differentiation of primary polydipsia from diabetes insipidus (DI) as a cause of polyuria and polydipsia is important to avoid water overload, which can result from inappropriate vasopressin therapy. We present a report of such a scenario:

A 57-year-old male was referred for ambulatory evaluation of polyuria and polydipsia which he had been experiencing since the age of 17, when he suffered closed head trauma from a minor motor vehicle accident. His brother also has a history of polyuria, but less intense. Medical history is unremarkable except for hyperlipidemia, for which he takes atorvastatin. Patient also reports increased water intake as he is frightened about becoming dehydrated.

The physical examination was unremarkable. Previous workup was extensive, including brain imaging, overnight water deprivation test, and a trial of desmopressin. MRI of the brain showed loss of posterior pituitary bright spot, but no other abnormalities. Overnight water deprivation test revealed low normal plasma sodium level at 137 mmol/l, urine specific gravity of 1.009, and urine osmolality of 176mOsm/kg. The patient was subsequently started on desmopressin, which was discontinued after a few weeks due to iatrogenic hyponatremia. The plasma sodium concentration was 117 mmol/l requiring hospitalization.

We were consulted at this time. Given this clinical scenario, what is the most likely diagnosis?

Discussion
Our case is noteworthy since the clinical presentation suggests a diagnosis of central DI, due to onset of polyuria and polydipsia after head injury, positive family history, and loss of posterior bright spot on pituitary MRI. Detailed history along with appropriate interpretation of routine laboratory studies, however, suggested a diagnosis of primary polydipsia.

Polyuria in adults is defined as urine output more than 3L/day (>40ml/kg/day). In the absence of the most common causes of polyuria, including uncontrolled diabetes mellitus or iatrogenic (furosemide, lithium, mannitol, intravenous fluids) or post-obstructive polyuria, three major categories remain: primary polydipsia, central DI, and nephrogenic DI.

The sustained increase in water intake in patients with primary polydipsia may be due to hypothalamic lesions of the thirst center (tumors, infiltrative disease) or more commonly due to underlying psychiatric illness. Polydipsia is reported in at least 20 percent of psychiatric in-patients, and frequently these patients are very difficult to restrain from their habitual fluid intake problem.

In patients with central DI, vasopressin secretion is decreased or absent. Anatomical causes of central DI can be at the level of the hypothalamus, where vasopressin is synthesized and where hypothalamic osmoreceptors are located (supraoptic or

Case Report: Primary Polydipsia vs. Central Diabetes Insipidus (DI) After Head Trauma

Finding the cause of polyuria and polydipsia is important to avoid inappropriate vasopressin therapy and resultant water overload.

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paraventricular nuclei), or at the level of the supraopticohypophyseal tract. The posterior pituitary consists only of the distal axons of the hypothalamic neurons. Lesions of the posterior pituitary rarely cause permanent DI, as hypothalamic nuclei can still produce and secrete vasopressin directly into the circulation. Thus, injury of the pituitary stalk, which is very close to the hypothalamus above the level of the median eminence, will cause central DI due to denervation of the posterior pituitary from the hypothalamus.3

During head trauma, the pituitary stalk is the most vulnerable, since the pituitary gland is well protected within its bony cage, the sella turcica. Depending on the severity of the pituitary stalk injury, the degree of central DI can significantly vary. DI may complicate the postoperative course in as many as 30 percent of patients who have undergone transsphenoidal surgery.4 This is usually temporary.

Some of these patients who sustained hypothalamic or pituitary stalk injury during neurosurgery or trauma will develop the classic triphasic pattern of central DI.4 The initial phase is polyuria starting soon after the injury, lasting a few days, followed by a second phase, in which stored vasopressin is released from the degenerating posterior pituitary and therefore patients will have either transitory normal water balance or will develop hyponatremia in cases of excess water intake. The third phase or permanent central DI develops when vasopressin stores are depleted, though case reports of recovery after prolonged time periods have been described.

