

DIABETES INSIPIDUS IN DOGS

Marie E. Kerl, DVM, DACVIM, DACVECC
Associate Teaching Professor
Department of Veterinary Medicine and Surgery
University of Missouri

Arginine vasopressin (antidiuretic hormone [ADH]) is a peptide hormone produced by the hypothalamus and stored in and released from the posterior pituitary gland. The three triggers for pituitary release of ADH are stimulation of the hypothalamic osmoreceptors by an elevation in peripheral osmolarity above normal (reference range, 290–310 mOsm); other hypothalamic stimuli, such as pain, fear, and anxiety; and a significant (>10%) decrease in blood volume as detected by cardiac baroreceptors. After ADH has been released from the pituitary gland, it interacts with receptors at the basolateral cellular surface of the renal collecting tubule and collecting duct, and aquaporins (specialized channels for free water transport) are formed on the luminal surface of the tubular cells and permit renal uptake of free water and concentration of urine. After the channels are formed, water follows a concentration gradient to move into the renal medullary interstitium, which is an area with an elevated osmolarity compared with circulation.

Diabetes insipidus (DI) is characterized by an absolute or relative lack of ADH. Clinically, patients with DI have intense thirst and failure to concentrate urine. Two forms of DI are recognized. The first form, central DI (CDI), occurs when there is failure of ADH production from the hypothalamus or pituitary gland. Congenital and acquired CDI may occur; the acquired form most commonly occurs from head trauma or hypothalamic or pituitary area neoplasia. The second form of DI, nephrogenic DI (NDI), occurs when the kidneys fail to recognize ADH or are unable to respond appropriately. CDI and NDI both cause the classic clinical findings of polyuria and polydipsia with hyposthenuric urine (urine specific gravity [USG] <1.008).

DIAGNOSTIC CRITERIA

Historical Information

- The classic finding of CDI or NDI is polyuria and polydipsia over time (typically, weeks to months). Polydipsia is defined by documenting water consumption in excess of 50–100 ml/kg/day; however, dogs with absolute CDI consume more than 100 ml/kg/day.
- Mental dullness, behavior changes, or seizures may occur with CDI caused by a hypothalamic or pituitary tumor.
- History of head trauma.

- NDI typically occurs secondary to another disease process, so clinical signs of chronic illness (e.g., weight loss, decreased coat luster, loss of appetite, nausea or vomiting) may be seen.

Gender Predisposition

- CDI and NDI: Typically none.
- Acquired NDI caused by pyometra: Intact female.

Age Predisposition

- Congenital CDI is usually diagnosed before age 1 year.
- Acquired CDI is typically diagnosed after age 6 years if caused by neoplasia.
- Congenital NDI is usually diagnosed before age 1 year.
- Acquired NDI: There is no age predisposition, but many diseases that cause acquired NDI occur in older dogs.

Breed Predisposition

- None.

Owner Observations

- The hallmark finding with DI is polyuria and polydipsia.
- CDI: Water consumption >100 ml/kg/day; mental dullness, behavior changes, or seizures caused by a hypothalamic or pituitary tumor may be reported in dogs with acquired CDI. Owners sometimes report that the dog prefers drinking to eating.
- NDI: Acquired NDI is most common, so clinical signs of the primary disorder may be seen.

Other Historical Considerations/Predispositions

- Congenital CDI and congenital NDI cause lifelong polyuria and polydipsia.
- Acquired CDI: In young dogs, acquired CDI may be a long-term sequela from head trauma. In geriatric dogs, acquired CDI is usually the result of hypothalamic or pituitary neoplasia.
- Acquired NDI: Most causes of polyuria and polydipsia in dogs result from interference with normal ADH function in the kidneys.

Physical Examination Findings

- Examination abnormalities depend on the underlying cause of DI.

