is complaining of significant pain in her right wrist. Temp is 98, pulse 110, respiratory rate 25.

The chest is clear. There is no abdominal distention, tenderness or guarding. There is no organomegaly. There is no edema. The neurological examination is within normal limits except for mild to moderate confusion. Patient's pre-op laboratory study shows serum sodium 118 mEq/L, potassium 3.9 mEq/L, Chloride 78 mEq/L, CO₂ 26 mEq/L, BUN 12 mg/dL, creatinine 0.9 mg/dL. Calcium 9.5 mg/dL, phosphate 3.6 mg/dL, magnesium 1.9 mg/dL, and albumin 3.9 g/dL. White blood count 5100 cells/uL, hematocrit 13.0 g/dL. Urinalysis shows trace protein, negative glucose, and no blood, RBC or WBC. Urine sodium is 41 mEq/L, urine osmolality 489 mosmol/kg and plasma osmolality 240 mosmol/kg. Her intake since this AM (over 6 hrs) including the period of surgery and the recovery room was 3 L of D5W. There was little estimated blood loss and she has made 100 ml of urine.

The post-op laboratory values are hematocrit 40%, WBC 5,500 cells/uL, BUN 10 mg/dL, creatinine 0.6 mg/dL, sodium 137 mEq/L, potassium 3.5 mEq/L, chloride 103 mEq/L, CO₂ 27 mEq/L, calcium 9.9 mg/dL, phosphate 3.9 mg/dL, and albumin 2.1 g/dL.

Question: What is the likely cause of this condition?

- A. Postoperative SIADH associated with pain and surgery
- B. Adrenal insufficiency
- C. Dilutional hyponatremia
- D. Hypothyroidism

Question feedback: (A)

Major abdominal or thoracic surgery is commonly associated with hypersecretion of ADH, a response that is probably mediated by pain afferents. The length and severity of this condition increases with increasing age.

Case 4: The fellow assigned to the case was interested in the problem and was planning to present it at the next conference. Without your

knowledge he had a plasma vasopressin level drawn. He now says to you that the vasopressin level was low, NOT high. He wants to know how that can be if the patient has hyponatremia and a concentrated urine.

Question: Your answer is which of the following?

- A. The laboratory made a mistake
- B. The patient likely has pseudohyponatremia due to marked hyperlipidemia
- C. The patient is taking oxcarbazepine

Question feedback: (C)

Hyponatremia associated with oxcarbazepine is not due to SIADH and vasopressin levels are not elevated. Rather, the drug directly enhances absorption of water in the collecting duct possibly by enhancing responsiveness to circulating ADH.

Case 5: You are asked to see a 19-years old male with a serum sodium of 123 mEq/L. He was in a good state of health until 4 months ago when he developed a persistent cough. He subsequently experienced 6 kg weight loss. He developed shortness of breath 5 days ago. He has a history of mild hypertension for which he was treated with atenolol 25 mg per day. He has a 24-pack year smoking history. He does not drink alcohol. He denies the use of any other medications or over-the counter supplements. On examination, he appeared cachectic but with no apparent acute distress. BP was 110/72 mmHg without orthostatic; pulse 68; RR 18; T 98.6; Wt 62 kg; Ht 159 cm. Heart had regular rhythm, no murmurs. Chest was dull to percussion with diminished breathing sounds at the right base. There was no edema. The remaining of the PE was normal. A chest X-ray showed a right pleural effusion and he was admitted for further evaluation. Laboratory study showed serum sodium 126 mEq/L, potassium 3.5 mEq/L, Chloride 91 mEq/L, CO₂ 24 mEq/L, BUN 6 mg/dL, and creatinine 0.7 mg/dL. Calcium 9.1 mg/dL, phosphate 3.2 mg/dL, magnesium 1.9 mg/dL, uric acid 3.5 mg/dL, and

albumin 3.6 g/dL. Urine osmolality was 305 mosmol/kg and serum osmolality 250 mosmol/kg.

Question 1: What are the causes of hyponatremia that should be considered in this case? (select all that apply)?

- A. Dilutional hyponatremia due to hyperglycemia
- B. Pseudohyponatremia due to hyperlipidemia
- C. SIADH
- D. Adrenal insufficiency
- E. Reset osmostat

Question feedback: (C and E)

The diagnosis of SIADH with a primary lung disease is extremely likely in this patient. Reset osmostat typically occurs in chronically ill, malnourished or cachectic patients with tuberculosis and this patient is certainly a candidate.

Question 2: How would you make the distinction between SIADH and reset osmostat in this patient?

- A. Water restriction
- B. Administration of vasopressin
- C. Administer a water load
- D. Expand the ECF volume with isotonic saline

Question feedback: (C)

A patient with reset osmostat will respond to a water load with a water diuresis when the serum sodium concentration falls below the “reset” level (typically 127-132 mosmol/L). A patient with SIADH will not respond with dilution of the urine.

