DIAGNOSIS OF CANINE HYPOTHYROIDISM: A CASE-BASED APPROACH

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Case 1 - Signalment: 3 yr old, CM, mixed breed dog. **History**: Presented for annual exam. Low activity and obesity despite limited feedings only problems noted. **PE**: Obese. Complete CBC, profile, urinalysis done. **Lab data**: Abnormalities were: WBC 17.5 x 10^3/μl (6.0-17.0); Neutrophils: 14.6 x 10^3/μl (3.0-11.5); Lymphs 0.7 x 10^3/μl (1.0-4.8); Monos 1.7 x 10^3/μl (0.2-1.4)

When trying to diagnose any disease, it is wise to remember that common things occur commonly; in other words, if common aspects of hypothyroidism are not present in a patient, then hypothyroidism is less likely to be present. Most affected dogs are middle aged to older. The age range is 6 months to 15 years, with a mean of 7 years. There is no gender predisposition. Likely many breeds are predisposed, but the most commonly affected breeds are Doberman pinschers and golden retrievers. Beagles and Borzois can have heritable thyroiditis.

Testing should be performed only if clinical signs are present, the most common of which are obesity/weight gain, lethargy/weakness and skin changes; alopecia and seborrhea are the most common dermatological abnormalities. Approximately 70% of hypothyroid dogs have a combination of skin and metabolic, e.g. weight gain, abnormalities.

With regard to reproductive function, no proof exists that male fertility or female heat cycles are affected. Conception rates might be affected. The only proven association is low birth weights and a higher incidence of periparturient mortality. Neurologic signs of hypothyroidism are rarely seen, but more commonly affect peripheral nerves than central. Cranial nerves are most likely the most commonly affected. Laryngeal paralysis is not associated with hypothyroidism and megaesophagus very rarely is. Seizures and aggressive behavior are unlikely to be associated.

Findings on routine laboratory tests can provide support for hypothyroidism. A mild, non-regenerative anemia is seen in 30-40% of hypothyroid dogs. Hyperlipidemia, cholesterol, triglycerides or both, is seen in $\geq$ 75% of hypothyroid dogs.

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 (NTI) is a bit different. In dogs with no known non-thyroidal illness, the diagnosis is more straightforward. Starting with measurement of total T_4 alone is reasonable and economical. If total T_4 is normal, it is highly unlikely that the dog is hypothyroid.[1-4] Since non-thyroidal factors such as drugs and NTI affect T_4, if the T_4 is below normal, the dog may or may not be hypothyroid[1-3]; further testing is required.

Case Summary: Serum T_4 concentration = 28 nmol/L (reference range 20-50 nmol/L). Based on minimal clinical signs and normal serum T_4 concentration, diagnosis of hypothyroidism ruled out.

Case 2 - Signalment: 6 yr old, FS, miniature Poodle. **History**: Presented for decreased activity, obesity despite being on a weight-loss program, thinning hair coat, heat-seeking behavior. **PE**: Obese; partial, bilaterally symmetrical alopecia. Complete CBC, profile, urinalysis done. **Lab data:** Abnormalities were: RBC x 10^6/μl 5.0 (5.5-8.5); Hemoglobin 11.2 g/dL (12-18); PCV 33 % (37-55); Lymphs 0.5 x 10^3/μl (1.0-4.8); Cholesterol 470 mg/dL (130-370)

The clinical findings suggestive of hypothyroidism are much stronger than in Case 1. Starting with measurement of serum T_4 is still a good first choice, but be prepared to do further testing if the serum T_4 concentration is below normal.

Free T_4 (fT_4) is the portion of total T_4 not bound to protein, representing 0.1% of total T_4. The fT_4 concentration is affected less by non-thyroidal factors. Accordingly, fT_4 is a more sensitive and more specific test for diagnosis of hypothyroidism as compared to total T4.[1] However, it is 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 with a low total T_4 concentrations.