- Dehydration occurs rapidly with any form of DI if access to water is accidentally or intentionally restricted.
- Neurologic signs, including mental dullness and seizures, may result from severe hypernatremia because of insufficient water intake.
- Congenital CDI: The examination is often unremarkable.
- Acquired CDI: Mental dullness, seizures, or neurologic deficits may be seen if central nervous system (CNS) disease is present; evidence of head trauma may be present.
- Congenital NDI: The examination is often unremarkable.
- Acquired NDI: Examination abnormalities are usually consistent with the underlying cause.
 - Pyometra: Vaginal discharge, lethargy, dehydration, fever, tachypnea, tachycardia, abdominal distension, palpable uterine horns.
 - Hyperadrenocorticism: Pendulous abdomen, truncal alopecia, muscle wasting.
 - Hypoadrenocorticism: Poor body condition (weight loss is a historical finding), loose stools, weakness, collapse, bradycardia.
 - Hypercalcemia: Lymphadenopathy, hepato- or splenomegaly, anal sac tumor, generalized weakness.
 - Hypokalemia: Muscle weakness, cardiac arrhythmia.
 - Pyelonephritis: Abdominal pain, fever, lethargy, renal asymmetry.
 - Liver failure: Poor body condition, mental dullness, abdominal distension.

Laboratory Findings

Complete Blood Count §

- The complete blood count is usually unremarkable but may show hemoconcentration from free water loss if the animal is dehydrated.
- Leukocytosis with left shift may occur with acquired NDI from pyometra or pyelonephritis.
- Eosinophilia and an absence of a stress leukogram may occur with hypoadrenocorticism.

Serum Biochemical Profile §

- CDI and congenital NDI: Sodium and chloride are typically in the high to normal range when the patient is hydrated and may be above the reference range if the patient is dehydrated. Hyperproteinemia occurs with dehydration.
- Acquired NDI: Laboratory findings are usually consistent with the underlying cause:
 - Pyometra: Azotemia, hypernatremia, hyperchloremia, hyperphosphatemia.

- Hyperadrenocorticism: Elevated alkaline phosphatase, hypercholesterolemia.
- Hypoadrenocorticism: Hyponatremia, hypochloremia, hyperkalemia, hypercalcemia, azotemia.
- Hypercalcemia.
- Hypokalemia.
- Pyelonephritis: Azotemia.
- Liver failure: Hypoglycemia, hypoalbuminemia, hypocholesterolemia, low blood urea nitrogen, hyperbilirubinemia.

Urinalysis §

- USG <1.008 with absolute CDI and <1.020 with acquired NDI or partial CDI.
- Proteinuria may indicate glomerular disease.
- Evidence of urinary tract inflammation (sediment containing white blood cells, red blood cells, bacteria, or casts) is sometimes seen in patients with pyelonephritis.
- If pyometra is suspected, blind cystocentesis should not be performed to obtain urine.

Urine Culture §

- Urine culture should be obtained aseptically by cystocentesis as part of the diagnostic evaluation for polyuria and polydipsia; this is done to evaluate for pyelonephritis.
- Gram-negative bacteria is the predominant cause of urinary tract infections.

Other Diagnostic Findings

Because acquired NDI is the most common cause of DI, the diagnostic testing listed below should be conducted to rule out all causes of acquired NDI before diagnostic testing for CDI or congenital NDI is conducted.

Plain-Film Radiography §

- Thoracic radiography should be performed in geriatric animals and animals with hypercalcemia to rule out neoplasia.
- Abdominal radiography is indicated to evaluate the size and shape of the kidneys, the presence of radiodense urinary calculi, liver size changes, and enlargement of the uterus in females.

Abdominal Ultrasonography §

- Small, asymmetrical, or irregular kidneys are consistent with chronic kidney disease; large kidneys are consistent with acute renal failure.
- Renal pelvic dilation is consistent with pyelonephritis (either active or chronic disease).
- Adrenomegaly is consistent with hyperadrenocorticism.
- A small, irregular, or mottled liver is consistent with liver disease or failure.

