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INFORMATION
SCIVAC Secretary
Palazzo Trecchi, via Trecchi 20 Cremona
Tel. (0039) 0372-403504 - Fax (0039) 0372-457091
commscientifica@scivac.it  www.scivac.it
Canine Hypothyroidism

Reto Neiger, Prof. Dr.med.vet., PhD, DACVIM, DECVIM-CA
Small Animal Clinic, Justus-Liebig University Giessen, Germany

KEY POINTS
Canine hypothyroidism is one of the most over-diagnosed disorders by veterinarians! This is due to over reliance on the measurement of total TT4 (TT4) concentrations in assessing thyroid function. Newer tests have been developed to distinguish true hypothyroidism from a low TT4 level as a result of medications or non-thyroidal illness. Treatment can usually be accomplished with once daily dosing of thyroxine and routine monitoring of TT4 levels is probably not necessary in asymptomatic treated patients.

Aetiology
A. Primary hypothyroidism
   1. Accounts for over 90% of cases
   2. May be due to lymphocytic thyroiditis, idiopathic atrophy, or neoplastic destruction
      a. Lymphocytic thyroiditis (50% of cases)
         i. Immune-mediated destruction of the thyroid
         ii. Antithyroglobulin antibodies present
         iii. Genetic predisposition (borzoi, beagle, great dane and cocker spaniel)
      b. Idiopathic atrophy (40-45% of cases)
         i. Degenerative disorder of thyroid follicular cells
         ii. No inflammatory infiltrate
         iii. Cause unknown
         iv. May be the end stage of lymphocytic thyroiditis
      c. Neoplastic destruction
         i. Canine thyroid tumours usually hormonally inactive
         ii. Hypothyroidism follows total destruction of the gland by tumour invasion, surgery or radiation

B. Secondary hypothyroidism
   1. Impaired TSH secretion
   2. Congenital malformation (German Shepherd dog), pituitary destruction, medications (glucocorticoids)
   3. Less than 5% of cases

C. Tertiary hypothyroidism
   1. Hypothalamic disorder resulting in decreased TRH secretion
      a. Congenital defects, mass lesions, destructive lesions
      b. Suspected in a line of giant schnauzers
   2. Abnormal TRH molecule
   3. Abnormal TRH binding in pituitary

D. Miscellaneous causes
   1. Congenital defects
      a. Thyroid dysgenesis
      b. Dyshormonogenesis
   2. Iodine deficiency
      a. Unlikely if eating commercial dog food
   3. Defect in conversion of T4 to T3
      a. Not documented to occur in man or animals
      b. Low T3 with normal T4 usually due to concurrent illness (Sick Euthyroid Syndrome) or medications
Clinical Signs
A. Adult dogs
1. Onset of signs 4-6 years
   a. High risk, large, and giant breeds develop signs at an earlier age
2. General signs
   a. Lethargic
   b. Exercise intolerant
   c. Increased weight without polyphagia. Morbidly obese animals are rarely hypothyroid.
3. Dermatologic
   b. Non-pruritic unless secondary infection
   c. Alopecia may be focal; "Rat tail"
   d. Dull, dry hair coat
   e. Hyperkeratosis and hyperpigmentation
   f. Increased skin thickness (myxedema)
   g. Secondary pyoderma
4. Reproductive
   a. Female
      i. Irregular estrus intervals
      ii. Gynecomastia, galactorrhea
   b. Male
      i. Recent evidence indicated no reproductive abnormalities in intact males dogs with experimentally induced hypothyroidism
5. Cardiovascular
   a. Bradycardia
   b. Arrhythmias
   c. Atherosclerosis
6. Ocular
   a. Corneal lipid deposits
   b. Keratoconjunctivitis sicca
   c. Corneal ulceration
7. Neuromuscular
   a. Weakness
   b. Peripheral polyneuropathy (Lower Motor Neuron disease)
   c. Facial nerve paralysis
B. Congenital (Cretinism)
1. Dwarfism
2. Inappetence
3. Lethargy
4. Delayed dental eruption
5. Alopecia or juvenile hair coat
6. Epiphyseal dysplasia

Laboratory Abnormalities
A. Haematology
1. Mild normocytic, normochromic, nonregenerative anemia
B. Biochemistry profile
1. Elevated serum cholesterol

Diagnosis of Hypothyroidism
A. Basal T4 concentration
1. As for all endocrine testing, check with the laboratory for normal values and to see if a given assay is validated for the species you are evaluating
2. In general, normal basal T4 levels support euthyroidism, but low levels do not confirm hypothyroidism as many factors affect basal T4 levels
3. A low T4 indicates the need for further testing (see below)
B. Basal T3 concentrations
1. Basal levels of little use in discriminating normal from hypothyroid as:
   a. Vast majority of T3 is intracellular
b. The majority of T3 produced by peripheral deiodination of T4

Factors causing low T4 and T3 in euthyroid animals
1. Hourly fluctuations
2. Fasting over 48 hours
3. Concurrent illness
4. Hyperadrenocorticism
5. Medications: Glucocorticoids, valium, anticonvulsants, propranolol, many others
6. Aging

Factors causing increased T4 and T3 in euthyroid animals
1. Obesity
2. Hourly fluctuations
3. Estrus, pregnancy
4. Medications: Estrogen, progesterone
5. Antithyroid antibodies

C. TSH stimulation test
1. Designed to eliminate variables affecting basal T3 or T4
2. Protocol depends on laboratory used. Check first.
3. A common protocol is 0.1 IU TSH/kg IV, serum T4 at time 0 and 6 hours post-TSH
4. Exogenous thyroid supplementation should be stopped 4 weeks prior to testing
5. Post-TSH T4 should be within or above normal post-TSH range for laboratory used.
6. Serum T3 response is more variable than T4 and less diagnostic
7. Human recombinant TSH (50 microgram intravenously) can be used in the dog although the cost may be prohibitive and the use of assays for free T4 by equilibrium dialysis has limited the use of TSH stimulation testing in dogs

Interpretation of TSH Stimulation Test
1. With primary hypothyroidism
   a. Pre and post-TSH T4 should remain below normal basal T4 range
2. Sick euthyroid
   a. Animals with non-thyroidal disease or drug-induced lowering of T4 and T3 will have a blunted response to TSH administration when compared to normal. Differentiating between the sick euthyroid syndrome and hypothyroidism can be difficult and depends on clinical signs, presence of concurrent illness or drug administration, and owners recollection of the onset of signs.

