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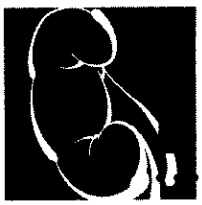


Roger A. Rodby

A 61-year-old male construction worker was taken to the emergency room after a witnessed seizure in a restaurant. His wife revealed that he had complained about fatigue, malaise, a mild headache, and a poor appetite over the last week. He had no significant past medical history except for an 80 pack-year history of cigarette smoking. There was no history of seizures, alcohol abuse, head trauma, or neurologic disorders.

The physical examination demonstrated a BP of 120/80 mm Hg, RR 24/min, and a temperature of 98.6°F. He was arousable but inattentive. The lungs were clear, the cardiac examination was normal, and there was no peripheral edema. The neurologic examination was nonfocal. Laboratory values revealed the following: sodium 105 mEq/L, potassium 4.0 mEq/L, chloride 70 mEq/L, bicarbonate 23 mEq/L, BUN 6 mg/dl, creatinine 0.6 mg/dl, uric acid 1.5 mg/dl (nl 3.5 to 5.0), and glucose 90 mg/dl.

QUESTION 1 The patient is markedly hyponatremic. What are the mechanisms by which salt and water homeostasis is maintained?

True hyponatremia (that associated with plasma hypoosmolality) is usually a result of water retention (or water and sodium retention: water > sodium) and therefore may be considered dilutional. Sodium loss by itself is rarely a cause of hyponatremia since the sodium concentration of the fluid that is lost would have to be higher than that of the serum. This is rarely the case, and therefore when hyponatremia is associated with sodium loss, it is usually also accompanied by water retention.

The key to understanding the development of hyponatremia depends on a knowledge of the normal mechanisms that maintain plasma osmolality and intravascular volume. Alterations in plasma osmolality are sensed by osmoreceptors located in the hypothalamus. These receptors are directly involved in water balance by controlling (1) water intake through the regulation of thirst and (2) water excretion through the regulation of urine osmolality by antidiuretic hormone (ADH). In response to a water load there is a decrease in plasma sodium and plasma osmolality. This results in the suppression of ADH release, thereby decreasing water reabsorption in the collecting duct. This allows excretion of the water load by creating a dilute urine. The kidney's handling of sodium is essentially unaffected by this mechanism. Therefore, hyponatremia is created by the kidney's handling of water, not by its handling of sodium, and hyponatremia may be seen with states of excess, normal, and depleted total body sodium. The key to understanding hyponatremia is to understand why sufficient amounts of water are not being excreted by the kidney. As will be discussed, the mechanisms leading to water retention often reflect volume-mediated ADH release, and the physical examination is critical in determining a patient's volume status. As is demonstrated in Fig. 9-1-1 on p. 526 the excretion of a water load depends upon (1) an adequate glomerular filtration rate (GFR), (2) normal proximal tubule handling of filtrate, (3) subsequent distal delivery of filtrate (steps 1 to 3 are critical since fluid must be delivered to the diluting segment), (4) dilution of filtrate through the resorption of sodium without water, and finally, (5) suppression of ADH release to prevent water reabsorption as a dilute filtrate passes through the collecting duct.

The inability to suppress volume-mediated ADH release is the most common cause of water retention and, therefore, hyponatremia. ADH secretion is controlled by osmoreceptors located in the hypothalamus and baroreceptors located in the vascular tree. These later receptors respond to any decrease in circulating volume by sending impulses to the brain to release ADH; this results in urinary concentration and water retention. If this water retention results in hyponatremia, osmoreceptor mediated ADH release will be suppressed. Nevertheless, water retention has preceded secondary to volume-mediated ADH release. Thus, plasma volume homeostasis always takes precedence over plasma tonicity homeostasis.

Volume depletion secondary to fluid loss from the body is a potent stimulator of ADH release. If these losses are replaced with more water than sodium, the ADH-mediated retention of water will lead to hyponatremia. On the other hand, total body fluid volume can be elevated, and ADH will not necessarily be suppressed if the fluid is either not in the vascular tree (edema or ascites) or if it does not adequately reach the tissues (congestive heart failure). Therefore, the term *effective circulating volume* has been used to refer to the actual volume of fluid that reaches tissue beds. It is similar to the cardiac output, except in the presence of tissue shunting where tissue perfusion may be compromised despite a normal or high cardiac output (e.g., cirrhosis). Therefore, a normal effective circulating volume ultimately depends on adequate tissue perfusion. This requires normal intravascular volume, cardiac function, and vascular tone. A defect in any of these factors may lead to a decrease in effective circulating volume and the subsequent release of ADH and water retention. Indeed, the most common causes of hyponatremia are related to ADH release (e.g., cardiac failure, cirrhosis, and nephrosis associated with a decrease in effective circulating volume).