- Hepatomegaly is consistent with hyperadrenocorticism or neoplasia.
- Splenomegaly is consistent with neoplasia.
- Uterine distension is consistent with pyometra.
- Ascites is consistent with liver failure.
- Lymphadenopathy is consistent with neoplasia.

Adrenocorticotrophic Hormone Stimulation Testing \$

- An excessive response (poststimulation cortisol >20 µg/dl) is consistent with hyperadrenocorticism.
- A lack of response (pre- and poststimulation cortisol <2 µg/dl) is consistent with hypoadrenocorticism.

Low-dose Dexamethasone Suppression Testing \$

- A failure to suppress (post-dexamethasone cortisol >1.4 µg/dl) is consistent with hyperadrenocorticism.

Bile Acid Testing \$

- Excessive response (postprandial bile acids >25 µmol/L) is consistent with liver disease.

Urine Protein:Urine Creatinine Ratio \$

- A ratio >1 in the absence of inflammatory urine sediment is consistent with renal protein loss.

Serum Osmolarity Testing \$

- Normal measured serum osmolarity is 290 to 310 mOsm/l in dogs.
- Dogs with DI usually have serum osmolarity measurements that are near or above the upper reference range.
- Dogs with psychogenic polydipsia (PP) usually have measurements in the low to low-normal range because thirst is not driven by osmolarity.

Urine Osmolarity Testing \$

- Measured urine osmolarity provides similar information to USG; it may be easier to interpret changes after water deprivation testing or vasopressin response testing.
- Urine osmolarity ranges for dogs that are hyposthenuric are typically <200 mOsm/l.

Modified Water Deprivation Test (WDT) \$-\$\$

After ruling out all more common diseases, DI should be differentiated from PP with either a modified WDT or an oral vasopressin response test.

- Water deprivation in an animal with DI may cause severe hypernatremia, azotemia, acute renal failure, coma, seizures, or death if the animal is not closely monitored.
- Animals that have lost appropriate medullary interstitium concentration secondary to any cause of chronic polyuria and polydipsia fail to concentrate urine. Some dogs with polyuria and polydipsia from acquired NDI may concentrate urine to some degree

CHECKPOINT

Some specialists believe there is never an indication to perform the modified water deprivation test because of potential excessive risk to the dog.

during a WDT, so all causes of acquired NDI should be ruled out before this test is conducted.

- Before absolute withholding of all food and water, oral intake of water should be gradually limited for 5 days before the initiation of the test to allow reestablishment of the medullary interstitium concentration. (This step distinguishes a classic WDT from a “modified WDT.”)
- At the time of complete water deprivation, body weight and complete physical examination with particular attention to clinical evidence of hydration status, USG, packed cell volume (PCV), total protein (TP), blood urea nitrogen (BUN), and sodium (Na⁺) should be recorded and reevaluated at 1- to 2-hour intervals until the test endpoint is reached. The test endpoint is urine concentration >1.025 or clinical dehydration (5% loss of body weight).
 - Urine concentration >1.025: The diagnosis is PP if all other causes of polyuria and polydipsia have been ruled out.
 - Urine concentration <1.025 and 5% dehydration: The diagnosis is DI.
- In partial CDI, urine may become somewhat concentrated during the WDT; however, it will not achieve complete concentration.
- If DI is diagnosed with WDT, a vasopressin response test should be conducted immediately. USG is measured and the urinary bladder emptied. Aqueous vasopressin is administered at 0.55 U/kg IM to a maximum dose of 5 U once. At 30-minute intervals for 2 hours, the physical examination is evaluated, the urinary bladder emptied, and USG measured.
 - Urine concentration >1.015 (urine osmolarity >600) after administration of aqueous vasopressin is consistent with CDI. No increase in urine concentration is consistent with NDI.
 - If no cause of acquired NDI is found, congenital NDI is suspected but is rare.
 - Dogs with partial CDI concentrate urine after administration of vasopressin.
- Dogs with DI typically become dehydrated within 4 to 8 hours; careful monitoring is essential throughout the testing period.
- Testing should be stopped if the dog develops mental dullness, obtundation, hypernatremia, azotemia, or dehydration.

