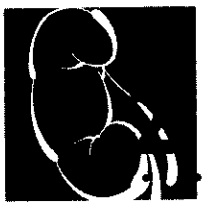
CASE



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A 20-year-old man was admitted to the hospital complaining of polyuria and increased thirst. He also noted a craving for ice water. He estimated a daily urine volume in excess of 9 to 10 L/day. There was no history of head trauma, headache, visual changes, diabetes, or psychiatric disease. Upon admission, his physical and neurologic examinations were normal.

The laboratory examination revealed: sodium 145 mEq/L, potassium 4.1 mEq/L, chloride 110 mEq/L, bicarbonate 23 mEq/L, BUN 8 mg/dl, creatinine 0.8 mg/dl, and blood glucose 96 mg/dl. The urinalysis revealed a specific gravity of 1.002; no glycosuria was present. His weight was 80 kg. The plasma osmolality was 290 mosm/L, and the urine osmolality was 60 mosm/L.

QUESTION 1 Define polyuria and what are the physiologic mechanisms that determine the daily urine output and allow for day-to-day changes in fluid intake?

Polyuria must be first distinguished from urgency and frequency resulting from lesions of the lower urinary tract. Since this may be difficult in some patients, a 24-hour urine volume measurement may be necessary to allow this distinction. It is difficult to define a normal urine flow in a 24-hour period. However, an understanding of the determinants of urine volume allow us to give a range of "normal" daily urine volumes. Under normal conditions, nitrogenous end-products (urea) and dietary electrolytes, when excreted into the urine, provide a daily solute load of approximately 600 mosm. The minimum amount of urine required to excrete this daily solute load depends on maximal urinary concentrating ability. Under optimal conditions the urine can be maximally concentrated to 1200 mosm/L. This would require only 500 ml of urine to excrete the daily 600 mosm solute load (0.5 L × 1200 mosm/L = 600 mosm). Assuming no insensible losses (for ease of calculation, as will be the case for this entire chapter), this would require a 500 ml water intake to maintain a steady state. Regular dietary habits usually exceed 500 ml water intake per day, and therefore the solute load is excreted in a less than maximally concentrated urine. One liter of water intake per day, (and therefore 1 L of urine output/day) would require that the urine be concentrated to 600 mosm/L to excrete the daily 600 mosm solute load; 2 L oral intake = 2 L of 300 mosm/L urine, 3 L intake = 3 L of 200 mosm/L urine, 6 L intake = 6 L of 100 mosm/L urine and 12 L of intake would produce 12 L of 50 mosm/L urine. Therefore, in persons whose urinary concentrating and diluting ability is intact, fluid intake determines urine output. Since an average intake of fluid is usually less than or equal to 3 L/day, polyuria is often defined by daily urine volumes that exceed 3 L.

In situations where renal concentration is impaired, the minimum urine output required to excrete a daily solute load increases. For example, if the maximum urinary osmolality obtainable is 300 mosm/L, 2 L/day of urine are required to excrete the daily 600 mosm solute load. Although this appears to represent a relatively severe inability to concentrate urine (normal being 1200 mosm/L), the patient with this condition is usually asymptomatic since a 2 L/day urine output would not appear excessive to most people. As urinary concentration becomes more impaired, urine output increases significantly, and symp-

tomatic polyuria is more likely to be seen. A patient with a maximum urinary osmolality (maximum Uosm) of 200 mosm/L would require 3 L/day to excrete the 600 mosm/day solute load; with a max Uosm of 100 mosm/L, 6 L of urine are required and with severe concentration defect of a maximum Uosm of 50 mosm/L, 12 L of urine/day are required. To avoid water depletion, the patient with a significant urine concentration defect must therefore replace urinary losses through oral intake of equal amounts of water.

If the daily solute load is increased, the urine output must increase for any given maximum Uosm. For example, if the daily osmotic load is increased from 600 to 800 mosm/day and the maximum Uosm is 100 mosm/L, the urine output must increase from 6 to 8 L/day to excrete this increased daily solute load. Therefore, when urinary concentration is impaired, urine output determines fluid intake, and urine output is a function of the daily solute load and the maximum Uosm obtainable.

QUESTION 2 Characterize primary as opposed to secondary polyuria, and what is a differential diagnosis of the polyuric state?

Polyuria can exist either as a primary response to "excessive" water intake or as a secondary response to a defect in urinary concentration. The key to understanding polyuria depends on the ability to distinguish an appropriate polyuria from one related to a defect in urinary concentration.