Conditions associated with volume depletion (either real or "effective") not only result in ADH release and water retention, but in the stimulation of the renin-aldosterone axis and sodium reabsorption. When the effective circulating volume is decreased, the continued retention of both sodium and water will eventually produce edema. Therefore, edema may serve as a clue to the presence of volume-mediated ADH release. This may be confirmed by the finding of low concentrations of sodium in the urine, usually <20 mEq/L, unless diuretics are being used. As is demonstrated in Fig. 9-1-2 on p. 527, water excretion is further impaired in these conditions by the adverse effects of volume depletion on distal delivery of filtrate.

QUESTION 2 **Additional labs reveal that the plasma osmolality is 219 mosm/L, urine osmolality 600 mosm/L, urine sodium 78 mEq/L. A chest x-ray revealed a right superior mediastinal mass. What is the differential diagnosis of hyponatremia?**

Because sodium is the major extracellular osmotically active particle, hyponatremia usually reflects a decrease in serum osmolality. If another osmotically active solute that is predominantly extracellular is present, water will leave the intracellular space to the extracellular space so that osmolar equilibration will occur. This is the basis for hyponatremia that is seen with hyperglycemia. Although it is true hyponatremia, it is not true hypoosmolality, and the measured serum osmolality should be elevated. This laboratory test is usually not necessary since an elevated blood glucose should indicate the etiology, and a simple estimation can be made of the expected reduction in sodium compared to the increase in blood glucose. The serum sodium concentration will decrease by about 1.6 mEq/L for each 100 mg/dl increase in blood glucose above 100 mg/dl. Plasma sodium dilution can be similarly seen when high doses of mannitol are administered intravenously.

As was discussed, the most common causes of hyponatremia are those associated with the edematous states of cardiac, hepatic, and renal diseases. This diagnosis can usually be made at the bedside when edema is present and requires little

if any further laboratory testing. Water retention in the edematous conditions may seem inappropriate because it occurs despite plasma dilution, but is only inappropriate from an osmotic standpoint. ADH release is considered inappropriate, that is, the syndrome of inappropriate ADH release (SIADH), only when there lacks both an osmotic and volume-mediated stimulus for its release. Therefore, the patient with SIADH appears euvolemic and should not have edema. The urine sodium will reflect the patient's volume status, which, unless the patient is volume depleted, will be >20 mEq/L. The urine osmolality need not be greater than the serum osmolality. As most normal individuals can dilute their urine to <100 mosm/L after a water load, any urine osmolality greater than this could be considered "inappropriate" (but only if a volume-mediated stimulus for ADH release is lacking).

The steps in the pathogenesis of the urinary biochemical findings in SIADH are demonstrated in Fig. 9-1-3 on p. 528. As water is retained related to an inappropriate release of ADH, mild volume expansion occurs. As water retention is the primary defect in this condition, water cannot be excreted to alleviate this volume expanded state. On the other hand, ADH has essentially no effect on sodium excretion, and therefore sodium is handled normally. A mild natriuresis can therefore occur to decrease the volume overloaded state. This natriuresis is secondary to inhibition of the renin-aldosterone axis in addition to the release of atrial natriuretic factor. Also associated with the volume expansion is a decrease in the proximal tubular reabsorption of sodium, thereby increasing distal sodium delivery. The increase in distal sodium delivery, in the setting of water reabsorption without proximal or distal sodium reabsorption in the collecting duct, leads to a urine with a high sodium concentration. The urine sodium can exceed the plasma sodium. Because sodium is handled normally, edema does not occur. This volume expansion leads to a high GFR that is reflected in a "low" BUN and creatinine. The uric acid is often below normal values as well. This may be related to the high GFR, although other mechanisms may be involved. Because the urine sodium tends to be high, patients with SIADH have greater reductions in the serum sodium than patients with hyponatremia and edematous states where sodium retention accompanies water retention. As a result, cases of severe hyponatremia are more likely to be secondary to SIADH than one of the edematous states.

