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DIAGNOSIS OF CANINE HYPOTHYROIDISM:
CASE-BASED APPROACH

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CASE 1
Signalment: 8 yr old, CM, English Bulldog
History: Presented for annual exam. Low activity and obesity despite limited feedings only problems noted.
Physical examination: Obese
Laboratory data: Complete CBC, profile, urinalysis done.
Abnormalities were: WBC 17.5 x 10³/µl (6.0-17.0); Neutrophils: 14.6 x 10³/µl (3.0-11.5); Lymphocytes 0.7 x 10³/µl (1.0-4.8); Monocytes 1.7 x 10³/µl (0.2-1.4)

The approach to a dog with no known non-thyroidal illness (e.g. renal disease, neurological disease, neoplasia, etc.) vs. a dog with non-thyroidal illness is a bit different. In dogs with no known non-thyroidal illness the diagnosis is more straightforward. Starting with a measurement of total T₄ alone is reasonable and economical. If total T₄ is normal, it is highly unlikely that the dog is hypothyroid. Since non-thyroidal factors such as drugs and illness affect T₄, if the T₄ is below normal, the dog may or may not be hypothyroid, and further testing is required.

Case Summary: Serum T₄ concentration = 28 nmol/L (reference range 20-50 nmol/L). Based on minimal clinical signs and normal serum T₄ concentration, diagnosis of hypothyroidism ruled out.

CASE 2
Signalment: 8 yr old, CM, English bulldog
History: Presented for decreased activity, obesity despite being on a weight-loss program, thinning haircoat, heat-seeking behavior.
Physical examination: Obese; partial, bilaterally symmetrical alopecia
Laboratory data: Complete CBC, profile, urinalysis done.
Abnormalities were: RBC x 10³/µl 5.0 (5.5-8.5); Hemoglobin 11.2 g/dL (12-18); PCV 33 % (37-55); Lymphocytes 0.5 x 10³/µl (1.0-4.8); Cholesterol 470 mg/dL (130-370)

The clinical findings suggestive of hypothyroidism are much stronger in this dog than in Case 1. Starting with measurement of serum T₄ is still a good first choice, but be prepared to do further testing if the serum T₄ concentration is below normal.

Free T₄ (fT₄) is the portion of total T₄ not bound to protein and represents about 0.1% of total T₄. Since the pituitary-thyroid axis functions to maintain free, not total, T₄ within a certain range, fT₄ is affected less by non-thyroidal factors and measurement of fT₄ is a better test of thyroid function. Accordingly, fT₄ is a more sensitive and more specific test for diagnosis of hypothyroidism, but it is also not as good a stand-alone test as once believed (see below). It can be the initial test for the diagnosis of hypothyroidism or can be used in dogs that have been found to have low total T₄ concentrations.

Free T₄ should always be measured by the equilibrium dialysis method. The other technique for measuring fT₄, analogue RIA, is not reliable and provides no additional diagnostic value over measurement of total T₄. Equilibrium dialysis is also the only RIA for measuring fT₄ that is unaffected by the presence of autoantibodies.

Primary thyroid failure is believed to be the cause of canine hypothyroidism in 99% of cases. Accordingly, negative feedback of thyroid hormones on the pituitary would be lost and TSH should increase. However, an elevated serum TSH occurs in only 63-85% of hypothyroid dogs, and if measurement of canine TSH were used alone for diagnosis of hypothyroidism, up to 37% of cases would be missed. Serum TSH can also be elevated in approximately 10% of euthyroid dogs with non-thyroidal illness. Therefore, measurement of TSH is best used not as a sole test but in conjunction with T₄ or, ideally, fT₄. Use of the combination will aid in identifying false-positive and false-negative results seen with assessment of TSH alone.

Measurement of baseline serum T₃ is of little value in differentiating hypothyroid from normal dogs. There is no apparent difference in serum T₃ concentrations between these groups.

Case Summary: Serum T₄ concentration was 13 nmol/L (borderline range: 12-19; reference range 20-50 nmol/L). Measurement of serum fT₄ concentration (by equilibrium dialysis) and serum TSH concentration were requested. The serum fT₄ concentration was 8 pmol/L (reference range 15-45 pmol/L, 10-14 pmol/L borderline) and serum TSH concentration was 0.25 ng/ml (normal <0.5 ng/ml).

