

Canine hypothyroidism: making a definitive diagnosis

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SYNOPSIS

Hypothyroidism is the most common canine endocrinopathy (population prevalence 0.2-0.8 per cent), but can be challenging to diagnose. It is important to use a combination of clinical assessment, such as signalment, presenting signs and clinical examination findings, as well as routine and then specific endocrine tests in order to make a definitive diagnosis. This article will help us to understand the changes seen at each of those steps and direct us to choose the most appropriate test for our patients.

INTRODUCTION

Ninety-five per cent of canine hypothyroidism is due to primary thyroid gland failure resulting from idiopathic atrophy or lymphocytic thyroiditis (due to immune-mediated destruction).¹ Secondary hypothyroidism is seen uncommonly (<5 per cent of cases) and results from decreased thyroid-stimulating hormone (TSH) production, usually as a result of pituitary neoplasia. Tertiary hypothyroidism as a result of reduced thyroid-releasing hormone (TRH) production is reported in man, but not in dogs. Congenital hypothyroidism is rare and results from thyroid agenesis, aplasia or hypoplasia leading to non-proportional dwarfism or cretinism (Table 1).

Table 1: Clinical signs of congenital hypothyroidism.

Clinical signs of congenital hypothyroidism	
Non-proportional dwarf	Puppy hair coat
Short broad skull	Thick skin
Short limbs	Alopecia
Mental dullness	Dyspnoea
Inappetence	Kyphosis
Delayed dental eruptions	Constipation
Short mandible	Gait changes
Goitre	Lethargy

SIGNALMENT

Hypothyroidism is most commonly diagnosed in middle age, with an average age of diagnosis at seven years. One study showed onset of clinical signs at two to three years in 22 per cent; four to six years in 33 per cent; and seven to nine years in 22 per cent of cases.² No gender predisposition is

reported, however Golden Retrievers, Doberman Pinschers, Labradors and Cocker Spaniels are predisposed.

CLINICAL SIGNS

Thyroxine is needed for normal cellular metabolic functions in all cells of the body, thus a deficiency in thyroxine affects almost all body systems. Clinical signs are therefore very varied and depend on the disease stage and may also differ between breeds. Most dogs with hypothyroidism have reduced activity and mental states, resulting in exercise intolerance and lethargy. Weight gain is seen in 48 per cent of cases as a result of up to a 15 per cent reduction in calorie expenditure.³ Their reduced metabolism makes hypothyroid dogs intolerant of cold temperatures.

The vast majority of dogs with hypothyroidism have dermatological signs (>80 per cent of cases) that vary depending on the duration and the severity of the disease. Thyroid hormones are needed to initiate the anagen phase of hair growth, so their absence leads to persistence of telogen and, as a result, hairs are easy to epilate. Alopecia usually starts over areas of friction, such as the tail (resulting in the classic “rat tail” appearance) and neck, and progresses over time to bilaterally symmetrical truncal alopecia (Figures 1 and 2). This usually spares the head and limbs, and is usually non-pruritic (Figure 3). Dorsal nasal alopecia is seen in some breeds, especially Retrievers (Figure 4).



Figure 1: Lateral hair loss on the tail of a dog with hypothyroidism.



Figure 2: Hair loss over an area of friction due to collar placement in a hypothyroid dog.



Figure 3: A seven-year-old rescued crossbreed dog with alopecia secondary to prolonged hypothyroidism, the head has been largely unaffected.



Figure 4: A five-year-old male neutered Golden Retriever with dorsal nasal alopecia secondary to hypothyroidism.

Hyperpigmentation and comedones, with seborrhoea or dry, scaly skin, is commonly seen. Bacterial or *Malassezia* dermatitis is also common. Breed-related differences are also noted, with Arctic breeds usually losing the primary hairs, leaving a coarse woolly appearance to the remaining hair. Increased hair coat (hypertrichosis) is sometimes seen in Boxers and Irish Setters. Delayed or poor wound healing is often reported (Figure 5).

Neurological signs are commonly seen in association with hypothyroidism, through a variety of mechanisms; these include mucopolysaccharide accumulation around nerves, hyperlipidaemia and central atherosclerosis. Generalised muscle weakness is common, leading to weakness, exercise intolerance and reduced reflexes. Abnormal electromyogram (EMG) changes are seen but clinical signs usually improve within three months of treatment. Peripheral vestibular syndrome and facial paralysis are rare complications of hypothyroidism. The relationship between laryngeal paralysis and hypothyroidism is controversial, however treatment generally does not improve laryngeal function. As of yet no causal relationship has been proven.



Figure 5: A non-healing wound that developed from a pressure sore over the ischium of the dog in Figure 3.

Thyroxine has inotropic and chronotropic effects, thus dogs with hypothyroidism commonly present with bradycardia (35 per cent of cases) and a reduced apex beat; however, clinical signs rarely result directly from cardiac dysfunction.⁴ Atrial fibrillation has been reported rarely, however more commonly encountered ECG changes include reduced R waves (50 per cent of cases), first-degree atrioventricular (AV) block and occasional ventricular ectopics.

Echocardiography may reveal decreased contractility as a result of impaired myocardial function. Administration of thyroxine to dogs in heart failure should be done with caution, as treatment increases tissue oxygen demands, both peripherally and within the myocardium.

Gastrointestinal signs are uncommon in hypothyroidism

but constipation has been seen as a result of decreased muscular activity. Diarrhoea is also reported, presumably as a result of decreased gastrointestinal motility and enzyme production. Some dogs with mega-oesophagus have been shown to be hypothyroid, which has been theorised to be due to hypothyroidism-induced myopathy or neuropathy; treatment of these dogs with thyroxine may improve their oesophageal function.⁵ Myasthenia gravis is commonly linked with hypothyroidism in man, however no causal relationship has been determined in dogs.