Free T_4 should always be measured by the equilibrium dialysis method. Other techniques for measuring fT_4 are not reliable and provide no additional diagnostic value over measurement of total T_4.[5] Equilibrium dialysis is also the only RIA for measuring fT_4 that is unaffected by the presence of autoantibodies.[6]

Primary thyroidal failure is believed to be the cause of canine hypothyroidism in 99% of cases.[7] 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.[1,4,8-10] In other words, if measurement of canine TSH were used alone for diagnosis of hypothyroidism, up to 1/3 of cases would be missed! Coversely, TSH can be elevated in approximately10% of euthyroid dogs with NTI.[1,9,11,12] Therefore, measurement of TSH is best used not as a sole test but in conjunction with T_4 or, ideally, fT_4. Use of a combination will aid in identifying false-positive and false-negative results seen with assessment of TSH alone.

Measurement of baseline serum T_3 is of little value in differentiating hypothyroid from normal dogs. There is no apparent difference in serum T_3 concentrations between these groups.[1,2,5]

Case Summary: Serum T_4 concentration was 13 nmol/L (borderline range: 12-19; reference range 20-50 nmol/L). Measurement of serum fT_4 concentration (by equilibrium dialysis) and serum TSH concentration were requested. The serum fT_4 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 is now a clinical dilemma. The question is whether this is a hypothyroid dog with a normal TSH or a euthyroid sick dog who's TSH has remained normal while the fT_4 is falsely lowered. The danger of falsely diagnosing a dog with hypothyroidism are threefold: 1. If clinical signs are incorrectly attributed to hypothyroidism, 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. If choosing option 2, make sure that you have objective measures of efficacy determined beforehand, e.g. normalization of serum cholesterol concentration and return to normal weight. Hair regrowth is not a good endpoint to use; the haircoat of euthyroid dogs can improve in response to thyroid supplementation. Be prepared to stop administering 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, Labrador retriever. **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. **PE**: Obese; partial, bilaterally symmetrical alopecia. Complete CBC, profile, urinalysis done. **Lab data:** Abnormalities were: RBC x $10^6/\mu l$ 5.0 (5.5-8.5); Hemoglobin 11.2 g/dL (12-18); PCV 33 % (37-55); Lymphs 0.5 x $10^3/\mu l$ (1.0-4.8); Cholesterol 470 mg/dL (130-370)

In a case that seems to be "text book" for hypothyroidism, starting with measurement of serum T_4 concentration is reasonable. If no other abnormalities are found other than those that can be explained by hypothyroidism and the serum T_4 concentration is very low, a presumptive diagnosis of hypothyroidism can be made. It would be ideal to measure fT_4 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 fT_4 concentration is much higher than that of serum TSH concentration, in a case such as this, if serum fT_4 concentration were low but serum TSH concentration was normal, I would believe the serum fT_4 concentration and start treatment for hypothyroidism.

Case Summary: Serum T_4 concentration was measured and was non-detectable. Due to financial considerations, fT_4 concentration was not measured. Therapy with L-thyroxine was instituted. Post-pill testing was done to ensure adequate serum T_4 concentration was achieved. Within 3-4 months clinical signs had resolved, further proving the diagnosis.

Case 4 - Signalment: 8 yr old, CM, English bulldog. **History**: Originally presented to his primary veterinarian for a geriatric screen and then was referred 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 (UPC) was determined and was 5.8 (normal <0.5). The dog had always received regular veterinary care. He lived in Alabama with no travel history. Vaccines were up-to-date, and he was receiving Interceptor for heartworm prevention. He was an indoor/outdoor dog.

The owners reported no problems. The dog's activity had decreased slowly over the past year and was attributed to aging. His appetite was normal. **Physical examination**: He was obese and had moderate to severe dental tartar and gingivitis. All else was unremarkable. **Lab data:** Abnormalities (CBC, profile and UA): WBC 17.5 x $10^3/\mu l$ (6.0-17.0); Segs: 14.6 x $10^3/\mu l$ (3.0-11.5); Lymphs 0.7 x $10^3/\mu l$ (1.0-4.8); Monos 1.7 x $10^3/\mu l$ (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 UPC, a tentative diagnosis of immune-complex glomerulonephritis (ICGN) was made. ICGN can be idiopathic or secondary to chronic immune stimulation. As dental disease could be a source of antigens, a dental procedure was performed. One month later, the UPC was essentially unchanged at 7.2; BP remained normal.