Polyuria secondary to excessive water intake is referred to as psychogenic polydipsia, and the reader should refer to Nephrology Case 1 for a discussion of the topic. As is demonstrated in that discussion, if urinary dilution is intact while undergoing a water load, water retention and plasma hypoosmolality (hyponatremia) are not seen unless water volumes in excess of 12 L/day are ingested. Water intake values less than this will still demonstrate significant polyuria, but hyponatremia should not be seen as long as urinary dilution is intact. When plasma hypoosmolality accompanies polyuria, it can usually be assumed that excessive water intake is driving the polyuria. Plasma hypoosmolality is easily detected by demonstrating hyponatremia, unless the hyponatremia is secondary to an intracellular to extracellular shift of water (secondary to an osmotically active substance that is being excluded from the intracellular space, i.e., glucose, mannitol). Thus, hyponatremia in the setting of polyuria and normoglycemia is usually indicative of psychogenic polydipsia.

Polyuria can also be caused by defects in urinary concentration related to the inadequate release of or response to antidiuretic hormone (ADH). ADH acts on the kidney to regulate the volume and osmolality of urine. When plasma levels of ADH are high, water reabsorption occurs in the collecting duct. As a result the urine becomes concentrated, and the urine flow decreases. Since about 10% of the glomerular filtrate reaches the collecting duct, in a normal person with a normal glomerular filtration rate of about 140 L/day, this results in the delivery of about 14 L of filtrate/day to the collecting duct. Since reabsorption from the collecting duct is predominantly dependent on ADH, a defect in this can lead to volumes of urine >10 L/day. Conditions that have defects in ADH mediated water reabsorption are termed *diabetes insipidus (DI)*. Central DI is due to the failure of synthesis or release of ADH usually related to hypothalamic or pituitary disease. It may be idiopathic, although in adults it is more commonly secondary to a destructive process in the ADH producing cells of the hypothalamus. This is usually related to head trauma, hypophyseal surgery, primary craniopharyngioma, metastatic brain tumors, sarcoidosis, tuberculosis, or histiocytosis. Patients with DI have polyuria with a hypotonic urine. Because they are always excreting a dilute urine, they often have a plasma osmolality (serum sodium) that is mildly elevated. For reasons that are unknown, the craving for ice and cold fluids is common to central DI. If water intake is adequate, plasma osmolality (serum sodium) can be main-

tained in the normal range. Despite the persistent loss of water and the tendency towards plasma hyperosmolality, as long as the patient has an intact thirst mechanism, is conscious, and has access to water, normal water intake will replete urinary water losses and prevent plasma concentration. Thus, the persistent polyuria and polydipsia are more of an inconvenience than a threat. When patients with this condition are either unconscious, lose their thirst mechanism, or are unable to obtain water, then the condition becomes life threatening as severe hypernatremia will rapidly develop.

Nephrogenic DI is secondary to a collecting duct unresponsiveness to ADH and can be acquired or congenital. The congenital form is a rare hereditary disorder that usually only manifests in males. It appears to be caused by a metabolic defect in the cyclic AMP-mediated increase in collecting duct permeability to water in response to ADH. Acquired nephrogenic diabetes insipidus, on the other hand, can be caused by a variety of diseases. Multiple myeloma, amyloidosis, sickle cell disease, hypercalcemia, hypokalemia, lithium carbonate, demeclocycline, methoxyflurane, and amphotericin B have all been invoked as causes of nephrogenic DI. There are other conditions in which urinary concentration does not increase despite the presence of adequate levels of ADH and therefore could technically be classified as causes of nephrogenic DI, but these are related to an abnormally low maximum medullary osmotic gradient (≤350 mosm/L), not an unresponsiveness to ADH. This is commonly seen in chronic renal disease. Sickle cell anemia can result in renal medullary infarction and present with a similar concentrating defect. Since these latter conditions are only associated with relatively mild impairments in urinary concentration, polyuria is not usually noted unless the solute load is significantly increased.