The interpretation of the case now becomes a clinical dilemma. The question is whether this is a hypothyroid dog with a normal TSH or whether this is a euthyroid sick dog whose TSH has remained normal while the fT₄ is falsely lowered. The danger of falsely diagnosing a dog with hypothyroidism are threefold: 1). If clinical signs are incorrectly attributed to hypothyroidism, then the true diagnosis will be delayed or never sought. 2). Thyroxine is a catabolic hormone. Administering a catabolic hormone to an ill patient may be detrimental. 3). The patient will needlessly be treated with thyroid hormone for the rest of its life. On the other hand, the danger of not treating hypothyroidism is that the clinical signs will progress. However, in a case such as this one, the clinical signs are relatively mild and benign and progression is typically insidious, i.e. not treating for a month will most likely not be detrimental in the long-term.

At this point there are 2 choices: 1). Retest in 4-8 weeks. 2). Start trial therapy for hypothyroidism. If choosing option 2, make sure that you have OBJECTIVE measures of the endpoint determined beforehand, i.e. normalization of serum cholesterol concentration and return to normal weight. Regrowth of hair is not a good endpoint to choose; the haircoat of euthyroid dogs will improve in response to thyroid supplementation. Be prepared to stop giving the thyroxine if the clinical signs do not improve given adequate post-pill levels and time. (You must measure post-pill levels to determine if the trial is successful or not.)

CASE 3
Signalment: 8 yr old, CM, English bulldog
History: Presented for lethargy, weight gain and obesity despite a poor appetite, bilaterally symmetrical alopecia (non-pruritic) that has been progressive over the past year, heat-seeking behavior.
Physical examination: Obese; partial, bilaterally symmetrical alopecia
Laboratory data: Complete CBC, profile, urinalysis done. Abnormalities were: RBC x 10^6/µl 5.0 (5.5-8.5); Hemoglobin 11.2 g/dL (12-18); PCV 33% (37-55); Lymphocytes 0.5 x 10^3/µl (1.0-4.8); Cholesterol 470 mg/dL (130-370)

In a case that seems to be textbook for hypothyroidism, starting with measurement of serum T4 concentration is reasonable. If no other abnormalities are found other than those that can be explained by hypothyroidism and the serum T4 concentration is very low, a presumptive diagnosis of hypothyroidism can be made. It would be ideal to measure a fT4 concentration by dialysis for confirmation, but it may be unnecessary. Measurement of serum TSH concentration is not worth the money in this situation. Given that the sensitivity of measuring serum fT4 concentration is much higher than that of serum TSH concentration measurement, in a case such as this if serum fT4 concentration were low but serum TSH concentration was normal, I would believe the serum fT4 concentration and start treatment for hypothyroidism.

Case Summary: Serum T4 concentration was measured and was non-detectable. Due to financial considerations, fT4 concentration was not measured. Therapy with L-thyroxine was instituted. Post-pill testing was done to ensure adequate concentration was not measured. Therapy with L-thyroxine in a case such as this if serum fT4 concentration were low but higher than that of serum TSH concentration measurement, clinical signs had resolved.

CASE 4
Signalment: 8 yr old, CM, English bulldog
History: Originally presented to his veterinarian for a geriatric screen and then was referred to the Auburn University Small Animal Clinic for evaluation of an incidental finding of proteinuria. On a urinalysis, a 2+ proteinuria was noted with a specific gravity of 1.014. A urine protein/creatinine ratio (UP/C) was determined to quantify the protein loss and was found to be 5.8 (normal <0.5).

The dog had received regular veterinary care at a private veterinary clinic. He lived in Alabama with no history of travel out of state. His vaccinations were up-to-date, and he was receiving Interceptor for heartworm prevention. He spent his days outdoors, but was a house dog at night.

The owners reported no problems, and had seen no evidence of coughing, sneezing, vomiting, diarrhea, polydipsia, polyuria or weight loss. The dog’s activity had decreased slowly over the past year and was attributed to aging. His appetite was normal.

Physical examination: On physical examination, the dog was noted to be obese, and he had moderate to severe dental tartar and gingivitis. Chest auscultation and abdominal palpation were within normal limits.

