CLINICAL VIGNETTE

Doc I'm Always Thirsty, Should I Be Worried? Diabetes insipidus Due to Lymphocytic Hypophysitis

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Introduction

Diabetes Insipidus (DI) is a rare disorder of water homeostasis due to dysfunction in the release of antidiuretic hormone (ADH) from the posterior pituitary (Central DI) or in the function of ADH at the level of its receptor in the nephron (Nephrogenic DI). DI can sometimes remain undiagnosed for many years given the compensatory mechanism of thirst which can maintain a normal fluid balance in these patients. When patients present with polyuria and polydipsia physicians should consider DI in their differential diagnosis.

Presentation

A 36-year-old female with no past medical history presents to clinic with concern for excessive thirst. The patient says that for the past months she has noticed increasing thirst and needing to drink around 230 ounces of water a day to keep up with her thirst. She also wakes up 5 to 6 times overnight to drink water. She says that she feels she urinates frequently for many years with recent worsening and need to urinate multiple times over night as well. Her thirst and urination significantly interfere with her daily activities. Review of systems was negative for headaches, visual symptoms, dizziness, weight loss, weight gain, irregular menses, galactorrhea. She has no history of head trauma and family history is negative for diabetes, and she does not have any family members with similar symptoms. Her only medication is drospirenone-ethinyl estradiol for birth control. She does not use supplements and her social and surgical history were noncontributory.

Her vital signs showed blood pressure 120/83, heart rate of 61, weight of 133 pounds, height of 5 feet 3 inches with a BMI of 23.58 kg/m^2. Her physical exam was normal including grossly normal visual fields and extraocular movements.

Her baseline labs were notable for sodium 137 mmol/L (135 - 146 mmol/L), potassium 4.2 mmol/L (3.6 - 5.3 mmol/L), creatinine 0.92 mg/dl (0.60 - 1.30 mg/dL), fasting glucose of 88 mg/dl (65 - 99 mg/dL), HbA1c 5.4% (<5.7%), calcium 9.1 mg/dl (8.6 - 10.4 mg/dL), urine specific gravity 1.005 (1.005 - 1.030). Her 24-hour urine volume was 5 L/24h (< 3 L/24h). She underwent an overnight water deprivation test to evaluate her polyuria and polydipsia. The morning after the water deprivation test her sodium increased to 146 mmol/L with osmolality of 298 mOsm/kg with low urine osmolality at 254 mOsm/kg with urine specific gravity of 1.007. This confirmed Diabetes insipidus (DI). She was given desmopressin with immediate improvement in her symptoms and increase in her urine osmolality to 766 mOsm/kg confirming central DI over nephrogenic DI. Her MRI pituitary showed signs of Lymphocytic Hypophysitis and an incidental 4 mm pituitary microadenoma. Pituitary hormone labs showed mildly elevated prolactin 56.2 ng/ml (3 - 23.1 ng/mL) with normal thyroid, growth hormone, cortisol and sex hormones. Twenty-four-hour urine cortisol was also normal. She was started on desmopressin given concern for central DI with excellent response without sleep interruption due to thirst or urination. Evaluation for causes of lymphocytic hypophysitis was unrevealing including normal IgG4, ferritin, ANCA, MTB-Quantiferon-Gold.

Discussion

Polyuria is defined as urine output above 3 L/day in adults. The baseline laboratory evaluation in a patient with polyuria should rule out hyperglycemia, hypercalcemia, renal dysfunction and hypokalemia.[1] The most common cause of polyuria is osmotic diuresis in the setting of hyperglycemia. Close evaluation of current medications should also be done to rule out medication induced polyuria from diuretics. Lithium use may raise concerns for nephrogenic DI.

