DIAGNOSIS OF POLYURIA/POLYDIPSIA: A CASE-BASED APPROACH

Ellen N. Behrend, VMD, PhD, DACVIM (Small Animal Internal Medicine)
Auburn University, Auburn, AL

CASE 1

Signalment: 12 year-old, castrated male mixed breed dog; **History:** Polyuria/polydipsia past few weeks; having accidents in the house. Lives in Alabama. Mainly indoors. Up-to-date on vaccines and heartworm preventive. No travel history; **Physical examination:** Obese; **Laboratory data:** Complete CBC, profile, urinalysis done. Abnormalities were: Calcium (mEq/L) 11.8 (9.0-11.2); urine specific gravity = 1.009 with 1-2 WBC/hpf and 2-3 RBC/hpf

WHAT IS POLYURIA/POLYDIPSIA?

Polydipsia has been defined as water consumption > 100 ml/kg/24 hr in dogs and cats[1] but some difference may exist between species and another definition given is > 90 ml/kg/24 hr in dogs and > 45 ml/kg/24 hr in cats.[2] Urine production usually follows water intake. Water consumption below these amounts, however, may still be consistent with such a diagnosis. Additional factors need to be considered when deciding if polyuria/polydipsia (pu/pd) are present. Animals that eat canned food drink less than those that eat dry food. Also, normal habits should be assessed. For example, even if water consumption is below 90-100 ml/kg/24 hr in a particular dog, if this is more than twice normal for that pet, a diagnosis of pu/pd may be warranted.

If doubt exists as to whether pu/pd is present, its presence can be verified by quantitating water intake at home; hospitalization can alter drinking habits. Urine specific gravity (USG) assessment may be helpful. If USG is >1.015 on a sample collected at home, pu/pd is unlikely to be present. A USG showing maximal renal concentrating ability (>1.030 in dogs, >1.035 in cats) rules out the possibility of pu/pd.[2] If the USG is >1.030 and the owner believes the patient is polyuric, the history should be re-evaluated to ensure the problem is not dysuria, incontinence or a behavioral issue.[3]

WHAT ARE THE CAUSES OF POLYURIA/POLYDIPSIA?

To answer that question, understanding of the mechanisms regulating thirst and urine production is helpful. Anti-diuretic hormone (ADH) is released from the posterior pituitary, with the main function of causing water retention. Without ADH, dilute urine is excreted. When ADH is present, pores open in the membranes of the collecting ducts allowing passive movement of water from the hypotonic tubule lumen to the hypertonic medullary interstitium and concentrated urine is produced.[4] Since reabsorption of water in this part of the nephron is passive, the osmotic force responsible, i.e. the concentrated renal medullary interstitium, is crucial. The main stimulus to ADH release is increased extracellular fluid (ECF) osmolality. Below 280 mOsm/kg, serum ADH concentration is very low to non-detectable. Above this point, even a 1% increase in ECF osmolality stimulates ADH secretion. Maximal ADH secretion occurs at an ECF osmolality of 320 mOsm/kg. Anti-diuretic hormone is also released in response to a 10% decrease in circulating blood volume.[4]

Thus, production of concentrated urine has 3 requirements: 1. Adequate serum ADH concentration and the ability of the kidneys to respond to ADH. 2. Function of at least 33% of total nephron number, i.e. when >2/3 of the nephrons are lost, urine concentrating ability is lost. 3. A concentrated renal medullary interstitium.

Causes of pu/pd can be divided into those causing primary polydipsia vs. primary polyuria (see Table). Primary polyuria is divided into the categories of osmotic diuresis, central diabetes insipidus (CDI), primary nephrogenic diabetes insipidus (NDI) and secondary NDI. CDI is caused by lack of ADH. In NDI, the kidneys' ability to respond to ADH is compromised. In primary NDI, the problem is intrinsic to the kidneys. With secondary NDI, a non-renal problem interferes with the kidneys' response to ADH.

