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DIAGNOSIS OF CANINE HYPERADRENOCORTICISM: CASE-BASED APPROACH

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CASE 1

Signalment: 10 yr old, CM, Miniature poodle

History: Presented for teeth cleaning

Physical examination: Severe dental tartar and moderate gingivitis

Laboratory data: Complete CBC, profile, urinalysis done. Abnormalities were: WBC 18.1 x 10^9/µl (6.0-17.0); Neutrophils: 15.3 x 10^9/µl (3.0-11.5); Lymphocytes 0.5 x 10^9/µl (1.0-4.8); Monocytes 2.3 x 10^9/µl (0.2-1.4); Eosinophils 0 x 10^9/µl (0.1-1.2); ALP 578 IU/L (35-280); urine specific gravity 1.015, urine protein 1+

Hyperadrenocorticism (HAC) was suspected in this dog due to the elevated ALP. On questioning, the owners thought maybe the dog was drinking more but were not sure. A urine specific gravity (USG) of 1.015 could be consistent with pu/pd.

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

The cost of Cortrosyn (cosyntropin, synthetic ACTH) has recently increased dramatically so an alternative to use of this compound for ACTH stimulation testing is commonly sought. Unfortunately, there is no good substitute. The best option to reduce the cost of the test is to use a low dose of Cortrosyn (5 mcg/kg IV) with blood samples drawn before and 1-hr post injection.4 Unused, reconstituted Cortrosyn can be stored refrigerated in plastic vials for up to 4 months and frozen for 6 months.5 If freezing Cortrosyn, do so in smaller aliquots as the effect of thawing and refreezing is unknown. Whether lower doses of Cortrosyn can be used for diagnosis of HAC is unknown.

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 468 nmol/L (reference range 220-560 nmol/L; 17.0 µg/dL reference range 8-20 µg/dL). In addition, urine protein/creatinine ratio (UPC) and blood pressure were measured as about 66% of dogs with HAC have proteinuria and/or hypertension. The UPC was 0.3 (normal <0.5) and systolic blood pressure was 130 mm Hg.

Since none of the tests for HAC are perfect, one question I always ask myself is what would be worse, a false-negative or a false-positive? In this case, I would say a false positive would be worse because it could sentence the dog to lifelong therapy that is unnecessary. When the only problem noted is a high ALP, I would rather miss the diagnosis now (and revisit the idea later if clinical signs progress) than falsely diagnose HAC. In general, the LDDST has a chance of a false negative of about 5% whereas with the ACTH stimulation test the chance is about 20%.6 The flipside, however, is that the LDDST, in dogs with non-adrenal illness (i.e. disease elsewhere besides the adrenals) has a chance as high as about 55% of giving a false positive. For the ACTH stim the chance of a false positive is about 15%.7 Therefore, for this case, I’d go with the ACTH stim.

This could be a good case to measure a urine cortisol:creatinine ratio (UCCR). The UCCR is best used to rule out the diagnosis of HAC. Most studies have found that almost all dogs with HAC have an elevated UCCR, but the majority of dogs with an elevated UCCR do not have HAC.1,8-10 Accordingly, if the ratio is normal there is little chance the dog has HAC, but if the ratio is high, another screening test such as the LDDST or ACTH stimulation test must be done to confirm the diagnosis. The UCCR is best measured on a urine sample collected at home. If, in this dog, the UCCR was normal, I would rule out HAC.

Measurement of serum sex hormone concentrations would not be helpful to me in this case. A syndrome termed “occult” hyperadrenocorticism (HAC) has recently been coined and refers to dogs that have clinical signs suggestive of HAC but normal ACTH stimulation test and/or LDDST results. Measurement of 17-hydroxyprogesterone (17OHP) has been advocated for diagnosis of “occult” HAC and is available through some commercial laboratories. The protocol requires ACTH stimulation testing with measurement of serum 17OHP concentration pre- and post-ACTH.

