DIAGNOSIS OF CANINE HYPERADRENOCORTICISM: A CASE-BASED APPROACH

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

Case 1 - Signalment: 10 yr old, CM, Miniature poodle. **History**: Presented for teeth cleaning. **PE**: Severe dental tartar and moderate gingivitis. **Lab data**: leukocytosis with neutrophilia, lymphopenia, monocytosis and eosinopenia; ALP 578 IU/L (35-280); urine specific gravity (USG) 1.015.

Hyperadrenocorticism (HAC) was suspected due to the elevated ALP. The owners were not sure if the dog was drinking more. A USG of 1.015 could be consistent with pu/pd. Consideration of the clinical picture is crucial before undertaking testing. The primary indication for pursuing a diagnosis of HAC is the presence of one or more of the common clinical signs and physical examination findings.[1] If only one clinical sign is present, it is usually polyuria/polydipsia, or alopecia and skin changes suggestive of an endocrine disease. Failure to identify multiple indicators for HAC does not rule out the disease. However, the more abnormalities identified, the stronger the indication to pursue testing. Less common clinical signs and physical exam findings add further support.

Less common clinical presentations of HAC include anestrus and testicular atrophy; ligament laxity which may lead to their tearing and lameness; facial palsy; and pseudomyotonia. Severe polyuria and/or urinary tract infection may lead to urine dribbling, especially when a dog is asleep, and owner-perceived urinary incontinence. Hypercoagulability may result in spontaneous thromboembolism, typically involving pulmonary vessels and causing acute respiratory distress. Cortisol-induced insulin resistance may promote diabetes mellitus and impair exogenous insulin responses. If less common clinical presentations are identified first, a thorough review of the history, physical exam findings, and routine laboratory test results often provide additional evidence for the disease.

Per the ACVIM Consensus panel: indicators for performing diagnostic tests for HAC are:

- Compatible history and physical examination findings;. The greater the number, the stronger the suspicion. Biochemical panel, CBC, urinalysis, urine protein:creatinine ratio results and blood pressure measurement by themselves are not indications to test.
- A pituitary macrotumor.
- A diabetic dog with persistently poor response to high dosages of insulin not attributed to another cause, including owner issues.
- An adrenal mass.
- Persistent hypertension. (The Panel did not reach consensus on this point. Some would not test if hypertension was the only abnormality present.)[1]

Which test to use to diagnose HAC, a low-dose dexamethasone suppression test (LDDST) or ACTH stimulation test (AST) depends on the situation. I make the following recommendations: 1. If a dog has no known non-adrenal illness (NAI) and moderate to severe clinical signs of HAC, do the LDDST. 2. If clinical signs are mild or only laboratory changes are present (e.g. increased ALP), do the AST. 3. If NAI is present[2], if the dog has received any form of exogenous glucocorticoid including topicals[3] or phenobarbital[4], do the AST.

Since no test for HAC is perfect, one question to ask is what would be worse, a false-negative or a false-positive result? In this case, I would say a false positive would be worse because it could sentence the dog to unnecessary lifelong therapy. When the only problem noted is a high ALP, I would rather miss the diagnosis now (and revisit the idea later if signs progress) than falsely diagnose HAC. In general, the LDDST has a chance of a false negative of about 5% whereas with the AST it is about 20%.[5] The flipside, however, is that the LDDST, in dogs with NAI, has as high as a 55% chance of giving a false positive. For the AST the chance of a false positive is about 15%.[2] Therefore, for this case, I'd go with the AST.

The cost of Cortrosyn (cosyntropin) can be high. The best option to reduce the cost of the test is to use a low dose (5 mcg/kg IV) of cosyntropin with blood samples drawn before and 1-hr post injection.[6] Reconstituted Cortrosyn can be stored refrigerated in plastic vials for up to 4 mths and frozen for 6 mths.[7] If freezing Cortrosyn, do so in smaller aliquots as the effect of thawing and refreezing is unknown. Compounded ACTH may be used with caution. Due to variability in duration of response to compounded ACTH[8], I recommend that when using compounded ACTH products samples should be collected before administration and at 1 and 2 hrs following injection. A generic cosyntropin has been tested, but the dose used was 250 mcg/dog and no dog with HAC was tested.[9]

Case Summary: On an AST, cortisol pre-ACTH was 224 nmol/L (reference range 10-160 nmol/L; to convert to mcg/dl divide cortisol in nmol/L by 27.6) and post-ACTH was 468 nmol/L (220-560 nmol/L). A urine protein/creatinine ratio (UPC) and blood pressure were measured as about 66% of HAC dogs have proteinuria and/or hypertension. Both were normal.

Previously, I would have said this could be a good case to measure a urine cortisol:creatinine ratio (UCCR). In older literature, almost all dogs with HAC had an elevated UCCR.[2,10-12] However, the most recent paper suggested a much lower sensitivity of UCCR measurement, and great variability exists between assays used.[13] It is also important to remember that the majority of dogs with an elevated UCCR do not have HAC.[2,10-12] If the ratio is high, another screening test, i.e. LDDST or AST, must be done to confirm the diagnosis. The UCCR is best measured on a urine collected at home. If in this dog the UCCR was normal, I would rule out HAC.

Case 2 - Signalment: 10 yr old, CM, Miniature poodle. **History**: Presented for teeth cleaning, increased water consumption. **PE**: Severe dental tartar and moderate gingivitis, bilateral partial alopecia, thin skin on ventral abdomen. **Lab data**: leukocytosis with neutrophilia, lymphopenia, monocytosis and eosinopenia; ALP 578 IU/L (35-280); USG 1.005, urine protein 1+.; UPC = 3.2 ; systolic blood pressure 185 mm Hg.

