Proceedings of the Southern European Veterinary Conference and Congreso Nacional de AVEPA

Oct. 18-21, 2012 - Barcelona, Spain

Next Conference:

Oct. 17-19, 2013 - Barcelona, Spain

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DIABETES INSIPIDUS AND CAUSES OF POLYURIA AND POLYDIPSIA:
MY APPROACH TO DIAGNOSIS AND TREATMENT

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Polydipsia is defined as a fluid intake >90 to 100 ml/kg/day in dogs and >45 ml/kg/day in cats. Polyuria is defined as a urine output >50 ml/kg/day in both dogs and cats (1,2). A healthy dog or cat drinks approximately 20 to 90 ml/kg/day, depending on the moisture content of its diet, and normal urine output varies between 20 to 45 ml/kg/day (1-3). Thirst and the renal control of salt and water excretion are the two main mechanisms for balancing water intake with water loss.

There are many potential causes of polyuria and polydipsia. Primary disorders of water balance (i.e. central diabetes insipidus, primary nephrogenic diabetes insipidus and primary polydipsia) although uncommon, should always be considered in the differential diagnosis of polyuria and polydipsia. In general, animals with these disorders have only one laboratory abnormality — a low urine specific gravity (SG) or osmolality. In most instances the more common causes of polyuria and polydipsia (e.g. hyperadrenocorticism, chronic renal failure, pyelonephritis and pyometra) have other specific and obvious abnormalities on screening laboratory tests (complete blood cell count, serum biochemical profile and urinalysis). In some cases, however, a low urine SG is the only abnormality found in animals with these latter disorders.

The work-up for polyuria and polydipsia can be tedious, time-consuming, expensive, confusing and not without significant patient morbidity, especially in those dogs and cats with normal or near-normal screening test results. This lecture focuses on the diagnostic approach, especially the problems associated with testing, and the treatment of dogs and cats with disorders of water balance.

DIFFERENTIAL DIAGNOSIS

The causes of polyuria and polydipsia can be divided into those that cause primary polydipsia (with secondary polyuria) and those that cause primary polyuria (with compensatory polydipsia). The major cause of primary polydipsia in dogs is thought to be psychogenic polydipsia. In contrast, the causes of primary polyuria are much more numerous and can be subdivided into the categories of: central diabetes insipidus; primary nephrogenic diabetes insipidus; secondary nephrogenic diabetes insipidus; and osmotic diuresis.

Primary Polydipsia

Psychogenic polydipsia or compulsive water drinking is usually the manifestation of a behavioural problem triggered by an environmental or emotional stimulus (1-3). Affected animals are typically hyperactive dogs kept in an exercise-restrictive environment. Although psychogenic polydipsia
develops most commonly in dogs, it does appear to develop occasionally in cats as a behavioural manifestation of hyperthyroidism (2,4).

Primary polydipsia could also result from a defect in the thirst mechanism leading to excessive thirst; the cause of this dipsogenic diabetes insipidus is usually idiopathic but may result from a variety of infectious, neoplastic or traumatic brain injuries. All of these causes of primary polydipsia are associated with suppression of AVP secretion secondary to excessive thirst. Abnormal AVP release has also been reported in dogs with suspected primary polydipsia, suggesting a primary disturbance in the regulation of AVP secretion in some cases (5,6).

Primary Polyuria

Central diabetes insipidus (also called pituitary, neurogenic, cranial or AVP-responsive diabetes insipidus) is a rare condition caused by a complete or partial deficiency of AVP (1-3,7). Deficiency of AVP varies in severity but in the majority of animals it is probably caused by loss or destruction of most of the AVP-producing neurons. In most dogs and cats, the cause of central diabetes insipidus is idiopathic, although the disorder may be familial in some cases. Less commonly, the disorder develops as a sequel to head trauma, neoplasia (i.e. invasive pituitary tumour or tumor metastasis to the pituitary gland or hypothalamus) or hypophysectomy for treatment of hyperadrenocorticism.