Roughly half the cases of central DI are caused by trauma (surgery or head trauma), tumors (lung cancer, leukemia or lymphoma) or infiltrative diseases (Langerhans cell histiocytosis, sarcoidosis, Wegener’s granulomatosis). The other half are due to idiopathic DI,6 where an autoimmune process is the most common culprit, especially in young adults. Among patients with idiopathic central DI, the most common finding on brain imaging is loss of the posterior pituitary hyperintense signal and pituitary stalk thickening.

The likelihood that pituitary stalk thickening is associated with central DI is 80 percent in young females with other endocrine autoimmune diseases in the presence of circulating antibodies to vasopressin secreting cells.6 In children with idiopathic central DI, pituitary stalk thickening is commonly associated with growth hormone deficiency,7 whereas children with normal MRI and other anterior pituitary endocrinopathies have a higher chance of having a structural suprasellar8 abnormality that may not be visible on initial imaging; therefore regular endocrine and neuroradiological follow-up is needed.

A rare cause of central DI is hypoxic encephalopathy (due to shock or cardiopulmonary arrest). The least common cause is familial central DI, an autosomal dominant disease caused by mutations in the arginine-vasopressin gene with onset of symptoms several months to years after birth.8

Gestational DI,10 with an incidence of approximately four in every 100,000 pregnancies, is also worth mentioning. As its name implies, it is a transitory form of DI in pregnancy caused by placental liberation of oxytocinase and thus resolves after removal of the placenta. Oxytocinase is a placental enzyme that indiscriminately breaks down oxytocin as well as vasopressin due to their similar molecular structures. Desmopressin, a synthetic analog of endogenous vasopressin, is resistant to oxytocinase and might be required in some patients with gestational DI.

Nephrogenic diabetes insipidus is characterized by genetic or acquired renal unresponsiveness to vasopressin and therefore decreases urinary concentrating ability. Vasopressin acts on two types of peripheral receptors: V1, mostly found on blood vessels, and V2, mostly found in the renal collecting tubules. The activation of V1 causes vasoconstriction, and activation of V2 receptors produces antidiuresis; hence two names for the same hormone, vasopressin or antidiuretic hormone (ADH). Vascular endothelial cells also have V2 receptors, where their activation induces secretion of von Willebrand factor.
A mild form of nephrogenic DI is frequently seen in elderly patients due to chronic renal insufficiency. In adults it can also be acquired due to drugs, among which lithium is the most common culprit. Other reversible causes include hypercalcemia or hypokalemia. In children, hereditary causes are more common (90 percent of cases of hereditary nephrogenic DI have X-linked inheritance).

Diagnosis
The diagnosis of DI depends on a careful and complete clinical evaluation, followed by random basic metabolic profile, plasma and urine osmolality, and a provocative test for confirmation. In a typical case of DI, random plasma sodium is above 143, serum osmolality is above 295mOsm/kg, and urine osmolality is below 150mOsm/kg. Patients with primary polydipsia also have low urine osmolality, but they may also have low normal plasma sodium and osmolality. These typical laboratory findings, however, will be present only in patients who don’t have access to water or patients with an impaired thirst center, like unconscious patients. Another laboratory finding, albeit nonspecific, is the serum uric acid level. Patients with DI usually have serum uric acid levels above 5mg/dl, while patients with primary polydipsia have levels below 5mg/dl.

The dehydration test is a universal provocative test that can be used to clinch a diagnosis of DI. Dehydration results in elevation of plasma osmolality, stimulating vasopressin secretion, which then causes appropriate concentration of urine. In patients with large volume polyuria and high clinical suspicion for DI, the test must be performed under medical supervision in a controlled setting to avoid the potential for extreme dehydration and its sequelae. This is because severe dehydration with resultant hypernatremia can develop within a few hours with potential serious sequelae. Failure to concentrate urine osmolality greater than plasma in response to adequate dehydration is diagnostic of DI.

In patients who cannot concentrate urine, a plasma osmolality and plasma vasopressin are drawn at the conclusion of the dehydration test when a desmopressin challenge test is performed. A patient is given 2lg of desmopressin intravenously or intramuscularly. Urine output and osmolality are recorded initially then hourly for an additional two hours. Patients with central DI will concentrate urine after receiving vasopressin, while patients with nephrogenic DI will not concentrate urine and have high vasopressin levels.