- At the conclusion of the test, water should be reintroduced gradually at 10 to 20 ml/kg every 30 minutes for 2 hours. If no adverse effects are seen, free-choice water may be resumed.

Oral Vasopressin Response Trial

- This test may be performed instead of the WDT to diagnose CDI.
- Some dogs with polyuria and polydipsia from acquired NDI may concentrate urine to some degree during WDT, so all causes of acquired NDI should be ruled out before this test is conducted, and the clinician should evaluate serum osmolality. Serum osmolality in the high-normal range is consistent with CDI; the low-normal range is consistent with PP.
- If CDI is suspected, oral desmopressin acetate (DDAVP; a synthetic analog of ADH) may be administered. Commercially available tablet sizes are 0.1–0.2 mg/tablet. The dosage during the trial is empirical (0.1 mg PO tid for 7 days for 20-kg dogs; 0.2 mg PO tid or 7 days for 40-kg dogs). Polyuria and polydipsia should resolve during the testing period. The owner may collect urine daily for USG evaluation.
- If clinical response is seen during the trial, the dose may be tapered to the lowest possible dose to control signs.

Computed Tomography or Magnetic Resonance

Imaging \$\$\$-\$\$\$\$

- Dogs that are diagnosed with CDI or PP that have not had polyuria and polydipsia throughout life should have brain imaging performed to rule out hypothalamic pituitary area masses and trauma.

Summary of Diagnostic Criteria

- Polyuria and polydipsia: Usually chronic and extreme.
- Sufficient diagnostic testing to exclude more common causes of polyuria and polydipsia and acquired NDI.
- Modified WDT: Failure to concentrate urine when 5% dehydrated. Subsequent urine concentration after administration of aqueous vasopressin confirms CDI.
- Oral vasopressin trial: Reduction of polyuria and polydipsia and increase of USG with tid administration of oral vasopressin analog.
- Brain imaging for diagnosis of CDI or primary polydipsia in dogs with recent onset of polyuria and polydipsia.

Diagnostic Differentials

- Other causes of polyuria and polydipsia should be ruled out.
- All disorders that cause acquired NDI should be ruled out.

- Diabetes mellitus and diabetic ketoacidosis: The patient should be evaluated for glucosuria or hyperglycemia, ketonuria, and metabolic acidosis.
- PP is a rare disorder in dogs. It is differentiated from DI by modified WDT or vasopressin response testing.
- Primary renal failure: The patient should be evaluated for renal azotemia and isosthenuria. If acute renal failure is present, the cause should be found.
- Sudden acquired retinal degeneration is diagnosed by normal visual appearance of the retina and lack of response to electroretinography. The condition mimics hyperadrenocorticism, but the underlying cause is unknown. Polyuria and polydipsia precede blindness by days to weeks but usually resolve with time after the onset of blindness.
- High sodium intake.

TREATMENT RECOMMENDATIONS

Initial Treatment

CDI

DDAVP should be given in the oral or nasal form. The form used should be dictated by the animal's response to treatment, owner preference and convenience, and cost of the treatment options for the individual animal.