SIADH has many causes but usually relates to either a paraneoplastic process, pulmonary or cerebral pathology, or a pharmaceutical agent. Since normal thyroid and adrenocortical hormone levels must be present to appropriately suppress ADH, hypothyroidism and adrenal insufficiency should be ruled out before a diagnosis of SIADH can be made.

Hyponatremia can result from excessive water intake in patients with normally functioning kidneys, psychogenic polydipsia, only when extremely large quantities of water are ingested. The urine can be diluted to 50 mosm/L in normal individuals when ADH is totally suppressed. An average daily osmotic load is about 600 mosm/day and consists mostly of urea, sodium, potassium, hydrogen ions, and their associated anions. These 600 mosm can be excreted in any number of urine osmolalities, depending upon water intake. Under water depletion, they are excreted into a concentrated urine. When water intake is abundant, they are excreted into a dilute urine. Given a maximally dilute urine of 50 mosm/L, 12 L of urine will excrete the daily osmotic load of 600 mosm. Therefore with a daily solute output of 600 mosm/day, a daily water intake in excess of 12 L will result in hyponatremia. Most patients with psychogenic polydipsia have psychiatric histories, take a number of psychotropic agents, and are frequent smokers, all of which are associated with the release of ADH. This superimposed SIADH prevents them from being able to dilute their urine maximally, and this decreases the amount of fluid intake necessary before hyponatremia occurs. Even a small change in maximally dilute urine from the normal of 50 mosm/L to 100 mosm/L reduces the allowable water intake by one half from 12 to 6 L/day (600 mosm/day = 6 L

of 100 mosm/L urine). In addition, psychotropic agents often have the anticholinergic side effect of creating a dry mouth. This may exacerbate water intake and hyponatremia.

If the osmotic load is greater, as would be the case on a high salt or high protein diet, water intake would have to increase before hyponatremia would ensue (800 mosm/day = 16 L of 50 mosm/L urine). Also, if the osmotic load is very low, which is the case in people who consume only beer or tea and toast (both diets consist mostly of water and carbohydrate that are free of osmotic solutes that need to be excreted), water intake need not be as excessive before water retention occurs. This is the basis for "beer drinkers hyponatremia" and "tea and toast hyponatremia." Given a daily osmotic load of only 100 mosm/day, despite a maximally dilute urine of 50 mosm/L, the ingestion of over 2 L of fluid may result in water retention and hyponatremia (100 mosm/day = 2 L of 50 mosm/L urine). Psychogenic polydipsia, beer drinkers hyponatremia, and tea and toast hyponatremia are distinguished from the other forms of hyponatremia by the fact that urinary dilution is intact, as demonstrated by a urine osmolality of <100 mosm/L.

Diuretic usage is often associated with hyponatremia. It must be appreciated that diuretics are often used in conditions associated with hyponatremia (i.e., the edematous states), and hyponatremia seen with diuretic usage may reflect the primary sodium and water retention state and not a primary effect of the diuretic. Nevertheless, by effecting urinary dilution (Fig. 9-1-1, step 4), they may impair water excretion, and if water intake is excessive, will result in hyponatremia. Also, by producing hypokalemia, an intracellular to extracellular potassium shift is accompanied by an extracellular to intracellular shift of sodium to maintain cellular electrical neutrality. This movement of sodium out of the extracellular compartment will lower the serum sodium. Finally, if diuretic usage results in intravascular volume depletion, ADH will be appropriately released. These three mechanisms make hyponatremia a common sequela of diuretic usage. Loop diuretics affect not only the ability to dilute the urine but the ability to concentrate it as well. This concentration defect decreases the kidney's ability to retain water, and therefore hyponatremia is less common and less severe with the loop diuretics than when seen with thiazide diuretics that effect only urinary dilution.

Renal failure is a common cause of hyponatremia. Of course, if renal failure is severe and no urine is produced, and water intake is greater than sodium intake, plasma dilution must occur. Hyponatremia can also be seen in patients with less severe reductions in GFR. As nephrons are lost, secondary to any chronic renal disease, the remaining glomeruli increase their filtered load. This excessive solute excretion per nephron has essentially the same effect on the nephron as an osmotic diuretic. This impairs the diluting segment and limits the kidney's ability to excrete a water load.