If the initial testing is unrevealing and the patient is confirmed to have dilute diuresis, further investigation is needed to differentiate excessive water intake or primary polydipsia (PP), from an inability to concentrate urine, or Diabetes Insipidus (DI). DI can be Central DI, caused by decreased production of ADH from the posterior pituitary or Nephrogenic DI with decreased ADH response in the collecting duct of the nephron. Thirst is important backup mechanism when pituitary or renal mechanisms fail to maintain body fluid homeostasis, but often at the expense of clinically pronounced polyuria and polydipsia.[2] Patients with DI and preserved thirst mechanism will not differ biochemically from patients with PP. Clinical signs which may be more indicative of PP includes history of psychiatric disorder and excessive thirst and urination during the day with lack of overnight symptoms.[1]

The water deprivation test is the best test to differentiate PP from DI. This can be done by asking the patient to abstain from drinking any fluids over an 8-hour period followed by collecting blood and urine tests. Water deprivation testing

requires careful supervision since in some cases of complete DI this can result in severe hypernatremia. The goal of the water deprivation test is to increase the serum osmolality above 295 mOsm/kg and serum sodium above 145 mmol/L to stimulate maximum ADH release from the posterior pituitary.[1] In our patient we were able to achieve this with water deprivation alone but in cases of partial DI or PP this may be harder to achieve with inconclusive diagnostic testing if the threshold values are not reached. In these cases, hypertonic saline infusion may be necessary. In the setting of an elevated serum osmolality, urine should be maximally concentrated with a urine osmolality above 750 mOsm/kg if the ADH function is normal. Patients where urine osmolality increases to more than 750 mOsm/kg after water deprivation testing rules out DI and the patient has PP. DI is diagnosed when the serum osmolality is elevated and the urine osmolality is inappropriately low, such with our patient. The second step of the water deprivation test is differentiating central DI from nephrogenic DI. This is achieved by measuring the response of the urine osmolality after a dose of desmopressin (DDAVP). After administering IV or intranasal DDAVP urine osmolality should increase more than 50% in central DI but will not increase as significantly in nephrogenic DI due to decreased response of the receptors to ADH.

Other methods of evaluating the function of ADH have been studied but are not widely available. Direct measurement of ADH is not helpful for the diagnosis of DI given the low diagnostic accuracy of this test and its availability limited to specialized centers. Recently the use of copeptin, the c-terminal glycoprotein of the ADH prohormone shows promise in diagnosis of DI.[2] A single baseline copeptin level of more than 21.4 pmol/L was found to be diagnostic for nephrogenic DI without the need for water deprivation testing. Baseline copeptin of less than 2.6 pmol/L has high sensitivity and specificity for central DI.[3] Copeptin can also be used during water deprivation testing in cases where the results are indeterminate. Unfortunately, at this time copeptin is not widely available in commercial labs limiting its use.

Once the diagnosis of central DI is established MRI pituitary is indicated to rule out structural causes. Central DI may occur due to lesions of the posterior pituitary or the hypothalamic median eminence resulting in deficient synthesis of ADH. Several acquired and congenital disorders can cause central DI. The most common acquired cause is pituitary surgery or head trauma. Pituitary surgery can lead to transient DI in 30% of cases and permanent DI in 2-10% of cases.[4] Central DI due to pituitary adenomas is extremely rare even in cases with complete anterior pituitary dysfunction. Another cause is autoimmune destruction of the pituitary cells or Lymphocytic Hypophysitis (LH) which presents with MRI findings of thickened pituitary stalk and symmetric enlargement of the pituitary. Central DI can also be caused by granulomatous, infectious, neoplastic or drug induced processes affecting the posterior pituitary.[2] About 30-50% of patients have idiopathic central DI after extensive work-up of secondary causes. In these cases, repeat MRI after 6 months may be indicated.

Our patient had signs of LH on MRI. LH is a rare disorder characterized by autoimmune inflammation of the pituitary gland. It can cause various degrees of pituitary dysfunction. Our patient only showed signs of posterior pituitary dysfunction and mildly elevated prolactin. In a large case series from China DI was the most common endocrine dysfunction seen in 72% of patients, although anterior pituitary hormone dysfunction was also commonly found.[3] The cause is usually unknown and is frequently associated with pregnancy. In certain patients it can reverse spontaneously but in other cases it can progress to fibrosis and permanent pituitary dysfunction.[2,5] LH can be associated with IgG4-related disease, hemochromatosis, sarcoidosis, tuberculosis, granulomatosis with polyangiitis or use of immunotherapy.[5] Secondary evaluation was negative in our patient's case. She was also found to have a pituitary microadenoma, which do not typically cause DI, so this was likely an incidental finding.

Conclusion

Polyuria and polydipsia should prompt the physician to consider DI. It is important to understand that patients may not show any biochemical abnormalities due to compensatory thirst mechanisms, and so, in-depth evaluation should be pursued. Treatment of compensated DI can significantly improve quality of life.

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