Prolonged polyuria and polydipsia, regardless of the cause, can decrease maximal urine concentrating ability, which can make primary polydipsia indistinguishable from partial nephrogenic DI.

The preferred imaging test in the work-up of central DI is an MRI of the hypothalamus-pituitary. On T1 images a bright spot in the posterior pituitary is useful for excluding a diagnosis of central DI. However, this finding is present in only about 80 percent of normal subjects. The bright spot is an area of hyperintense signal on T1 images, which corresponds to the portion of the posterior pituitary where neurosecretory granules containing vasopressin are stored. Therefore the intensity varies with the amount of stored vasopressin and will be low in severely dehydrated patients (due to uncontrolled diabetes mellitus or nephrogenic DI) or can be completely absent in patients with central DI.

Ideally, treatment of polyuria and polydipsia should always be directed toward the underlying cause. Unfortunately, that may not be possible in the majority of the patients with central DI. Drug therapy, however, is not necessary in patients with mild DI if they have free access to fluids. In patients with central DI and intact thirst center where polyuria significantly interferes with their daily activities or sleep, desmopressin 5-10mcg once or twice daily is administered. In contrast to vasopressin, desmopressin has a much longer duration of action, is devoid of pressor effects, and in the ambulatory setting may be administered orally or intra-nasally. Thiazide is the only available treatment for nephrogenic DI. Psychiatric assessment and intervention are frequently needed for a patient with primary psychogenic polydipsia.
Assessing Our Diagnosis

Based on this information, why does the patient in our clinical scenario more likely have primary polydipsia rather than DI?

The acute onset of polyuria and polydipsia after a closed head injury does suggest a diagnosis of central DI (due to complete or partial loss of vasopressin). The prolonged duration of his symptoms, low normal plasma sodium levels, and his statements that he’s “frightened about dehydration,” however, favors a diagnosis of primary polydipsia (due to psychological issues or hypothalamic thirst center injury). Additionally, patients with DI (central or nephrogenic) usually present with plasma sodium levels above 142, while a level less than 137 strongly suggests primary polydipsia.

Other misleading findings in this case are a suggestive family history and abnormal imaging. Recall that hereditary hypothalamic DI starts in infancy or early childhood, and up to 20 percent of normal subjects can have an absent bright spot in the pituitary.

The goal of the overnight water deprivation test is to assess pituitary secretion of vasopressin in response to water deprivation and the kidney’s response to vasopressin. Urine osmolality above 600mOsm/kg excludes DI (indicates normal vasopressin secretion and normal kidney’s concentrating ability in response to dehydration). Urine osmolality below plasma osmolality can be seen in primary polydipsia (indicates a normal kidney’s diluting ability in response to excess water ingestion) or in DI (central due to inappropriate pituitary secretion of ADH or nephrogenic due to inappropriate kidney response to ADH). Therefore, in this patient the low urine osmolality could represent DI or primary polydipsia. The concurrent plasma sodium level of 137mmol/l makes the diagnosis of DI unlikely.

In some patients, it can be difficult to differentiate partial hypothalamic DI from primary polydipsia, in which case a trial of desmopressin may be considered. If a standard dose of desmopressin improves symptoms without reduction of sodium, then the patient almost certainly has partial central DI. However, if the desmopressin does not improve symptoms and/or the patient develops hyponatremia, then the patient likely has some abnormality of the thirst center and primary polydipsia.

Finally, although checking random ADH levels is almost intuitive, rarely does it prove useful in the diagnostic process. Falsely high or falsely low levels can be seen due to unreliable assays or physiologic suppression of ADH in patients with primary polydipsia.

Conclusion

The diagnosis of DI is often made clinically, while laboratory tests provide confirmation. Patients with primary or psychogenic polydipsia are distinguished by longstanding history of polyuria in the setting of increased water intake. Symptoms of underlying psychiatric problems commonly seen in these patients can be very subtle, and in most of the cases routine plasma sodium levels, urine osmolality, and overnight dehydration test are enough to make a correct diagnosis.