Up to this point, all causes of hyponatremia represent "true hyponatremia," although not all of the situations are associated with hypoosmolality. "Pseudohyponatremia," on the other hand, is not true hyponatremia but relates to how sodium is measured with some techniques. Serum consists of an aqueous component (water) and a nonaqueous or solid component (proteins and lipids). These, by volume represent 93% and 7%, respectively, of serum. Therefore, a liter of serum can be considered to consist of 930 ml of a liquid phase and 70 ml of a solid phase. Sodium is found only in the liquid phase, and when its concentration is measured in that phase alone, it is approximately 154 mEq/L. Since there is only 930 ml of this liquid phase, the total number of mEq of sodium is 143 (154 mEq/L × 0.93 L = 143 mEq). If the solids are then added, the new volume is 1 L. The total sodium content stays the same but with the new volume of 1 L, the sodium concentration is 143 mEq/L. If the solid phase of the blood is significantly increased, as is the case in severe hyperproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia) and severe hyper-

lipidemia, the effect of this phenomena is amplified. Although uncommon, pseudohyponatremia should be suspected when serum is grossly lipemic or obviously hyperviscous. The diagnosis requires demonstration of hyponatremia in the presence of measured normal plasma osmolality, usually by freeze point depression.

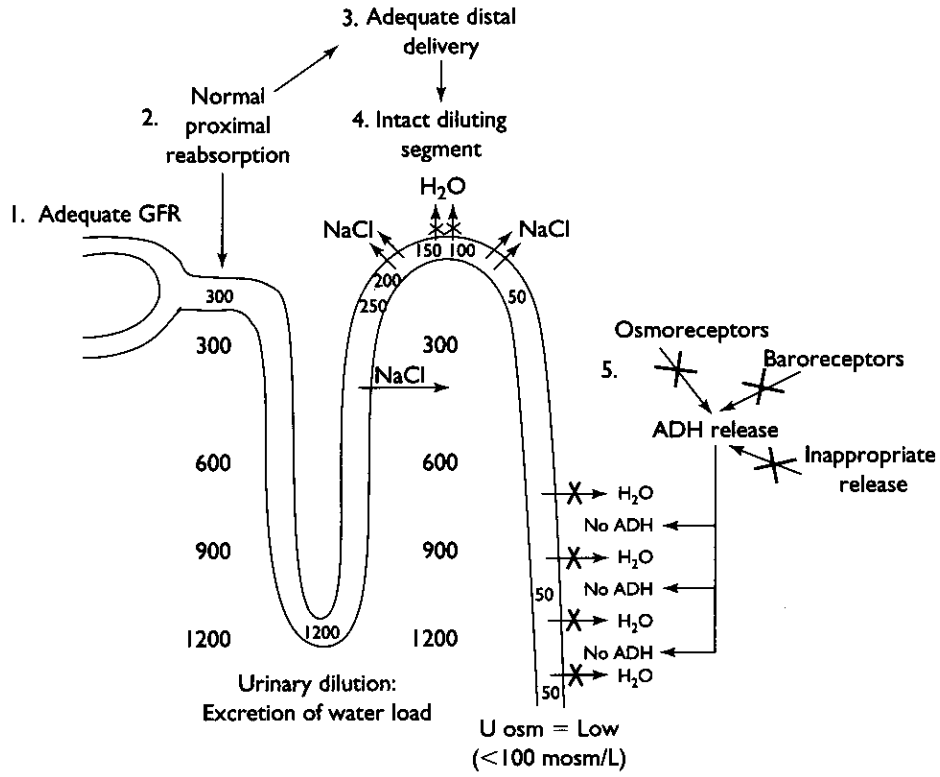
The first step in the workup of the patient with hyponatremia is an examination of the patient's volume status. If edema is present, sodium retention has occurred in addition to water retention, and the patient either has a decrease in effective circulating volume or renal failure. If the patient shows signs of intravascular volume depletion without edema, the hyponatremia is similarly related to volume-mediated ADH release. If the patient appears euvolemic and hyperglycemia is not responsible for the hyponatremia, measurement of the serum and urine osmolality and the urine sodium may help distinguish the etiology. A simplified approach to the differential diagnosis of hyponatremia is presented in Fig. 9-1-4 on p. 529.