A solute or osmotic diuresis, usually related to excessive excretion of urea, glucose, or sodium, causes polyuria by two mechanisms: (1) an increase in the solute load and (2) a decrease in urinary concentrating ability. Although an increase in daily solute load will increase the minimum urine output even when urinary concentration is normal (1200 mosm/day solute load × 1200 mosm/L maximum Uosm = 1 L/day minimum urine output), this will not result in polyuria unless urine osmolality is affected as well. For example, if the solute load is increased from 600 to 1200 mosm/day and the max Uosm is decreased from 1200 mosm/L to 300 mosm/L, the minimum urine required to excrete this daily solute load increases to 4 L and would present as polyuria. In fact, a defect in urinary concentration is common in disorders associated with a solute or osmotic diuresis. This is a result of two factors. When large amounts of a nonreabsorbed solute (glucose, urea, or sodium in the sodium loaded patient) are present in the urine, an increase in medullary blood flow occurs and results in a medullary "washout" of the osmotic gradient. Also, if large amounts of hypotonic fluid accompany the solute load, ADH becomes chronically suppressed. As ADH is partially responsible for creating the medullary gradient through the recycling of urea, its chronic suppression results in a decrease in the medullary osmotic gradient and therefore the ability to concentrate the urine. This process will only affect the ability to create a medullary concentration gradient above that of serum. Thus, although urinary concentration is impaired, the patient with a solute or osmotic diuresis will have a urinary osmolality that is at least isosmotic (i.e., ≥300 mosm/L).

A solute diuresis from glucosuria is usually related to hyperglycemia and is easily diagnosed. A urea solute diuresis is usually secondary to excessive oral or intravenous (total parenteral nutrition) protein feeding. If there is a question about this diagnosis, one can measure the 24-hour urine urea nitrogen. When translated into mg/day, and divided by 28, one can estimate the daily osmotic load in mosm/day that is being produced as a result of protein catabolism. Overjudicious administration of sodium-containing intravenous fluids may also result in a sodium

solute diuresis. This diagnosis is confirmed by demonstrating a decrease in urine output following a decrease in the fluid administration rate.

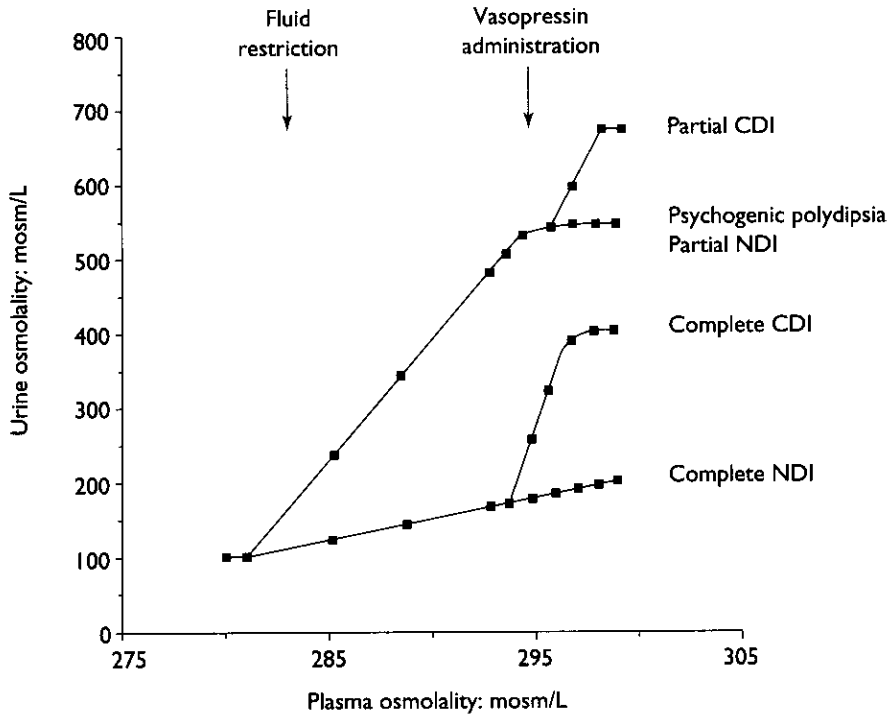
QUESTION 3 Within 6 hours of a fluid deprivation test, the patient's body weight decreased to 78 kg, the plasma osmolality rose to 303 mosm/L, and the urine osmolality rose to 150 mosm/L. Five units of aqueous pitressin (vasopressin) were given subcutaneously, and the urine osmolality rose to 500 mosm/L. What is the water deprivation test, and how does it help in the differentiation of polyuria?

From the above discussion it would appear easy to classify the causes of polyuria based on the serum and urine osmolality. The patient with primary polydipsia should have a plasma osmolality (serum sodium) on the low side of normal in addition to a dilute urine (<250 mosm/L). The patient with diabetes insipidus should have a plasma osmolality (serum sodium) on the high side of normal and a dilute urine (<250 mosm/L). The patient with a solute or osmotic diuresis should have a urine osmolality close to plasma (isosthenuria). In addition, certain clinical clues may help direct one's attention to a specific diagnosis. For example, a polyuric patient with a psychiatric history and episodic polyuria is suggestive of psychogenic polydipsia. A history of head trauma or neoplasm associated with the sudden onset of unrelenting polyuria, often accompanied by the craving for ice water, suggests central DI as the underlying disorder.