Further diagnostics were initiated to find possible underlying disease processes for ICGN. 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 wks later, after all test results had been obtained, the UPC was 8.6, BP and cholesterol were moderately elevated (190 mm Hg and 412 mg/dl, respectively). In order to determine the pathology underlying the proteinuria (e.g. glomerulonephritis vs. amyloidosis) and whether the disease process was reversible, a renal biopsy was performed; 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 BP was 140-150 mm Hg and the UPC was approximately 4.3. However, persistent hypercholesterolemia, obesity and poor hair regrowth after abdominal ultrasound were noted, and a diagnosis of hypothyroidism was considered.

Given the complexity of this case, I would start with measurement of serum total T_4, fT_4, and TSH concentrations. The effect of NTI on testing for hypothyroidism is quite significant. In one study, 223 dogs with normal thyroidal function but with NTI 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]

	% abnormal			
Disease severity	Total T4	T3	Free T_4	TSH
All dogs	31	16	22	8
Mild disease	8	3	8	11
Moderate disease	28	18	17	6
Severe disease	60	27	44	8

Of 69 dogs with low T4, 45% 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.[9,11]

Possibly, in order affect thyroid hormones, a NTI must cause systemic problems. For example, moderate to severe arthritis had no effect on thyroid testing.[13] However, transient systemic illness can have prolonged effects on thyroid testing. Therefore, in sick dogs, the first choice for diagnosis of hypothyroidism is a TSH, fT_4 and T_4 combination, 2nd is a combination of TSH and fT_4 and third a combination of TSH and T_4. If the results are conflicting (some parameters suggest hypothyroidism while others do not), the ideal would be to resolve the NTI, if possible, and then retest.

If resolution of the other disease is not possible, diagnosis of hypothyroidism poses a clinical dilemma as in Case 2. The clinician must 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. 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 T_4, fT_4 and TSH concentrations were measured. Serum T_4 was 13 nmol/L (normal 20-55 nmol/L; borderline 12-19 nmol/L), fT_4 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 NTI 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 wks.

The dog improved on treatment. Blood pressure remained normal, the UPC stabilized at approximately 3.2 and cholesterol remained very mildly elevated (380-400 mg/dl). Two months after stabilization, T_4 was still below normal (16 nmol/L), but the fT_4 (18 pmol/L) and TSH (0.02 ng/ml) were within normal. Hypothyroidism was ruled out.

Case 5 - Signalment: 9 yr old, CM, Cavalier Spaniel. **History**: Presented for geriatric examination. Doing well at home. **PE**: Normal. Complete geriatric profile done. **Lab data:** All within normal limits except ALP = 254 IU/L (normal 10-95) and T_4 = 12 nmol/L (normal 20-50).

What to do now? I believe in geriatric screening in some scenarios; thyroid testing in dogs is not one of them. One thing to consider with random testing (i.e. not testing based on the presence of clinical signs), what is the predictive value of a test? Sensitivity and specificity look at a test from the viewpoint of the patient. Sensitivity is the chance that an

animal with the disease will test positive and specificity is the chance that an animal that doesn't have the disease will test negative. Sensitivity and specificity are NOT affected by the prevalence of the disease in a population tested. Positive predictive value (PPV) tells you how likely it is that an individual with a positive test result actually has the disease. Negative predictive value (NPV) tells you the likelihood that an animal with a negative test result does not have the disease. The PPV and NPV are greatly affected by prevalence of disease. If you randomly test for a disease in a population, the PPV goes way down.

In addition, T4 is not that easy to interpret and depends on so many things including age. There is an age effect[14] that no laboratory takes into consideration in their reference intervals.

Case Summary: I would not recommend treating this dog without clinical signs, regardless of the T_4 measurement.

Case 6 - Signalment: 4 yr old, FI, Dobie. History: Presented for breeding examination. Doing well at home. PE: Normal. Lab data: All within normal limits except ALP = 254 IU/L (normal 10-95) and T_4 = 82 nmol/L (normal 20-50).

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, management of the hypothyroidism does not differ.

In general, the clinical and prognostic significance of autoantibodies is unknown.[15,16] If autoantibodies are suspected, measure fT_4 for the best assessment of function.[6] If the fT_4 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 fT_4 is low, the dog is likely hypothyroid. One study followed 234 dogs with normal T_4 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.[17] 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.