In the broadest sense, the term nephrogenic diabetes insipidus may be used to describe a diverse group of disorders in which structural or functional abnormalities interfere with the ability of the kidneys to concentrate urine. In animals with nephrogenic diabetes insipidus, the renal tubules are insensitive to the antidiuretic effects of AVP, despite appropriate AVP release from the pituitary gland (1-3).

Primary nephrogenic diabetes insipidus is an extremely rare congenital structural or functional defect of the kidneys. Secondary or acquired nephrogenic diabetes insipidus, in contrast, is the most common cause of polyuria and polydipsia in dogs and cats and may be caused by a number renal, endocrine and metabolic disorders. These disorders include: renal failure; pyelonephritis; hyperadrenocorticism; hypokalemia; hypercalcemia; liver disease; and pyometra.

Many of the acquired forms of nephrogenic diabetes insipidus are potentially reversible with correction of the underlying illness or disorder. Again, renal medullary washout can contribute to polyuria in animals with any of these disorders because increased tubular flow and volume decreases the reabsorption of sodium and urea, and reduces the medullary interstitial hypertonicity of the kidneys.

Osmotic Diuresis

Osmotic diuresis occurs when the concentration of an osmotic solute (e.g. urea, glucose) present in the glomerular filtrate exceeds the proximal tubular capacity for reabsorption. This impairs the passive reabsorption of water and results in increased obligatory water loss. Conditions in which solute or osmotic diuresis contributes to polyuria include diabetes mellitus, primary renal
glucosuria and chronic renal failure as well as the diuresis that follows relief of a postrenal obstruction (postobstructive diuresis).

**DIAGNOSTIC APPROACH TO POLYURIA & POLYDIPSIA**

Differentiating between the causes of polyuria and polydipsia is relatively easy when the different disorders are manifested in their classic forms. For example, polyuria that develops after a known head trauma, continues after water restriction and decreases after AVP administration does not require additional tests to justify the diagnosis of central diabetes insipidus. A diagnosis of congenital nephrogenic diabetes insipidus is equally clear if polyuria occurs in a young animal with similarly affected litter mates that have normal screening laboratory tests (including renal function), negative urine cultures and whose polyuria fails to respond to fluid restriction or administration of AVP analogues (e.g. desmopressin).

Often, however, the clinical setting is of minimal help in making a diagnosis and it is then necessary to perform more detailed diagnostic tests. The initial information gathered should allow the inclusion or exclusion of the many common medical disorders associated with polyuria and polydipsia before a diagnostic work-up for the less common disorders of central diabetes insipidus, primary nephrogenic diabetes insipidus or psychogenic polydipsia is embarked upon.

**Historical Features**

An accurate history is invaluable when initially investigating an animal with polyuria and polydipsia and may help to rule out some of the more common differential diagnoses. When an owner complains of an animal's excessive urination, it is important to first determine if polyuria and polydipsia truly exist as opposed to dysuria, pollakiuria, stranguria or incontinence. Consideration must also be given to the animal's overall health, diet, recent drug administration and environmental factors.

**Age, breed, sex and reproductive history:** Some disorders that cause polyuria and polydipsia develop more frequently in certain age groups or breeds of dogs or cats. For example, hyperadrenocorticism – one of the most common causes of polyuria and polydipsia in dogs – typically develops in middle to old-aged smaller breeds such as the Miniature Poodle (8). Most of the other common causes of polyuria and polydipsia (e.g. diabetes mellitus, renal disease and pyometra) are also found in older animals but primary polydipsia occurs most frequently in young, hyperexcitable, large-breed dogs (1-3). Renal failure, diabetes mellitus and hyperthyroidism – the three most common causes of polyuria and polydipsia in cats – all typically develop in older cats.

The reproductive history may also provide helpful clues as to the cause of polyuria and polydipsia, especially in dogs. For example, pyometra is typically a disorder of middle-aged, intact bitches, with clinical signs of polyuria and polydipsia developing during or immediately after the diestrus phase of the estrus cycle. With hyperadrenocorticism, intact bitches may show prolonged anestrus, whereas males may develop testicular atrophy or have a decreased libido (8).