D. TRH stimulation test
1. To differentiate secondary from tertiary hypothyroidism. Measurement of cTSH concentrations is also recommended.
2. Evaluates release of TSH in response to stimulation by TRH
3. TSH stimulation test should be performed first to document thyroid responsiveness
4. Lack of post-TRH T4 increase implies primary or secondary hypothyroidism. If the animal has a normal response to TSH administration, then secondary hypothyroidism is diagnosed.
5. Follow protocol recommended by your lab
6. Primarily used in evaluating patients with suspected or known abnormalities involving one or multiple pituitary hormones; i.e., pituitary dwarfs or animals with CNS lesions

E. Free T4
Recently, determination of free T4 (fT4) by equilibrium dialysis, has been shown to correlate very well with results of TSH stimulation testing in the diagnosis of canine hypothyroidism. Evaluation of fT4 allows us to assess the biologically active fraction of thyroid hormone and has been shown to be much less affected by non-thyroidal factors (medications, concurrent illness, binding abnormalities, etc). The term “sick euthyroidism” is often used to describe the effect of these various non-thyroidal factors on decreasing TT4 concentrations in the face of normal thyroid function. Although a number of fT4 assays are commercially available, only those that employ a dialysis step are valid in the dog.

F. Canine TSH Assay
Recently, an advance in the diagnostic approach to hypothyroidism was achieved with the advent of a reliable assay for canine TSH (cTSH). A kit for cTSH (Diagnostic Products Corporation; DPC Inc) is now available and should help in our approach to the patient with suspected hypothyroidism. A cTSH together with a free T4 by dialysis should provide the most relevant information with respect to thyroid function. A patient with
hypothyroidism should have an elevated cTSH in conjunction with a decreased fT4. However, with the current cTSH assay, up to 25% of patients with confirmed hypothyroidism have a cTSH concentration within the normal range.

G. Antithyroglobulin and anti-T3 and anti-T4 autoantibody testing:
The presence of antithyroglobulin antibodies indicates the presence of lymphocytic thyroiditis. Occasionally, these animals may also have anti-T3 and anti-T4 (rare) autoantibodies. The presence of thyroiditis does not equal a diagnosis of hypothyroidism. Animals with thyroiditis likely will become hypothyroid in the future but the decision on whether to supplement with thyroid hormone should be based on the presence of clinical signs and abnormal function tests (low TT4, low fT4ED and an elevated cTSH level). Animals with thyroiditis should not be used for breeding.

H. Trial therapy with thyroxine
1. Has been advocated as a diagnostic aid for hypothyroidism
2. Response to therapy is nonspecific however and normal animals may show some clinical effect due to the anabolic effects of thyroxine
3. Indiscriminate therapy with thyroxine, while it may not be harmful, is not cost-effective and may lead to a delay in obtaining a correct diagnosis and instituting proper therapy. Supplementing a sick, euthyroid animal may be detrimental.

As can be seen from the preceding discussion the diagnosis of hypothyroidism depends on a combination of clinical signs, results of routine laboratory tests, and tests of thyroid function. Measurement of fT4 by equilibrium dialysis together with a cTSH provides the most accurate information regarding thyroid function.

Treatment of Hypothyroidism
Sodium levothyroxine (T4)
1. Dose
   a. Dog:
      i. 0.22mg/m^2 q24h. Not to exceed 0.8 mg or
      ii. 0.10 mg/10kg BW q24h.
   b. Decrease initial starting dose by 75% if concurrent heart disease, hypoadrenocorticism, or diabetes mellitus is present
2. Response to therapy
   a. Attitude, activity, and appetite generally improve within 1-2 weeks
   b. Dermatologic abnormalities improve 4-8 weeks
3. Failure to respond to therapy
   a. Wrong diagnosis
   b. Inappropriate dosage or frequency of administration
   c. Poor absorption of T4
   d. Use of desiccated thyroid is discouraged
4. Monitoring therapy
   a. Not routinely needed unless there is a poor response to therapy or signs of thyrotoxicosis (PU/PD, restlessness, polyphagia, weight loss) are present.
   b. Monitoring Therapy
      i. Wait one month after starting therapy or changing dosage
      ii. Inquire about owner compliance and expiration date of medication
      iii. Measure serum T4 immediately prior to next dose (trough)
      iv. Normalization of serum cTSH levels may be the best way to monitor therapy but this requires that an elevated cTSH existed prior to therapy. Samples for cTSH may be obtained 2-3 weeks after starting supplementation and concentrations are not dependent on the time the sample is obtained relative to the dosing of thyroxine.
**SUMMARY**
Canine hypothyroidism is a well recognized though probably overly diagnosed disorder in the dog. Newer tests have allowed us to distinguish between true hypothyroidism and non-thyroidal illness. Low TT4 measurements should be confirmed with evaluation of fT4ED and cTSH concentrations. Approximately 25% of hypothyroid patients have normal cTSH levels using current assays. Recent evidence has shown that once daily dosing with thyroxine is appropriate in most patients.

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