Results have been reported in a study of 23 dogs with clinical and laboratory findings suggestive of hyperadrenocorticism (HAC). Of the 23 dogs, 11 had an elevated cortisol response to ACTH. Of 10 dogs with normal ACTH stimulation test results, 6 had a positive LDDST. All 23 had an elevated 17OHP response to ACTH.11 The conclusion of the study was that serum 17OHP concentration post-ACTH stimulation is elevated in dogs with classic as well as occult HAC and that measurement of serum 17OHP concentration is a marker of adrenal dysfunction.

This author believes that interpretation of the results of Ristic et al is not as clear-cut. Of the 23 dogs, 17 had an ACTH stim or LDDST consistent with HAC and thus were not truly cases of “occult” HAC. In addition, 2 of the 23 dogs were treated with triolostane, a cortisol synthesis inhibitor, and they had clinical improvement despite an increase in 17OHP concentrations.12 Consequently, the role of 17OHP in the pathogenesis of “occult” HAC must be questioned. Lastly, the specificity of the test may be as low as 70%, i.e. the chance of a false positive result is 30%.13,14 In one study of 35 dogs with neoplasia who did not have adrenal disease, 30% had an elevated serum 17OHP concentration post-ACTH stimulation.13

Besides 17OHP, the endocrine lab at Tennessee will also measure cortisol, estradiol, progesterone, testosterone, and androstenedione pre- and post-ACTH. However, the clinical significance of this test has not been determined. Although measurement of serum sex hormones in this fashion was previously recommended for diagnosis of Alopecia X, a recent paper found that Alopecia X has no relation to serum sex hormone concentrations.15 Furthermore, treatment with mitotane of dogs with elevated serum sex hormone concentrations and normalization of sex hormone concentrations may or may not result in clinical improvement.
CASE 2
Signalment: 10 yr old. CM, miniature poodle
History: Presented for teeth cleaning
Physical examination: Severe dental tartar and moderate gingivitis, owner noted increased water consumption, bilateral partial alopecia, thin skin on ventral abdomen
Laboratory data: Complete CBC, profile, urinalysis done. Abnormalities were: WBC 18.1 x 10^9/µL (6.0-17.0); Neutrophils: 15.3 x 10^9/µL (3.0-11.5); Lymphocytes 0.5 x 10^9/µL (1.0-4.8); Monocytes 2.3 x 10^9/µL (0.2-1.4); Eosinophils 0 x 10^9/µL (0.1-1.2); ALP 578 IU/L (35-280); urine specific gravity 1.005, urine protein 1++; UPC = 3.2 (normal <0.5); 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 a classic Cushings case and, if the dog does have Cushing's, should be treated as soon as possible. Therefore, I judge that a false negative is worse (would delay treatment). Since the LDDST has a smaller chance of a false negative, I would do that test first. In addition, an advantage to the LDDST is that it may differentiate between pituitary-dependent HAC (PDH) and an adrenal tumor (AT) as well as determine if HAC is present or not. Results on LDDST consistent with PDH are:
1) Suppression of serum cortisol at 4 hours post-dexamethasone but not at 8 hours (check with your laboratory for their definition of suppression; in most labs it is a serum cortisol concentration of less than approximately 30 nmol/L or 1.0-1.5 mcg/dl). Lack of suppression of serum cortisol concentration but a decrease to <50% of baseline at 4 and/or 8 hours post-dexamethasone. 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 pituitary- or adrenal-dependent. Differentiation must be achieved by other means such as measurement of serum endogenous ACTH concentration or abdominal ultrasound, both of which can definitively diagnose an AT.

Since false positive and false negative results are possible with either the LDDST or ACTH stim, if there is any doubt about the accuracy of the results, I always perform the other test for confirmation. 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 ACTH stim must be done. One study found the chance of a false negative on the UCCR to be as high as 25%. Given that, in a case where I really suspect HAC, even if the HAC is normal, I'll still do the LDDST or ACTH stim. In other words, in cases like this dog, whether the UCCR is normal or not, the next step would still be an LDDST or ACTH stim (preferably LDDST), so the UCCR would not add any information.