**Overall health:** The presence of nonspecific clinical signs (e.g. anorexia, polyphagia, lethargy, weight loss or gain) may be helpful in determining the cause of the polyuria and polydipsia. For example, lethargy and gastrointestinal signs could suggest hepatic disease, renal failure or hyperadrenocorticism. Polyphagia could suggest hyperadrenocorticism or diabetes mellitus in...
dogs, or hyperthyroidism or diabetes in cats. Weight gain is common in animals with hyperadrenocorticism, whereas weight loss is one of the most common signs in hyperthyroid cats (4,8).

**Diet:** When evaluating an animal with polyuria and polydipsia, the nature and composition of the diet should always be taken into account. This is especially true if polyuria and polydipsia develop around the time of a diet change. Because the water content in food is an important source, dogs or cats fed primarily dry food invariably drink more water than those fed canned food. Feeding a low-protein diet can result in renal medullary washout and polyuria (2).

**Recent drug administration:** In all animals with polyuria and polydipsia any current or recent administration of drugs should be ruled out. Medications that frequently cause polyuria and polydipsia include glucocorticoids, phenobarbital, primidone and diuretics. Chronic administration of progestogens to intact bitches for estrus suppression can lead to acromegaly (growth hormone excess), which causes secondary diabetes mellitus (and polyuria and polydipsia) in many dogs.

**Environmental factors:** In dogs with primary polydipsia it may be possible to identify a stressful lifestyle change that preceded the onset of polydipsia and polyuria. Common examples include the arrival of a new baby, or moving to a new house or apartment. In contrast, polyuria that develops after head trauma could suggest damage to the AVP-secreting neurons or disruption of the pituitary stalk resulting in central diabetes insipidus.

**Physical Examination**

Many common disorders associated with polyuria and polydipsia can be ruled out by performing a careful and complete physical examination. One should especially carefully palpate the animal’s abdomen to evaluate kidney and liver size. In intact bitches external genitalia should be examined for vaginal discharge suggestive of pyometra. Lymph nodes should be carefully palpated since generalized enlargement could suggest lymphoma with secondary hypercalcemia. The perianal area should also be carefully palpated, particularly in bitches, for anal sac adenocarcinoma, which can cause hypercalcemia. Findings suggestive of hyperadrenocorticism include potbelly, bilaterally symmetrical hair loss and hepatomegaly. In animals with pyelonephritis, fever or perirenal pain may be present. The presence of cataracts in dogs, or hind limb neuropathy in cats, suggests diabetes mellitus. In cats, one should always palpate the cervical area for a thyroid nodule, because hyperthyroidism is a relatively common cause of polyuria and polydipsia (4).

In contrast, dogs and cats with diabetes insipidus or primary (psychogenic) polydipsia typically are alert and active and seldom show any abnormalities on physical examination. Dehydration is rarely detected on physical examination; this would develop only if the owner has restricted the animal’s access to water.

**Measurement of Water Consumption**

The first step in any suspected case of polyuria and polydipsia is to establish that the problem actually exists, preferably by a combination of history, random urine SG determinations and, if necessary, home measurement of water consumption over several days.
If the daily water intake is found to be normal or if a random urine SG determination is >1.035, additional history should be obtained to rule out other urinary tract disorders (such as urinary incontinence or dysuria) that commonly are confused with polyuria. If, however, random urine SG are consistently <1.030 in dogs and <1.035 in cats, and daily water intake is >100 ml/kg for dogs and 45 ml/kg for cats, polyuria and polydipsia are indeed present and a diagnostic work-up to determine the cause is warranted.