QUESTION 3 The patient presented chiefly with changes in mental status. What is the pathophysiology by which hyponatremia leads to symptoms?

As water is retained and the plasma sodium and osmolality decrease, an osmotic gradient is created across all cell membranes. This leads to water movement from the extracellular space into virtually every cell in the body. Because the volume of the cranial cavity is strictly limited, even a small increase in brain cell water could lead to a marked increase in intracranial pressure. The brain therefore requires a mechanism to maintain cellular volume despite otherwise deleterious changes in extracellular osmolality. When this process is inadequate, cerebral edema occurs and is responsible for the presenting signs and symptoms of hyponatremia. Both the rate of development and the severity of hyponatremia are important factors in the pathogenesis of these neurologic changes. If hyponatremia develops acutely, the onset of neurologic symptoms is more rapid at any given decrease in plasma sodium since adaptation by brain cells is not immediate.

In chronic hyponatremia, patients develop fewer and less severe symptoms because of the brain's ability to adapt to a hypoosmolar environment. As the osmolalities between the extracellular and intracellular compartments must equilibrate as water is retained, this can occur only through one of two processes. Water may move from the extracellular space into the intracellular space and is what occurs in the majority of the cells of the body. As this process occurs in the brain, cerebral swelling is limited by the finite size of the cranial vault and would result in an increase in intracranial pressure, which could have a disastrous outcome. The only other means by which equalization of osmolalities could occur is through the removal of solute, without water, from the cell. This process similarly achieves osmotic equilibrium, but without the need for cellular swelling. This mechanism occurs in the brain and appears to be fairly unique to that organ. Brain cells pump intracellular solutes, primarily potassium and organic osmolytes such as free amino acids, out of the cell. Water does not follow these solutes, thus leading to an equalization of extracellular and intracellular osmolalities. This results in a near normalization of brain water, size, and intracranial pressure. This process is not immediate, and therefore acute reductions in the serum sodium may result in cerebral edema and symptomatic hyponatremia. In addition, this mechanism cannot completely protect the brain at all levels of serum sodium. Although the likelihood of hyponatremia being symptomatic depends on the rate of drop of serum sodium, severe reductions, even over a prolonged period, may be too great for this process to protect the brain.

As a general rule it is uncommon to see symptomatic hyponatremia with serum sodium levels >125 mEq/L although the rate of decrease appears to be as important as the degree of decrease. Below 120 mEq/L, patients may develop headache, disorientation, gait disturbances, muscle cramps, hiccups, lethargy, and obtundation. Sei-

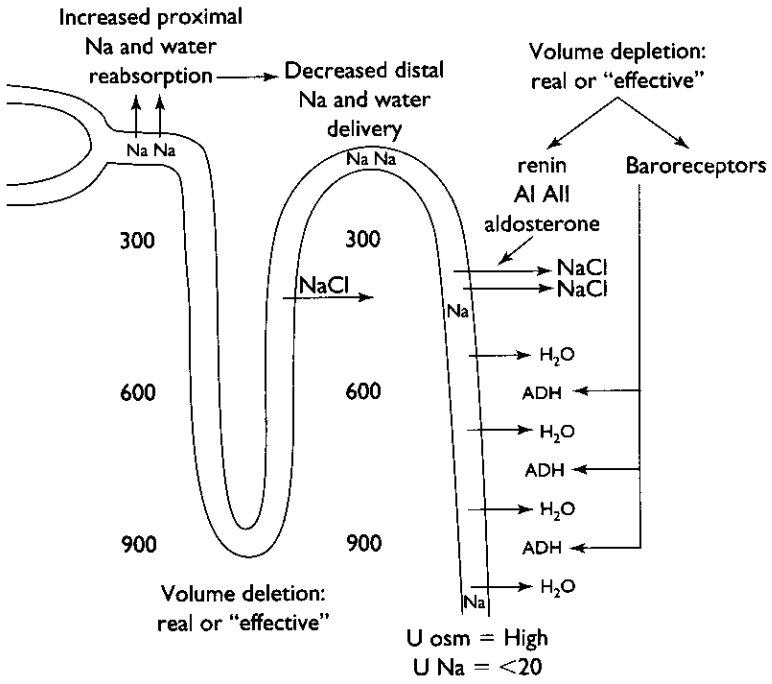


9-1-1 Excretion of a water load depends on 5 factors: (1) formation of a filtrate at the glomerulus, (2 and 3) delivery of filtrate to a "diluting segment," (4) formation of a dilute urine by removing sodium without water, and finally (5) suppression of ADH.

zures and coma may appear when the sodium concentration approaches 110 mEq/L. Still, severe hyponatremia, with serum sodium levels <110 mEq/L, can be asymptomatic if developed over a long enough period of time.