CAUSES OF POLYURIA/POLYDIPSIA
Primary Polydipsia
Psychogenic polydipsia
Liver failure
Neurological disease

Primary Polyuria
Osmotic diuresis
Chronic renal failure
Diabetes mellitus
Primary renal glycosuria
Post-obstructive diuresis
Central diabetes insipidus
Primary nephrogenic diabetes insipidus
Secondary nephrogenic diabetes insipidus
Acromegaly
Drug administration
Intestinal leiomyosarcoma (paraneoplastic)
Leptospirosis*
Liver failure
Hyperadrenocorticism
Hypercalcemia
Hyperthyroidism
Hypoadrenocorticism
Hypokalemia
Hyponatremia
Portosystemic shunt
Pyelonephritis
Pyometra
Renal medullary washout
Very low protein diet

*Possible, but not proven

A complete history and physical examination should never be underestimated as an important tool for diagnosis of any disease. For pu/pd, the presence of post-obstructive diuresis or drug administration as a cause can be ruled out on the basis of history. Medications that can cause pu/pd include corticosteroids, phenobarbital, and diuretics. In dogs, use of progestins can lead to acromegaly. The owner should also be asked about any recent diet changes since water content of food is an important water source and low protein diets can lead to low renal medullary tonicity.[3] Questions specific to possible differential diagnoses should also be asked.

A CBC, biochemical profile and urinalysis alone can rule out a number of differential diagnoses. If the cause for pu/pd remains unknown after the minimum database has been performed, a urine culture should be submitted regardless of the urine sediment exam to determine if occult pyelonephritis is present. Pyelonephritis is not always accompanied by fever and perinephric pain, and in dilute urine a sediment exam can be misleading. If the cause is then still not apparent, hyperadrenocorticism should be ruled out in dogs by use of an ACTH stimulation test or low-dose dexamethasone suppression test.[4,5] Pu/pd may be the only clinical sign present.

CASE SUMMARY: Ionized calcium was normal. Urine culture was submitted and an *E. coli* grew (>100,000 cfu/ml). The dog was placed on an appropriate antibiotic for 4 wks. Cultures were performed 1 wk after starting antibiotics and 1 week after therapy was stopped. Both negative. Pu/pd resolved. Plan: Reculture urine 4 weeks later.

CASE 2

Signalment: 13 year-old, spayed female miniature Poodle; **History:** Polyuria/polydipsia past few weeks. Mainly indoors. Up-to-date on vaccines and heartworm preventive; **Physical examination:** Normal; **Laboratory data:** Complete CBC, profile, urinalysis done. Abnormalities were: neutrophils 12.5 x $10^3/\mu l$ (3.0-11.5); lymphocytes 0.7 x $10^3/\mu l$ (1.0-4.8); ALT: 130 IU/L (10-120); ALP: 322 IU/L (11-210); urine specific gravity = 1.011 with inactive sediment; protein 1+. Urine culture negative.

As with any other diagnostic work-up, look for the more likely and more common causes first before moving on to less likely diseases. In dogs, the 3 most common causes of pu/pd are renal failure, hyperadrenocorticism (HAC) and diabetes mellitus. In cats, the 3 most common causes are renal failure, diabetes mellitus and hyperthyroidism.

Trying to diagnose psychogenic polydipsia, CDI or primary NDI should be the LAST step in a diagnostic work-up for pu/pd. First, psychogenic polydipsia, CDI and primary NDI are very uncommon. Second, in order to correctly interpret the results of the modified water deprivation test (MWDT), a test that can be performed to differentiate these three conditions, all secondary NDI causes must be ruled out first. Secondary NDI can look like primary NDI or partial CDI with respect to results of the MWDT. Last, the MWDT is a time-consuming and potentially expensive test to perform.