The most effective way to delineate between the disorders associated with a dilute urine, and to differentiate central from nephrogenic DI, is to perform a water deprivation test. Since the patient with psychogenic polydipsia will often go to great surreptitious lengths to obtain water, the water deprivation test may need to be done under constant supervision if this diagnosis is being entertained. Although the water deprivation test can be initiated as an outpatient, with fluid restriction overnight before arrival at the clinician's office, a severely polyuric patient with DI could become severely water depleted over this time. This may put the patient at risk. Therefore, we recommend that the test be performed under observed conditions. The patient with psychogenic polydipsia will, when fluid restricted, demonstrate an appropriate decrease in urine flow and a significant increase in urine osmolality. The patient with DI will continue to be polyuric with water deprivation. The urine osmolality may increase mildly in the DI patient after fluid restriction as volume depletion occurs and distal tubular and collecting duct urine flow rates slow, allowing ADH-independent water reabsorption to occur. This may allow the urine osmolality to increase, but usually not greater than 250 mosm/L.

During the water deprivation test, patients should not be allowed to lose >3% to 5% of their body weight. Hourly weights and measurements of urine and plasma osmolality are obtained. When the plasma osmolality reaches 300 mosm/L, 5 units of aqueous vasopressin are administered subcutaneously. Hourly urine and plasma osmolality measurements are continued. An even mildly elevated plasma osmolality of 300 mosm/L will maximally stimulate ADH release in a normal individual, therefore values above this are not required before the administration of ADH. Patients with central DI respond with an increase in urine osmolality and a decrease in urine output, while those with nephrogenic DI do not. Fig. 9-2-1 demonstrates the various patterns of response in urine output and urine osmolality to this test. As demonstrated, "partial" nephrogenic and partial central DI may be difficult to distinguish from psychogenic polydipsia. Patients with "partial diabetes insipidus" have incomplete defects, and although cannot maximally concentrate their urine, usually are able to achieve a max Uosm of close to 300 mosm/L. This is a mild concentrating defect and rarely causes significant polyuria under conditions of a normal solute load. Therefore, the need to distinguish these partial DI disorders from psychogenic polydipsia is uncommon.

The water deprivation test is therefore useful in distinguishing the two forms of diabetes insipidus



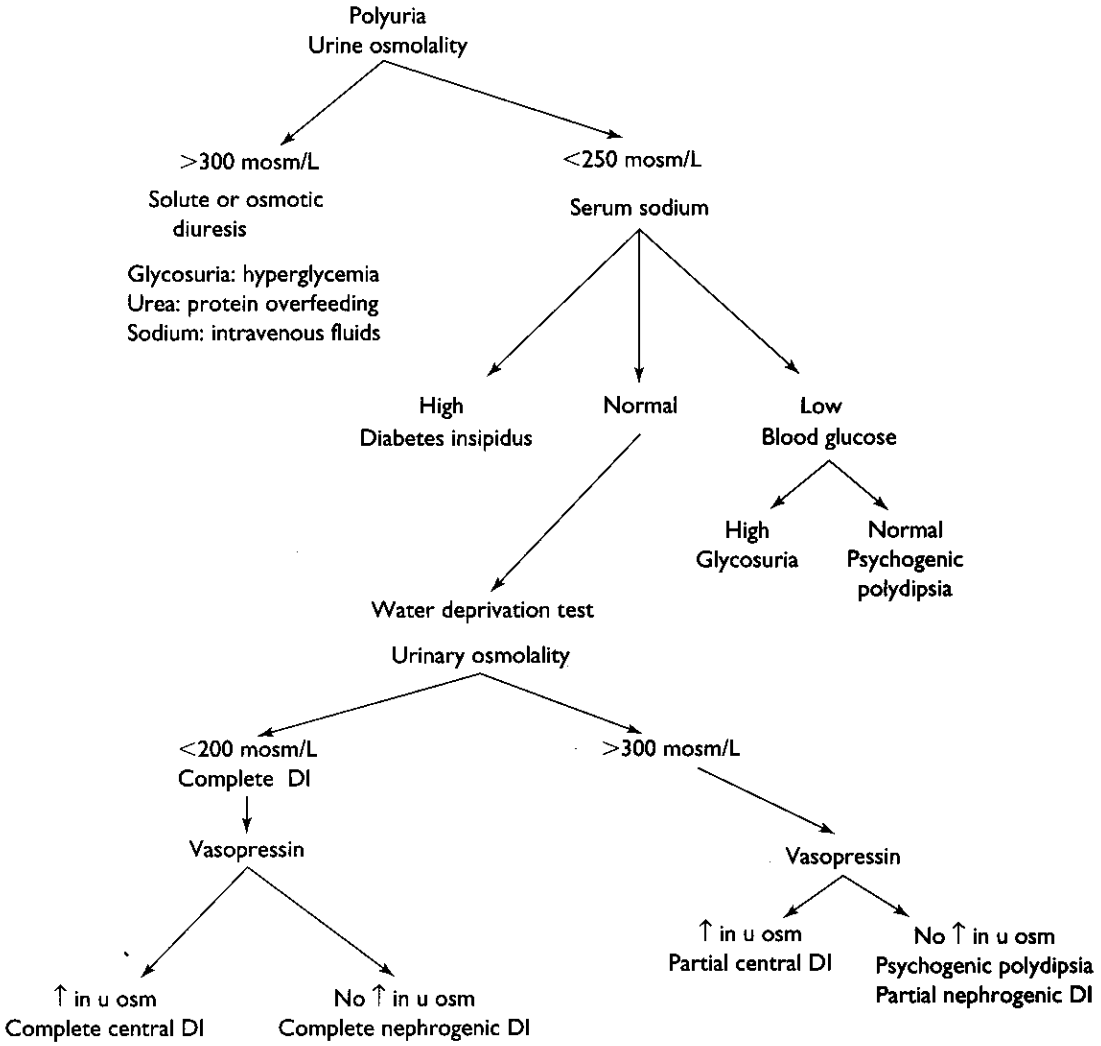
9-2-1 Different response patterns of urine osmolality to water deprivation test. Response in patients with "partial" diabetes insipidus disorders may be confused with psychogenic polydipsia although the need for this distinction is uncommon (see text).