QUESTION 4 What is the treatment of hyponatremia, and what are the considerations for the patient with asymptomatic as opposed to symptomatic hyponatremia?

Since true hyponatremia is secondary to water retention, simple water restriction must accompany the treatment of all of these conditions. As long as the intake if fluid is less than the body's insensible losses of water, eventually this maneuver alone will correct the serum sodium. Treatment beyond that is directed at the physiologic process that led to water retention. In most cases this includes an attempt to suppress ADH release. In the total body sodium depleted patient, repletion of sodium through the administration of intravenous saline will result in suppression of the volume-mediated response of ADH, and the patient will excrete a dilute urine. In the edematous patient, suppression of ADH may not be as easily achieved. Improvement of cardiac function with inotropes and afterload reduction may result in a decrease in ADH release and a more dilute urine in the patient with cardiac failure. Chronic water restriction is difficult to comply to and may not be an effective option by itself. Loop diuretics (in conjunction with water restriction) are often necessary as an additional treatment modality in the



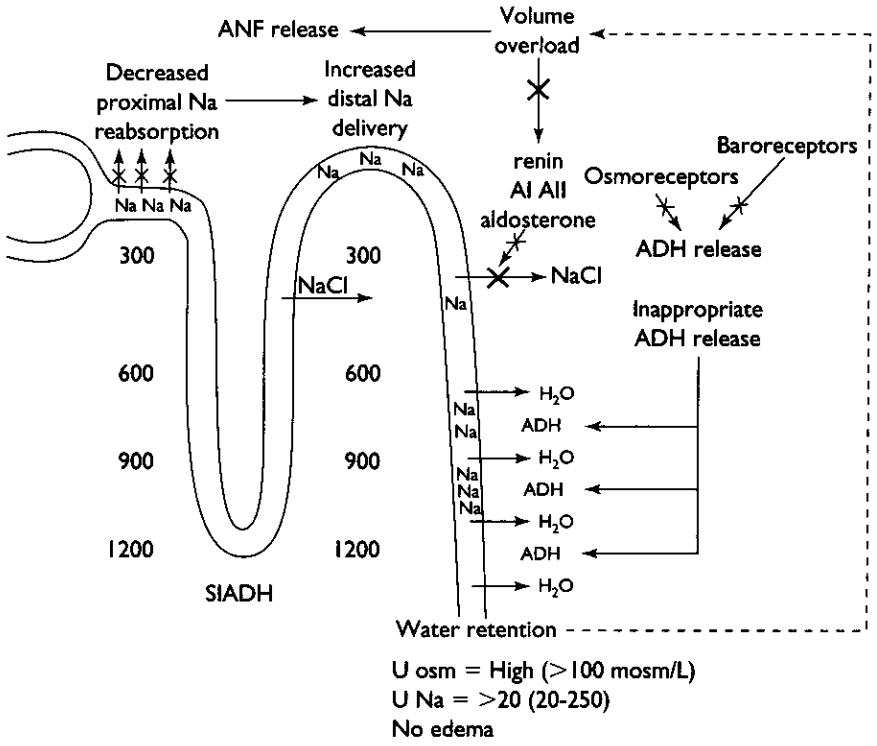
9-1-2 Urinary dilution is impaired in states associated with either a true or "effective" decrease in circulation volume. This inability to dilute is related to effects of a decrease in distal delivery of filtrate to diluting segment and stimulation of ADH release. Urine is not only concentrated but is relatively sodium free, in an attempt to replete volume.

edematous patient. This may seem contraindicated since diuretics can cause hyponatremia, but the effect that diuretics have on the serum sodium is a function of the water intake. Since loop diuretics inhibit both concentration and dilution, the water loaded patient will retain water and lower the serum sodium concentration, and the water restricted patient will lose water and raise the serum sodium. By "poisoning" the ascending loop of Henle, loop diuretics decrease the osmolality of the medullary interstitium. Therefore, even if ADH cannot be suppressed, the effects of this hormone will be attenuated by the use of a loop diuretic, and the urine will become more dilute. Finally, there may be a therapeutic advantage to the sodium loss that is achieved with diuretic usage in the edematous patient.