In this case, serum ALP activity is not very high and no other signs of hyperadrenocorticism (HAC) besides pu/pd are obviously present. However, Cushing's needs to be ruled out. Approximately 10% of dogs with HAC have a normal serum ALP activity. In addition, about 66% have proteinuria and/or hypertension. This dog may be proteinuric (1+ protein on urinalysis; a urine protein/creatinine (UPC) ratio is needed to quantify), and blood pressure should be measured. Even if the only abnormality identified (with measurement of liver enzyme activity, UPC, blood pressure, etc.) were pu/pd, HAC should still be ruled out. In cases such as these, I prefer an ACTH stimulation test.

Assessment of hepatic function via measurement of bile acids is not indicated in this case given the (lack of) clinical signs and laboratory findings. However, if liver function is at all questionable or liver enzymes (ALT and/or ALP) are moderately to severely increased, bile acids should be measured before an MWDT is performed.

CASE SUMMARY: An ACTH stimulation test was performed. Serum cortisol concentration pre-ACTH was 224 nmol/L (reference range 10-160 nmol/L; 8.1 μg/dL reference range 1-5 mcg/dl) and post-ACTH was 832 nmol/L (reference range 220-560 nmol/L; 30.1 μg/dL reference range 8-20 μg/dL). Systolic blood pressure was 190 mm Hg. UPC was 3.4. A diagnosis of HAC was made.

CASE 3

Signalment: 4 year-old, FS, Standard Poodle; **History:** Recurrent vomiting/diarrhea past 1-2 mth. Treated with fluids and antibiotics and always got better but then relapsed. Past 2 days she was anorectic and vomiting ~ 8X/day; **Physical examination:** Thin, 5% dehydrated; **Laboratory data:** Complete CBC, profile, urinalysis done. Abnormalities: Hematocrit 35% (37-55); BUN: 50 mg/dl (7-28); Creatinine: 2.0 mg/dl (0.9-1.7); Albumin: 4.7 g/dl (2.7-4.5); Na: 128 mEq/L (145-158); K: 6.2 mEq/L (4.1-5.5); Cl: 95 mEq/L (106-127); USG = 1.015 with inactive sediment.

The most likely differentials for this dog are hypoadrenocorticism and/or renal failure. Care should be taken in evaluating USG in azotemic patients in which a cause for pu/pd other than renal failure may also be present. A combination of inadequately concentrated urine and azotemia does not necessarily denote renal disease. Any cause of CDI or primary or secondary NDI can prevent the kidneys from concentrating urine in the face of prerenal causes of azotemia such as dehydration. If the cause for pu/pd is corrected, the azotemia will resolve if the kidneys are normal

CASE SUMMARY: An ACTH stimulation test was performed. Serum cortisol concentration pre-ACTH was <14 nmol/L (reference range 14-160 nmol/L; <0.5 μg/dL, reference range 1-5 mcg/dl) and post-ACTH was <14 nmol/L (reference range 220-560 nmol/L; <0.5 μg/dL, reference range 8-20 μg/dL). A diagnosis of hypoadrenocorticism was made and therapy initiated with DOCP and prednisone. At recheck one month after stabilization, serum Na, K, BUN and creatinine concentrations were normal and the USG was 1.032.

CASE 4

Signalment: 8 yr old FS yellow Labrador; **History:** For the past 2 weeks she has been lethargic and has had a decreased appetite. Over the past month, she has had some accidents in the house; **Physical examination:** normal; **Laboratory data:** Complete CBC, profile, urinalysis done. No abnormalities on bloodwork. Urine specific gravity = 1.004 with inactive sediment. Urine culture negative. ACTH stimulation test normal. UPC and BP normal.

Now is the time to do an MWDT. If the decision is made to perform a MWDT, decrease the patient's water consumption slowly e.g. 120 ml/kg/day 72 hrs prior to the test, then 90 ml/kg/day 48 hrs prior and then 60-80 ml/kg/day for the last 24 hours.[4] Prolonged pu/pd leads to renal medullary washout, and this gradual decrease allows for re-concentration of the renal medulla. The patient should be watched carefully during this time for dehydration.