Again, the question to ask is: Which is worse, a false-positive or a false-negative? This dog is an archetypal HAC case and, if the dog does have HAC, should be treated as soon as possible. Therefore, I judge that a false negative is worse. Since the LDDST has a smaller chance of a false negative, I would do that test first. In addition, the LDDST may also differentiate between PDH and an adrenal tumor (AT). Results on an LDDST consistent with PDH are: 1. Suppression of serum cortisol at 4 hrs post-dexamethasone (dex) but not at 8 hrs 2. Lack of suppression of serum cortisol concentration but a decrease to <50% of baseline at 4 and/or 8 hrs post-dex. If a dog meets either or both of these criteria, PDH is present. If a dog does not meet the criteria, there is still at least a 50-50 chance the HAC is PDH or AT. Differentiation must be achieved by other means.

Since false positive and false negative results are possible with either the LDDST or AST, if there is any doubt about the accuracy of the results, perform the other test. This is not a case in which I would measure a UCCR. I highly suspect HAC. If the UCCR is elevated suggesting HAC, another test such as the LDDST or AST must be done. One study found the chance of a false negative on the UCCR to be as high as 25%.[2] Given that, in a case where I strongly suspect HAC, even if the UCCR is normal, I'll still do the LDDST or AST. In other words, in cases like this dog, whether the UCCR is normal or not, the next step would still be an AST or, preferably, the LDDST, so the UCCR would not be helpful.

Case Summary: On an LDDST, pre-dex cortisol 242 nmol/L (reference range 10-160 nmol/L), 4-hr post-dex cortisol 58 nmol/L (reference range <30 nmol/L), 8-hr post-dex cortisol 25 nmol/L (reference range <30 nmol/L).

In theory, the important post-dex sample for determining if HAC is present is at 8 hr. If that is abnormal, the results are consistent with HAC. In this case, the 8-hr sample is borderline. Also troublesome is the fact that the 4-hr was not adequately suppressed. Given a high suspicion of HAC in this dog, I would now do an AST. Even though overall the ACTH stim is more likely to give a false negative, dogs with HAC can have a false negative on the LDDST and a true positive on the AST. If, in this case, the ACTH stim is positive, I would treat based on the clinical signs (clinical judgment as to which test to believe). Based on the LDDST, if the dog has HAC, it is PDH and no differentiating tests need to be done.

Case 3 - Signalment: 10 yr old, CM, Miniature poodle. **History**: Presented for teeth cleaning, pu/pd. **PE**: Severe dental tartar and moderate gingivitis, bilateral partial alopecia, thin skin; Labs: leukocytosis with neutrophilia, lymphopenia, monocytosis and eosinopenia; ALP 578 IU/L (35-280); USG 1.005, urine protein 1+; Urine protein/creatinine ratio = 3.2 (<0.5); systolic blood pressure 185 mm Hg; LDDST: Pre-dex cortisol 242 nmol/L, 4-hr post-dex cortisol 186 nmol/L, 8-hr post-dex cortisol 186 nmol/L.

This dog has HAC based on the findings, but which type must now be determined. Treatment options and protocols and prognosis vary depending on the form present. The choices for differentiation include a high-dose dex suppression test (HDDST), measurement of endogenous ACTH (eACTH) concentration or abdominal ultrasound. On an HDDST, the criteria for determining if a dog has PDH are: 1. Suppression of serum cortisol at 4 and/or 8 hrs post-dex. 2. Lack of suppression of serum cortisol but a decrease to <50% of baseline at 4 and/or 8 hrs post-dex. Lack of suppression in

response to the high dose does NOT mean a dog has an AT. For those animals that do not suppress on a HDDST, approximately 50% have PDH.[14,15] Therefore, the HDDST can never confirm the presence of an AT, and if no suppression is seen on an HDDST another differentiation test must be done. Also, if an LDDST was done for screening and failed to determine if the dog had PDH, the HDDST is also unlikely to give the differentiation.[14]

For measurement of eACTH, special handling is required, but only a single blood sample is required and the presence of an AT or PDH can be confirmed. Unfortunately, a "grey zone" exists; if the eACTH concentration falls in that range, it is impossible to determine if the dog has PDH or AT. Chance of getting a "grey zone" result is 18%.[5] If eACTH measurement is repeated, the chance drops to 4%.[5] The accuracy of eACTH likely depends on the assay used with less assays systems (e.g. Immulite 1000) likely having poorer discrimination.[1]

Ultrasound can be very helpful depending on the skill of the ultrasonographer. If both adrenal glands are not visualized, however, it should not be assumed that the dog has an AT.

Discordance sometimes occurs between the results of differentiating tests. Episodic cACTH secretion, poor eACTH assay sensitivity, degradation of ACTH and changes in dexamethasone are potential explanations. Stress and the presence of multiple adrenal disorders (i.e. cortisol-secreting AT or PDH with pheochromocytoma; cortisol-secreting AT and PDH) may also influence ACTH concentrations. Ectopic ACTH secretion and food-stimulated cortisol secretion could also cause discordance.

Case Summary: Since the LDDST did not differentiate, the HDDST was unlikely to be helpful (see above), so an eACTH sample was submitted. The eACTH concentration was 76 pg/ml (eACTH >15 pg/ml consistent with PDH).

References available from author upon request.