Case 6: A 19-years old male presents to the ER after 5 days of not feeling well. One week ago he began to take his father's diuretic as he had developed some peripheral edema and abdominal swelling. He claims to have not eaten in 6 days and his only intake was beer. He had been told to have chronic hyponatremia several months ago with a serum sodium consistently in the range of 128-132 mEq/L. Urine osmolality was 445 mosmol/kg. Workup revealed normal renal and adrenal function. Chest x-ray was normal. He was

on no medications. He was given a diagnosis of SIADH and was subsequently lost to follow-up. Blood pressure was 100/70 mmHg. Lab studies were: sodium 106 mEq/L, potassium 3.4 mEq/L, chloride 78 mEq/L, CO₂ 22 mEq/L, BUN 10 mg/dL, creatinine 1.0 mg/dL, urine sodium 10 mEq/L and urine osmolality 686 mosmol/L.

Question: What was the likely sequence of events leading to severe hyponatremia in this patient?

- A. Worsening SIADH
- B. Chronic mild hyponatremia plus superimposed ECF volume contraction and heavy beer drinker (low solute intake)
- C. Dilutional hyponatremia
- D. Adrenal insufficiency

Question feedback: (B)

He likely had a severe limitation on his ability to excrete free water due to a chronic problem with superimposed volume concentration from the diuretics and low solute intake associated with massive beer intake.

Case 7: He was given 2 liters of normal saline over the next 4 hrs after which he began to excrete clear urine with a sp of 1.002. He excreted 6 liters over the next 10 hrs at which point his serum sodium was 129 mEq/L. His fluid therapy was changed to 5%DW because of the fear of too rapid correction of his hyponatremia. At that point it was noted that his urine osmolality was 453 mosmol/kg.

Question: What was the likely sequence of events?

- A. Reset osmostat complicated by volume contraction and beer drinker potomania
- B. SIADH complicated by volume contraction and low solute intake
- C. Volume contraction and low solute intake
- D. Osmotic diuresis

Question feedback: (A)

The patient had a reset osmostat accounting for his chronic hyponatremia. Superimposed volume

contraction and potomania prevented his ability to excrete the water load. When he was repleted with saline, this corrected the volume contraction and provided solute to allow free water to be excreted. When his serum osmolality exceeded his "reset" point, he began to respond by concentrating his urine.

Case 8: You are asked to see a 2-years old boy because of a congestive heart failure. His medications include digoxin and furosemide. On examination, he is lethargic and in mild respiratory distress, with a blood pressure of 100/54 mm Hg and irregular pulse of 104. Rales are present in ¼ of the upper lobe of his lung fields, and there is 2+ ankle edema. Lab studies reveals the following: sodium 125 mEq/L, potassium 3.3 mEq/L, chloride 95 mEq/L, CO₂ 24 mEq/L, BUN 11 mg/dL, creatinine 0.8 mg/dL, fasting blood glucose 90 mg/dL, serum osmolality 230 mosmol/kg and urine osmolality 600 mosmol/kg.

Question: Which of the following statement concerning his hyponatremia are true?

- A. She most likely has SIADH
- B. Hyponatremia can easily be managed with water restriction
- C. A plasma concentration below 125 mEq/L typically represents near end-stage cardiac disease
- D. The hyponatremia is due to a decrease in cardiac output (effective volume depletion) which indicates a baroreceptor response and neurohumoral stimulation

Question feedback: (C and D)

In state of congestive heart failure, a decrease in cardiac output (effective volume depletion) initiates a baroreceptor response which triggers the renal response via secretion of the three "hyponatremia" hormones (renin-angiotensin II system, antidiuretic hormone (ADH), and nor-epinephrine).

The severity of the defect in water excretion (due to the neurohumoral activation) and of the associated reduction in the plasma sodium concentration parallels the severity of the heart disease. Patient survival is significantly reduced (in comparison to normonatremic patients) once the plasma sodium concentration falls below 137 mEq/L. A low plasma sodium concentration below represents near end-stage disease.

Case 9: A 50-kg male has SIADH due to a tumor; the plasma sodium is in a steady state and 120 mEq/L, and plasma potassium is 4.0 mEq/L. there are no symptoms attributable to hyponatremia. Assume that the ECF volume is normal and that the patient is consuming a usual diet.

Question: How much water restriction would correct the hyponatremia?

- A. 4.3 liters
- B. 3.375 liters
- C. 2.3 liters

Question feedback: (B)

Physiologically, in patients with SIADH, the total body sodium (TBNa) is normal but the total body water (TBW) is increased proportionately to the

fall in plasma sodium (PNa) concentration, due to overproduction of ADH.

Because TBNa is the product of TBW x PNa concentration, the excess water gain in SIADH can be estimated using the following equation:

TBNa (TBW x PNa) in normal subjects = TBNa (TBW x PNa) in SIADH patient or

$$(50\text{kg} \times 0.6) \times 135\text{mEq/L} = (\text{TBW} \times 120\text{ mEq/L})$$

or

$$\text{TBW in SIADH patient} = 50\text{ kg} \times 0.6 [30\text{ liters}] \times 135\text{ mEq/L} : 120\text{ mEq/L}$$

or

$$\text{TBW in SIADH patient} = 33.750\text{ liters}$$

The excess water gain in patient with SIADH can now be calculated from the difference between normal subject and SIADH patient TBW

or

$$\text{Water gain in patient with SIADH} = \text{SIADH TBW} - \text{Normal TBW}$$

or

$$\text{Water gain} = (33.750\text{ liters}) - (30.00\text{ liters})$$

$$\text{Water gain in SIADH patient} = 3.375\text{ liters}$$