from psychogenic polydipsia. These conditions are associated with a hypotonic urine. The patient with an osmotic or solute diuresis is easily distinguished from the former diagnoses by the demonstration of an isosmotic or slightly hypertonic urine, ≥300 mosm/L. Fig. 9-2-2 summarizes the approach to the polyuric patient, using the baseline urinary osmolality and the water deprivation test.

QUESTION 4 What is the appropriate mode of therapy for the polyuric patient?

The treatment of the various disorders associated with polyuria is fairly straightforward. If a solute diuresis is diagnosed, one simply has to decrease the solute load. Glycosuria is managed through improved diabetic control. A urea solute diuresis should respond to a decrease in protein intake. A saline diuresis should respond to a decrease in the intravenous fluid administration rate.

Central DI responds to ADH replacement, but it should be stressed that the goal in treating this disorder is to decrease, not normalize, daily urine output. Attempts at trying to normalize urine output risk inappropriate water retention and hyponatremia, if excessive ADH is administered and water intake continues. This would, if it occurred, be considered an iatrogenic form of SIADH. A nasal spray preparation of a long-acting vasopressin analog, DDAVP, is now commercially available and is both effective and convenient. Patients with mild central DI may require this therapy only at bedtime to prevent or minimize nocturia. Since urine output is a function of solute



9-2-2 Approach to patient with polyuria based on urine osmolality, serum sodium, and response to water deprivation test.

intake in patients with concentrating disorders, patients with DI should avoid high solute (sodium) diets.

Patients with nephrogenic DI do not respond to ADH replacement. As long as patients maintain an intact thirst mechanism, polyuria may be the only complaint. This can be decreased by a pharmacologic regimen aimed at moderately reducing extracellular fluid volume. Thiazide diuretics and salt restriction produce a mild volume depleted state. As a result, less filtrate is delivered to the collecting duct where the defect exists, and polyuria lessens. Loop diuretics may result in the same sodium depleted state but should be avoided because of the adverse effects on urinary concentration, which do not exist with thiazide diuretics.

CASE SUMMARY A 20-year-old man presents with a history of severe polyuria. Upon further questioning he can pinpoint the exact date on which his urine output increased. He also claims to crave very cold fluids. These aspects of his history are highly suggestive of central DI. His serum sodium is on the high side of normal, which makes psychogenic polydipsia unlikely. His urine is dilute despite this increase in plasma osmolality, indicating a urinary concentration defect. The patient undergoes a water restriction test, and his urine osmolality increases minimally, further ruling out psychogenic polydipsia. He has an excellent response to ADH that confirms the diagnosis of central DI. He should receive treatment with intranasal DDAVP to achieve a daily urine output of no less than 3 L/day. A computed tomography scan of his head demonstrated a craniopharyngioma. The patient underwent successful surgical removal but unfortunately continues to have central DI and will be maintained on intranasal DDAVP.

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