Laboratory data: Complete CBC, profile, urinalysis done. Abnormalities were: WBC 17.5 x 10^3/µl (6.0-17.0); Neutrophils: 14.6 x 10^3/µl (3.0-11.5); Lymphocytes 0.7 x 10^3/µl (1.0-4.8); Monocytes 1.7 x 10^3/µl (0.2-1.4); Albumin 2.2 g/dL (2.7-4.5); 4+ proteinuria in urine with 1.021 specific gravity; urine protein/creatinine ratio = 7.5 (normal <0.5)

Blood pressure: normal

Due to the magnitude of the UP/C, a possible diagnosis of immune-complex glomerulonephritis (ICGN) was made. ICGN can be idiopathic or secondary to chronic immune stimulation. As the dental disease could be a source of antigens, a dental procedure was recommended and was performed. One month post-dental, the UP/C was essentially unchanged at 7.2 and blood pressure remained normal.

Further diagnostics were initiated to find possible underlying disease processes that could initiate immune stimulation. Three-view chest radiographs were obtained to rule out neoplasia (primary or metastatic) as well as other pulmonic diseases, and they were within normal limits. Abdominal ultrasound was normal. An occult heartworm test was negative. Serology for Ehrlichia canis, Bartonella and Lyme’s disease was negative. PCR for Bartonella spp. and Ehrlichia spp. was negative. Urine culture yielded no growth.

At re-evaluation approximately 4 weeks later, after the results of all the tests had been obtained, the UP/C was 8.6, systolic blood pressure was moderately elevated at 190 mm Hg and the cholesterol was moderately elevated (412 mg/dl). In order to determine the pathology underlying the proteinuria (e.g. glomerulonephritis vs. amyloidosis vs. structural glomerulopathy) and whether the disease process was reversible, an ultrasound-guided renal biopsy was performed. The histopathological diagnosis was glomerulonephritis. Enalapril was prescribed (0.5 mg/kg daily) to decrease proteinuria and blood pressure.

On subsequent rechecks the dog was doing well. Systolic blood pressure was 140-150 mm Hg and the UP/C was approximately 4.3. However, persistent hypercholes terolemia (persistent), obesity and poor hair regrowth after abdominal ultrasound were noted, and a diagnosis of hypothyroidism was considered.

Given the complexity of the case, I would start with measurement of serum total T4, fT4, and TSH concentration. The effect of non-thyroidal illness on testing for hypothyroidism is quite significant. Two hundred twenty-three dogs with normal thyroidal function but with non-thyroidal illness were divided into those with mild, moderate and severe disease. Mildly ill dogs were considered to have clinical signs of disease but could be treated as outpatients, moderately ill dogs were sick enough to generally require hospitalization and more aggressive treatment and severely ill dogs required intensive care and advanced treatment. Interesting results were obtained.12

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Total T4</th>
<th>T3</th>
<th>Free T4</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dogs</td>
<td>31</td>
<td>16</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Mild disease</td>
<td>8</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>28</td>
<td>18</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Severe disease</td>
<td>60</td>
<td>27</td>
<td>44</td>
<td>8</td>
</tr>
</tbody>
</table>

Of the 69 dogs with low T4, 45% also had a low fT4 whereas only 8.7% also had a high TSH. Only 1.8% of sick dogs had a low T4 and fT4 in combination with a high TSH.12

Similar results have been obtained from other studies as well. In 49 dogs with a variety of illnesses, T4 was low in 22% but TSH was elevated in only 12%.9 In 127 dogs with "severe disease" that caused the owners to euthanatize their dog, 65% had at least one abnormal value. Overall, 59% had decreased T4, 32% had decreased fT4 and 8% had increased TSH.11 Forty percent had only a decreased T4, 5% had only a decreased fT4, 5% had increased TSH, 43% had decreased T4 and fT4, and 7% had decreased T4 and increased TSH. No dog had decreased fT4 and increased TSH.11

Possibly, in order affect thyroid hormones, a non-thyroidal illness must cause metabolic or systemic problems. For
example, moderate to severe arthritis had no effect on thyroid testing. However, even transient systemic illness can have effects on thyroid testing and the alterations may be prolonged. Two studies have been done in which endotoxin was administered to dogs to cause transient hypothyroidism. After 1 dose, 25% of dogs had decreased T₄, fT₄ was normal, but TSH was not measured. In dogs given endotoxin every 12 hours for 8 doses, T₄ decreased during treatment. Interestingly, T₄ then returned to normal but decreased again into the hypothyroid range at days 2-16 after administration ceased. TSH and fT₄ were not affected.