Patients with psychogenic polydipsia should be easy to treat because mild water restriction alone prevents the development of hyponatremia. This "restriction" is only relative since the patient with normal urinary dilution can still ingest several liters of water per day without the development of hyponatremia. Nevertheless, this is often difficult because the delusions that frequently accompany the psychiatric disease often involve water ingestion. Diuretics should be avoided in this condition since urinary dilution is normal. Their usage would exacerbate the hyponatremia if excessive fluid intake remains constant.

The low solute intake-related hyponatremias ("tea and toast" and "beer drinkers") are rare but are easily treated with an increase in solute (sodium and protein) and a decrease in water intake. Diuretics should similarly be avoided as urinary dilution is also intact in these conditions.

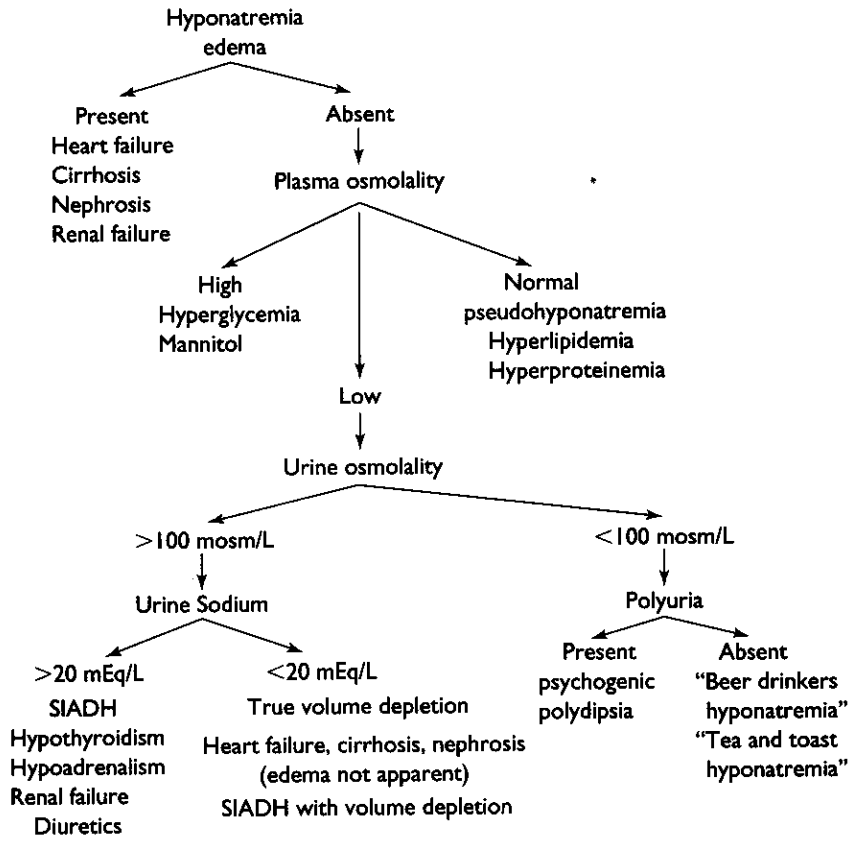
Since the primary defect with the SIADH is ADH release, ADH suppression may not be easily



9-1-3 Because sodium is handled normally in SIADH, sodium excretion in urine reflects the volume status of patient. Because this tends to be high as water is retained, the urine sodium reflects this and is elevated. This natriuresis prevents edema formation.

accomplished unless related to a drug that can be discontinued. Treatment is aimed at water restriction in addition to decreasing the effects of ADH. The latter can be easily achieved with a loop diuretic. Lithium and high dose demeclocycline (1200 mg/day) have been used as they have the ability to directly block the effects of ADH on the collecting duct, but toxicity (lithium) and cost (demeclocycline) may limit their usage. If loop diuretics and fluid restriction alone are unsuccessful in maintaining the patient's serum sodium, the patient with chronic SIADH may benefit from an increased solute diet, high in dietary sodium and protein. This will allow a greater daily water intake. This can be achieved with salt tablets (17.4 g NaCl/day = 600 mosm/day) and/or oral administration of urea (36 g/day = 600 mosm/day). By increasing the daily osmotic load from 600 mosm/day to 1200 mosm/day, the patient would be able to increase his or her daily intake of fluid by 100%. Most patients with SIADH can be adequately managed with a loop diuretic, a high sodium diet, and modest fluid restriction.