Minimum clinicopathological data

Once a problem of water balance is confirmed, a practical diagnostic approach is to first rule out the more common causes of polyuria and polydipsia in dogs and cats. These are listed below in Table 1 in order of most to least common. Recommended initial diagnostic tests include the following:

- Complete blood cell count (CBC)
- Serum biochemical profile with electrolytes
- Serum total thyroxine (T<sub>4</sub>) determination in middle-aged to older cats

A careful evaluation of this initial database, together with the history and results of physical examination, usually provides the diagnosis immediately (e.g. overt renal failure, hyperthyroidism or diabetes mellitus) or offers clues to as to the underlying cause of the polyuria and polydipsia. For example, dogs with hyperadrenocorticism commonly have a stress leucogram (i.e. neutrophilia, lymphopenia and eosinopenia). Over 90% of dogs with hyperadrenocorticism also have high alkaline phosphatase (ALP) activity, whereas over half have hypercholesterolemia (8).

In contrast, physical examination findings and routine blood work are generally unremarkable in animals with less common causes of polyuria and polydipsia such as central diabetes insipidus, primary nephrogenic diabetes insipidus, and psychogenic polydipsia. When abnormalities are present, they are usually secondary to dehydration caused by water restriction by the owner. Such abnormalities may include a slightly increased packed cell volume (PCV) or hypernatremia.

Complete urinalysis

Urinalysis is a major key in determining the presence of a water balance problem and the disorder causing the polyuria and polydipsia. The most important features of urinalysis are: the SG or osmolality; the presence or absence of glucose, protein or bacteria; and the cellularity of the sample.

A urine SG <1.030 in dogs and <1.035 in cats suggests a concentrating defect and supports the complaint of polyuria (1-3). Persistent glycosuria is diagnostic for primary renal glycosuria or, more commonly, diabetes mellitus. Significant proteinuria in the presence of an inactive urinary sediment and dilute urine can be associated with hyperadrenocorticism, pyelonephritis, pyometra, glomerulonephritis, or other glomerulopathy. An active urine sediment (pyuria, hematuria, or bacteriuria) in a sample obtained by catheterization or cystocentesis supports urinary tract infection and possible pyelonephritis. Because urine sediment examination may be misleading in
an extremely dilute urine sample, a urine culture should always be done to rule out pyelonephritis, regardless of sediment examination findings.

If the results of the above tests are unhelpful the direction of further diagnostic work-up can often be based on the urine SG. For example, dogs and cats with a SG >1.030--1.035 without glycosuria, are probably not polyuric and need no further work-up, at least for polyuria and polydipsia.

**Urine SG <1.008:** A urine SG consistently <1.008 in a middle-aged to older dog is usually associated with diabetes insipidus, psychogenic polydipsia, atypical hyperadrenocorticism or atypical leptospirosis.

In these dogs with atypical hyperadrenocorticism, polyuria and polydipsia can be major clinical signs but other characteristic clinical signs may be mild or absent. In addition, these dogs with atypical disease may lack the serum biochemistry abnormalities commonly associated with hyperadrenocorticism (i.e. elevated serum alkaline phosphatase activity and hypercholesterolemia). Results of adrenal function tests in these dogs are usually consistent with mild hyperadrenocorticism.

More recently an atypical form of leptospirosis has been recognized. These dogs present with an acute onset of polyuria and polydipsia, hyposthenuria, or isothenuria, but have no other laboratory abnormalities. The urine concentration defect is thought to be an acquired form of nephrogenic DI. Azotemia does not develop. In dogs not previously vaccinated for leptospirosis, leptospira infection can be confirmed by positive leptospirosis serology or use of molecular detection of leptospiral DNA by polymerase chain reaction (PCR) testing performed on urine samples (9-11). In dogs previously vaccinated for leptospirosis, a 4-fold rise in convalescent titers is often diagnostic of the atypical form of this disease. Treatment is with antibiotics such as penicillins or doxycycline.

In general, when considering polyuric dogs with a urine SG of <1.008, hyperadrenocorticism and atypical leptospirosis should be ruled out first before testing for central diabetes insipidus and primary polydipsia. There are several reasons for making this recommendation:

1. DI and primary polydipsia are much less common than hyperadrenocorticism.
2. The diagnostic tests of choice to differentiate these disorders – the water deprivation test or a therapeutic trial with the AVP-analogue desmopressin – are time-consuming and expensive.
3. Also, dogs with hyperadrenocorticism may respond to these tests in a manner similar to dogs with central diabetes insipidus, resulting in a misdiagnosis.
4. Moreover, water deprivation testing a dog with leptospirosis would be a major contraindication because of the possibility of causing significant patient morbidity.