Therefore, in sick dogs, the first choice for diagnosis of hypothyroidism would be a combination of TSH, fT₄ and T₄. 2nd choice is a combination of TSH and fT₄ and third choice is a combination of TSH and T₄. If the results are conflicting (some parameters are suggestive of hypothyroidism while others are not), the ideal would be to resolve the non-thyroidal illness, if possible, and retest the dog at that time. Alternatively, a TSH stimulation test could be done with recombinant human TSH (rhTSH), if available (Thyrogen®, Genzyme Corp.). Current recommendations are to use 50 mcg of rhTSH IV for dogs < 29 kg and 100 mcg IV for dogs > 29 kg. Serum T₄ concentration should be measured before injection and 4 hr post. In normal dogs, serum T₄ concentration should increase by 20 nmol/L or to at least 40 nmol/L (to convert to mcg/dl, divide value in nmol/L by 12.87). If either one or both of the criteria is met, the dog is not hypothyroid. If neither criteria is met, the dog is hypothyroid (S. Daminet, personal communication).

A vial of Thyrogen® contains 1100 mcg of rhTSH. Once reconstituted, the vial should be divided into 50 mcg aliquots and frozen in syringes at -20°C. At this temperature, the rhTSH is stable for at least 8 weeks. Based on the cost of a vial, a dose of 50 mcg would cost $30 (S. Daminet, personal communication).

If resolution of the other disease is not possible or testing with rhTSH is not available, the diagnosis of hypothyroidism poses a clinical dilemma as in Case 2. It is up to the clinician to decide how high their index of suspicion is for hypothyroidism, e.g. what clinical signs are present that could be attributed to hypothyroidism alone and not to the other disease process. The same drawbacks to treating or not treating exist as before but not treating could have more devastating consequences if some of the severe clinical signs are caused by the hypothyroidism, e.g. neuropathy. It may be best to treat the dog for hypothyroidism while still looking for other possible etiologies of the clinical signs.

**Case Summary:** A total serum T₄, fT₄ and TSH concentrations were measured. Serum T₄ concentration was 13 nmol/L (normal 20-55 nmol/L; borderline 12-19 nmol/L), serum fT₄ was 11 pmol/L (normal 15-45 pmol/L, borderline 10-14 pmol/L) and the TSH was 0.04 ng/ml (normal <0.5 ng/ml). Due to the effect that non-thyroidal illness can have on thyroid function testing, the dog was judged to be most likely euthyroid based on a normal TSH and minimal clinical signs. A recheck was recommended in 4-6 weeks.

The dog improved on treatment. Blood pressure remained normal on enalapril, the UP/C stabilized at approximately 3.2 and cholesterol remained very mildly elevated (380-400 mg/dl) as well. Two months after stabilization, the thyroid panel was repeated. Total T₄ was still below normal (16 nmol/L), but the fT₄ (18 pmol/L) and TSH (0.02 ng/ml) were within normal. Hypothyroidism was ruled out.

**MEASUREMENT OF THYROID AUTO-ANTIBODIES**

Except in the evaluation of breeding dogs, measurement of thyroid auto-antibodies does not add much to evaluation of dogs for possible hypothyroidism. If a hypothyroid dog has auto-antibodies then it can be determined that the underlying etiology is lymphocytic thyroiditis as compared to idiopathic hypothyroidism. However, the management of the hypothyroidism does not differ.

In general, the clinical and prognostic significance of autoantibodies is unknown. If autoantibodies are suspected, measure fT₄ for the best assessment of function. If the fT₄ concentration is normal, thyroid function is normal at that time but the patient should be re-evaluated periodically (e.g. q. 3 mths) for development of hypothyroidism. If fT₄ is low, the dog is likely hypothyroid. One study followed 234 dogs with normal T₄ and TSH levels and elevated anti-thyroglobulin antibodies (TGAA) for 1 year. Only 19% developed clinical signs of hypothyroidism or consistent laboratory values. Another 57% remained TGAA positive without signs or laboratory evidence of hypothyroidism, 8% went from positive to borderline results and 15% became TGAA negative. The final outcome of all the dogs is unknown (i.e. how many would become hypothyroid if followed for more than one year), but it can be said that not all dogs with autoantibodies will become hypothyroid, as at least 15% do not.

References available from author upon request.