- Oral DDAVP: \$\$\$
 - Commercially available tablet sizes are 0.1–0.2 mg/tablet. The dose is empirical and may be tapered to the lowest dose and frequency needed to control clinical signs. Tablets have very poor bioavailability, and higher doses or dose increases are often necessary.
 - Dosages are 0.1 mg total PO tid for 20-kg dogs and 0.2 mg total PO tid for 40-kg dogs given until a response is seen. The dose should then be tapered to the lowest dose needed to control signs.
 - The anticipated cost for a 20-kg dog requiring 0.1 mg PO tid for control is \$350 to \$400 per month depending on the pharmacy's cost of the drug.
 - Treatment is lifelong.
- DDAVP nasal drops: \$\$\$
 - The drops are commercially available in a 0.1-mg/ml nasal spray. The nasal spray preparation may be administered as conjunctival drops.
 - The dose is empirical and may be tapered to the lowest possible dose. The starting dose is 1–4 drops sid–bid of the nasal spray applied in the conjunctival sac.

Congenital NDI

- Drugs to replace ADH are ineffective for this form of DI.

- A low-sodium diet may help alleviate clinical signs caused by reduction of glomerular filtration. \$
- Salt-restricted diets have <0.6 g/1,000 Kcal metabolizable energy. \$
- Thiazide diuretics inhibit sodium reabsorption in distal nephron segments to cause renal sodium wasting. This causes extracellular volume contraction, resulting in increased absorption of sodium and water in the proximal tubule. A slight increase in urine osmolarity and decrease in urine volume occur as a result of lower sodium in the distal segments. This treatment may occasionally cause mild hypokalemia. \$
 - Hydrochlorothiazide: 2.5–5 mg/kg PO q12h.
 - Chlorthiazide: 20–40 mg/kg PO q12h.
- Radiation therapy for hypothalamic or pituitary area mass: Prognosis is guarded to poor if neurologic signs are present at the time of diagnosis. \$\$\$\$

Acquired NDI

- The underlying disorder should be treated.

Alternative/Optional Treatments/Therapy

- Free-choice water administration: \$
 - Dogs with DI may remain stable without drug therapy if free-choice water is available at all times and dehydration does not occur.
 - Polyuria and polydipsia will continue; the patient should be given free access to areas to urinate. (This option may not be acceptable for owners without ready access to outdoor areas for the dog.)

Supportive Treatment

- Free-choice water administration: Even with drug therapy for DI, free-choice water should always be available. \$
- A low-sodium diet may help alleviate clinical signs by reducing glomerular filtration. Salt-restricted diets should have <0.6 g/1,000 Kcal metabolizable energy. \$

Patient Monitoring

- Dehydration may occur rapidly if water is restricted intentionally or accidentally or if the dog becomes ill and self-reduces water intake. Dehydration causes mental dullness or obtundation, hemoconcentration, hypernatremia, and prerenal or renal azotemia.
- Neurologic signs associated with hypothalamic or pituitary area masses may develop.
- Radiation therapy of the hypothalamic or pituitary area may cause secondary hypothyroidism, ocular damage, or blindness, depending on the radiation field.

Home Management

- Free-choice water administration: Even with drug therapy for DI, free-choice water should always be available. \$
- Salt-restricted diet. \$

Milestones/Recovery Time Frames

- Congenital CDI and NDI: The disease is lifelong, and a cure is not possible.
- Acquired CDI: If CDI is acquired secondary to trauma, clinical signs may improve with time or may be permanent. If CDI is acquired secondary to hypothalamic or pituitary neoplasia and the mass shrinks with radiation therapy, polyuria and polydipsia may improve or resolve. Brain tumors may reoccur after radiation treatment.
- Acquired NDI: The prognosis depends on the clinician's ability to diagnose and treat the primary disease.

Treatment Contraindications

- Water should not be restricted unless a supervised WDT is being performed.

PROGNOSIS

Favorable Criteria

- CDI acquired secondary to trauma may resolve.
- Acquired NDI may be managed or cured if the underlying cause can be treated.

Unfavorable Criteria

- Patients with CNS tumors causing acquired CDI have a guarded to poor long-term prognosis. If neurologic signs are present at the time of diagnosis, the prognosis for response to radiation therapy is poor.
- If renal failure, severe hypernatremia, or neurologic signs develop after water restriction, prognosis is guarded.

RECOMMENDED READING

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