When the test begins, stop all access to water. At this point the patient needs to be monitored carefully as dehydration can occur quickly. Empty the bladder and obtain an exact body weight. Measure USG and, if possible, a urine and serum osmolality. A BUN should be measured and hydration status assessed.[4] Do not do an MWDT if azotemia,

dehydration, hypercalcemia or significant systemic disease is present. During the test, empty the bladder every 60-120 minutes and measure USG and, if possible, urine osmolality. Assess body weight and hydration hourly. Measurement of serum osmolality periodically is ideal but not always available.[4]

An endpoint to the test is reached when: USG is >1.030 in dogs or 1.035 in cats; the patient is clinically dehydrated, azotemic or appears ill; the serum osmolality is 320 mOsm/kg; or there is a loss of 5% of body weight.[4] There is no specific time limit to this test, and in patients with mild pu/pd, an MWDT can take longer than 12 hours. If the endpoint has not been reached when the clinic is closing, the patient can be transferred to an overnight facility for continuation of the MWDT, or the animal can be provided with a maintenance water amount (2.75 ml/kg per hour that the animal is unobserved). The next morning, the patient should be weighed, the USG measured, the water withdrawn and the test continued until an endpoint is reached.[3]

If the patient has concentrated adequately at the endpoint, the diagnosis is psychogenic polydipsia. If there is inadequate concentration, the bladder is emptied, water is still withheld and aqueous ADH administered (0.55 U/kg IM with a maximum of 5 U per dog or cat). The bladder is then emptied every 30 minutes for 1-2 hours.[4] Alternatively 10 to 20 μg of the sterile preparation of desmopressin acetate (DDAVP), a synthetic vasopressin analogue, can be given intravenously or 20 μg of DDAVP (approximately 4 drops of the 100 μg/ml intranasal preparation) can be administered into the conjunctival sac.[6] Measurement of USG or urine osmolality should occur every 2 hours for 8 hours and then at 12 and 24 hours. The maximal response to intravenous desmopressin usually occurs 4 to 8 hours after administration, but it may take up to 24 hours.[3] If adequate concentration occurs (i.e. USG > 1.018 or urine osmolality increases at least fivefold), the diagnosis is CDI. If urine still remains unconcentrated, the diagnosis is NDI.

CDI can be differentiated into partial, where ADH release is subnormal but still present, and complete where no ADH release occurs. In an MWDT, those with partial CDI show some concentrating ability in response to absolute water deprivation and then increase another 10-50% in response to administration of exogenous ADH. Those with complete CDI will not concentrate in response to dehydration but will when given exogenous ADH.[4,7]

CDI can be congenital, idiopathic or due to trauma or inflammation or a pituitary tumor. In a dog >6 years old, the most common cause of CDI, either partial or complete, is a pituitary tumor. Even if neurological signs are absent, diagnostic imaging is warranted.[7]

An option to the MWDT when psychogenic polydipsia, CDI and primary NDI remain as the only possible differential diagnoses is to evaluate response to DDAVP therapy. In some clinics this has become the test of choice as compared to the MWDT for differentiating these three causes of pu/pd.

The patient's 24-hour water intake for 2-3 days is measured allowing free-choice water. A urine sample is collected at a given time each day to check urine osmolality and USG. After these initial days, the patient is treated with DDAVP by administering the intranasal preparation (1-4 drops placed in conjunctival sac) or the oral tablets (0.1 mg) every 12 hours for 5-7 days.[6] Water intake is monitored and a urine sample obtained on the 5th to 7th day at the same time of day as before treatment. A dramatic reduction in water intake and/or increase in urine concentration (i.e. >50%) provides strong evidence for CDI. Moderate response is consistent with partial CDI.[4] A mild response is suggestive of psychogenic polydipsia. If no response is seen, NDI is present.

CASE SUMMARY: An MWDT was performed and complete CDI diagnosed. A CT scan of the brain was normal. Therapy with DDAVP was initiated. After a few months, the medication costs were decided to be too much. The dog remained outside during the day when the owners were not at home. Plenty of fresh water was available at all times. She was brought inside at night and given a dose of DDAVP.

References available upon request.