In cats, a urine SG consistently <1.008 is associated with either diabetes insipidus or hyperthyroidism. Obviously, hyperthyroidism should be ruled out first before initiating testing procedures for diabetes insipidus. It is also important to realize that the finding of a urine SG...
<1.008 in a cat or dog excludes mild (occult) renal disease, so precautions associated with the water deprivation test are not necessary.

**Urine SG between 1.008 and 1.029:** A urine SG of 1.008–1.012 or greater (but <1.030) can be associated with hyperadrenocorticism (dogs), hyperthyroidism (cats), or stage 1 renal insufficiency (including atypical leptospirosis) or pyelonephritis, as well as psychogenic polydipsia and partial forms of diabetes insipidus.

Again, when considering animals with a urine SG >1.008 hyperadrenocorticism and hyperthyroidism should first be ruled out. With this group of disorders, pyelonephritis and early renal insufficiency should next be ruled out before evaluating the animal for psychogenic polydipsia and diabetes insipidus with a water deprivation test. Performing a water deprivation test as a diagnostic tool in the face of unsuspected renal insufficiency or pyelonephritis could induce overt renal failure or urosepsis (1-3). To avoid this complication, a sensible approach is to do the following:

1. Perform a urine culture to help exclude pyelonephritis and associated urinary tract infection.
2. Consider leptospirosis serology and urine PCR testing.
3. Evaluate renal size and architecture by abdominal radiography or, preferably, renal ultrasonography. The ultrasonographic appearance of renal parenchymal disease (chronic renal failure) includes increased cortical echogenicity and loss of a distinct corticomedullary junction. The kidneys may appear smaller than normal and have an ill-defined or irregular border. Similar sonographic findings, in addition to a dilated renal pelvis, are characteristic of pyelonephritis.

If urine culture results are negative, leptospirosis serology and urine PCR testing are negative, and radiographic or ultrasonographic findings are equivocal, a creatinine or iohexol clearance test or renal biopsy may be indicated. In rare cases, the urine culture may be negative even if pyelonephritis is present. If clinical or ultrasonographic findings suggest occult pyelonephritis, a therapeutic trial with an appropriate antibiotic (e.g. enrofloxacin) should be instituted.

**SPECIFIC TESTS TO DIFFERENTIATE DIABETES INSIPIDUS FROM PRIMARY POLYDIPSIA**

Several different diagnostic approaches can be used to confirm central diabetes insipidus, nephrogenic diabetes insipidus and primary (psychogenic) polydipsia. The water deprivation test is generally considered by most authorities to be the best diagnostic test to differentiate between these disorders. However, the water deprivation test is labor intensive, difficult to perform correctly, unpleasant for the animal, relies heavily on repeated emptying of the bladder and can lead to untoward complications and misdiagnosis in some animals. Another common diagnostic approach is to consider a therapeutic trial with the AVP analogue desmopressin (2,12-14).
REFERENCES AND FURTHER READING


Table 1: Differential rule outs for polyuria and polydipsia in dogs and cats, listed from most to least common

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<thead>
<tr>
<th>Dogs</th>
<th>Cats</th>
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<tbody>
<tr>
<td>Hyperadrenocorticism</td>
<td>Chronic renal failure</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Diabetes mellitus</td>
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<tr>
<td>Chronic renal failure</td>
<td>Hyperthyroidism</td>
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<td>Pyelonephritis</td>
<td>Hypercalcemia</td>
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<tr>
<td>Pyometra</td>
<td>Pyelonephritis</td>
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<tr>
<td>Hypercalcemia</td>
<td>Hypokalemia</td>
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<tr>
<td>Atypical leptospirosis</td>
<td>Acromegaly</td>
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<td>Psychogenic polydipsia</td>
<td>Postobstructive diuresis</td>
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