Case Summary: An LDDST was performed. Predexamethasone cortisol concentration was 242 nmol/L (reference range 10-160 nmol/L; 8.8 µg/dL, reference range 1-5 µg/dL), 4-hr post-dexamethasone cortisol concentration was 38 nmol/L (reference range <30 nmol/L; 1.4 µg/dL, reference range <1.0 µg/dL) and 8-hr post-dexamethasone cortisol concentration was 25 nmol/L (reference range <30 nmol/L; 0.9 µg/dL, reference range <1.0 µg/dL).

In theory, the important post-dexamethasone sample for determining if HAC is present or not is the 8-hr sample. If that is abnormal, the results are consistent with HAC. In this case, the 8-hr sample is normal but borderline. In addition, the 4-hr was not adequately suppressed and that is troublesome to me.

Since false positive and false negative results are possible with either the LDDST or ACTH stim, if there is any doubt about the accuracy of the results, perform the other test for confirmation. Given my high suspicion of HAC in this dog, I would recommend doing an ACTH stim to investigate further. Even though overall the ACTH stim is more likely to give a false negative, there are dogs with HAC in which the LDDST gives a false negative and the ACTH stim is positive. If, in this case, the ACTH stim is positive, I would treat based on the clinical signs and the ACTH stim result (clinical judgment as to whether to believe the LDDST or the ACTH stim).

Based on the results of 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
Physical examination: Severe dental tartar and moderate gingivitis, owner noted increased in water consumption, bilateral partial alopecia, thin skin on ventral abdomen
Laboratory data: Complete CBC, profile, urinalysis done. Abnormalities were: WBC 18.1 x 10^9/µL (6.0-17.0); Neutrophils: 15.3 x 10^9/µL (3.0-11.5); Lymphocytes 0.5 x 10^9/µL (1.0-4.8); Monocytes 2.3 x 10^9/µL (0.2-1.4); Eosinophils 0 x 10^9/µL (0.1-1.2); ALP 578 IU/L (35-280); urine specific gravity 1.005, urine protein 1++; UPC = 3.2 (normal <0.5); systolic blood pressure 185 mm Hg.

LDDST: Predexamethasone cortisol concentration was 242 nmol/L (reference range 10-160 nmol/L; 8.8 µg/dL, reference range 1-5 µg/dL), 4-hr post-dexamethasone cortisol concentration was 186 nmol/L (reference range <30 nmol/L; 6.7 µg/dL, reference range <1.0 µg/dL) and 8-hr post-dexamethasone cortisol concentration was 186 nmol/L (reference range <30 nmol/L; 6.7 µg/dL, reference range <1.0 µg/dL).

This dog has HAC based on all the findings, but it is now important to decide if the dog has pituitary- or adrenal-dependent disease. Treatment options and protocols and prognosis varies depending on which form of the disease is present. The choices for differentiation include a high-dose dexamethasone suppression test (HDDST), measurement of endogenous ACTH (eACTH) concentration or abdominal ultrasound. Each has advantages and disadvantages. The HDDST is probably the easiest to do in private practice. On an HDDST, different criteria exist for determining if a dog has PDH: 1) Suppression of serum cortisol at 4 hours post-dexamethasone but not at 8 hours (check with your laboratory for their definition of suppression; in most labs it is a serum cortisol concentration of less than approximately 30 nmol/L or 1.0-1.5 mcg/dl) 2) Suppression of serum cortisol at 4 and 8-hrs post-dexamethasone. 3) Lack of suppression of serum cortisol concentration but a decrease to <50% of baseline at 4 and/or 8 hours post-dexamethasone. 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 an AT and 50% have PDH. 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. Lastly, if an LDDST was done for screening and failed to determine if the dog had PDH, the HDDST is also unlikely to

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For measurement of endogenous ACTH, special sample handling is required, but the only a single blood sample is required and the presence of an AT or PDH can be confirmed. Unfortunately, there is a “grey zone” of eACTH concentration where, 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” non-diagnostic result is about 18%. If eACTH measurement is repeated, the chance drops to 4%. Ultrasound can be very helpful depending on the skill of the ultrasonographer at finding the adrenal glands. If both adrenal glands are not visualized, it should not be assumed that the dog has an AT.

Case Summary: Based on the LDDST, the dog had HAC, but it could not be determined which type. Since the LDDST did not also 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.