Severe hyponatremia, no matter what the cause, may require acute intervention. If the patient is asymptomatic, the brain's defense mechanisms have been successful in preventing cellular swelling, and fluid restriction alone should be sufficient. If the patient has symptomatic hyponatremia, either as a result of too rapid a fall or too severe a reduction in the serum sodium to avoid cellular swelling, treatment is aimed at rapidly reducing brain water. This can be achieved with hypertonic saline, usually accompanied by a loop diuretic to assist in urinary dilution. An increase in the serum sodium of 5 to 10 mEq/L (10



9-1-4 Approach to patient with hyponatremia based on presence or absence of edema and values of plasma and urine chemistries.

to 20 mosm/L) will decrease brain water significantly and should be attempted immediately in the symptomatic patient. After this increase has been achieved or after the patient becomes asymptomatic, whichever comes first, the patient is placed on fluid restriction alone to allow a slower correction. Increases in the serum sodium greater than 12 mEq/day are discouraged as this has been associated with the later development of central pontine myelinolysis (CPM), from which the patient may never recover. The clinical features of CPM include motor abnormalities that may insidiously progress to flaccid quadriplegia, respiratory paralysis, pseudobulbar palsy, and alterations in mental status with coma. This sequela appears to be more common in women, especially those who are postoperative. Too rapid a correction in the extracellular osmolality may actually lead to brain cell dehydration and may be the pathophysiologic explanation for CPM. Because of the concerns of the development of this dreaded condition, patients with symptomatic hyponatremia need to be treated very carefully. Those that are asymptomatic should not be treated aggressively, and fluid restriction alone should suffice. Special care must be taken in treating symptomatic SIADH patients with intravenous fluids. Although normal saline has a sodium concentration of 154 mEq/L and would be expected to raise a patient's serum sodium when administered, it can actually result in a worsening of hyponatremia. This is the result of the kidney's

continued retention of water in the face of sodium excretion. In other words, the kidney can extract the water out of the normal saline and excrete the sodium, thereby further lowering the serum sodium concentration. It is in this situation that the urine sodium concentration can exceed that of the serum. If normal saline is administered with a loop diuretic, this phenomenon will not occur since urinary concentration will be impaired. Therefore, if normal saline is being used as a therapy for the symptomatic patient with SIADH, a loop diuretic must be administered simultaneously for this treatment to be effective. This is not necessary when using 3% saline since the kidney cannot concentrate beyond the 3% being administered. Patients with symptomatic hyponatremia secondary to psychogenic polydipsia should be able to correct themselves fairly rapidly, with fluid restriction alone.

QUESTION 5 What are the pertinent positives of this case, and what is your treatment guideline?

The patient presents with symptomatic hyponatremia. He appears euvolemic and has no edema. His blood chemistries demonstrate a low serum osmolality, creatinine, uric acid, and a normal blood glucose. The urine is concentrated with a "high" sodium content. These findings are all consistent with SIADH (Fig. 9-1-4) and is most likely secondary to a paraneoplastic process related to his lung mass. Thyroid and adrenal function should be evaluated.

Because he is symptomatic, he should immediately receive hypertonic saline with a loop diuretic to decrease cerebral edema. His serum sodium should be followed every hour or two, and when it approaches 115 mEq/L, the hypertonic saline and diuretic should be discontinued, and he should be put on fluid restriction alone to minimize the risk of the later development of CPM. Chronic therapy will require fluid restriction with the possible addition of a loop diuretic and a high salt diet. If his urine osmolality remains constant at 600 mosm/L, he will be "allowed" an intake of 1L fluid/day if he has an osmotic output of 600 mosm/day. A loop diuretic, by poisoning the ascending loop of Henle, will decrease the medullary osmotic gradient. This would result in a urine concentration that is closer to 300 mosm/L. This maneuver by itself would allow an increase in the daily fluid intake to 2L if the daily solute intake remains at 600 mosm/day (2 L/day of 300 mosm/L urine = 600 mosm/day). Other therapies may be necessary if these are not sufficient.

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