Hypothyroidism leads to reduced libido, testicular atrophy and reduced sperm production in male dogs and may lead to increased inter-oestrus intervals in females; this is due to the need for thyroxine in normal luteinising hormone and follicle-stimulating hormone production. Increased TRH levels in response to low thyroxine concentrations can stimulate prolactin secretion, leading to inappropriate lactation. Ocular signs occur rarely, however lipid deposits can develop secondary to hyperlipidaemia and there is a very variable improvement with treatment. Corneal ulceration, uveitis and glaucoma have all been reported secondary to hypothyroidism; tear production is also reduced, although whether this progresses to overt keratoconjunctivitis sicca is unclear.⁶

In man, hypothyroidism leads to a reduction in factor VIII, IV and vWF:VIII antigen, with reduced factor VIII levels reported in hypothyroid dogs, which improve with treatment. Studies have also reported reduced von Willebrand factor (vWF), however these dogs were shown to have underlying concurrent von Willebrand disease, with reduced vWF as a result of hypothyroidism reducing protein turnover. In these dogs, once the hypothyroidism was treated, vWF levels increased. It is rare for hypothyroidism to present as a coagulopathy.⁷

Myxoedematous coma is caused by severe hypothyroidism and animals present collapsed, with profound weakness, bradycardia and hypothermia; this can progress rapidly to stupor and coma.⁸ Myxoedema occurs as mucopolysaccharides and hyaluronic acid accumulate within the dermis. These bind water leading to increased skin thickness and the finding of non-pitting oedema on clinical examination. This is classically seen around the face and jowl area, giving the so-called "tragic" expression. Prompt recognition of myxoedema allows early diagnosis and treatment, with early and aggressive treatment being critical to survival. As a result, the diagnosis of myxoedematous coma is made clinically with thyroxine levels being confirmed at a later stage; these are often extremely low. Treatment centres on the intravenous administration of levothyroxine, as oral drug absorption is unpredictable (the recommended dose is 5µg/kg bid; this dose is reduced by 50-75 per cent if cardiac failure is present). Aggressive symptomatic management of hypothermia, hypovolaemia and electrolyte changes is also needed.

LABORATORY FINDINGS

Routine laboratory findings are often suggestive of hypothyroidism, with haematological and biochemical

changes present as a result of the insufficient thyroxine. Haematology reveals a mild (PCV 28-36 per cent) non-regenerative (normocytic, normochromic) anaemia in around 30-50 per cent of cases. This is a result of a decreased response to erythropoietin, decreased oxygen consumption in tissues and an increase in 2,3-DPG concentrations leading to more efficient oxygen delivery. Increased number of target cells (leptocytes) may be present as a result of increased cholesterol within the erythrocyte membrane. Iron deficiency is seen occasionally as a result of impaired gastrointestinal absorption, and macrocytic megaloblastic anaemia is reported in man as a result of impaired cobalamin metabolism. Increased white cell numbers are usually indicative of concurrent infection (eg. pyoderma) and platelet numbers can be increased, but their volume reduced.

Biochemistry commonly reveals hyperlipidaemia (cholesterol >10mmol/l in 75 per cent of cases), as thyroid hormones control all aspects of lipid metabolism; this accumulation predisposes to atherosclerosis. Mild increases in alanine transaminase (ALT) and alkaline phosphatase (ALKp) may be seen (in around 30 per cent of dogs), possibly in relation to hepatic lipidosis. Elevations in creatine kinase (CK) and aspartate aminotransferase (AST) are proportional to clinical signs of myopathy; although CK may also be elevated due to decreased clearance from the circulation. Urinalysis is usually normal, however it occasionally reveals evidence of glomerular nephritis in association with immune-mediated thyroiditis. Fructosamine levels are increased in around 80 per cent of hypothyroid dogs as a result of decreased protein turnover. Levels are usually only mildly elevated and it is usually relatively straightforward to differentiate these elevations from diabetes patients. Fructosamine should therefore be used cautiously for monitoring in hypothyroid dogs with concurrent diabetes mellitus.

ENDOCRINE TESTS

As discussed earlier, it is important to remember that a diagnosis of hypothyroidism is a clinical diagnosis and should be based on clinical signs as well as laboratory tests. None of the endocrine tests is 100 per cent accurate, with variable sensitivity and specificity. There are also a number of possible factors, such as medication and non-thyroidal illness, that have a significant effect on thyroid function. All of these factors can combine to make a definitive diagnosis of hypothyroidism difficult. Total T4 (TT4) is the first-line test for diagnosing hypothyroidism as it is cheap, widely available and straightforward to measure. It is very sensitive but not specific as many different factors can affect TT4 levels. These include numerous classes of drugs and diseases (Table 2).⁹ Normal values make hypothyroidism very unlikely (<5 per cent of hypothyroid dogs in studies have TT4 values above the lower limit of the reference interval), however low results do not confirm the disease. In addition to non-thyroidal factors there is also daily fluctuation in TT4 values (occasionally to below the reference range), this does not follow a circadian pattern, therefore recommendations for

sampling are difficult. Larger and medium-sized breeds tend to have lower TT4 values compared to smaller breeds, with significant variations between individual breeds (eg. sight hounds and sled dogs have much lower TT4 values when compared to normal reference intervals). Obese dogs also have increased TT4 values compared to non-obese dogs of the same breed. Normal TT4 values have also been shown to progressively decline with age. Total T3 (TT3) has a lower diagnostic accuracy than TT4, thus the measurement of both TT3 and free T3 (fT3) is not particularly helpful in the diagnosis of hypothyroidism.

Table 2: Factors which affect thyroid function tests.^{9,10}

Factors affecting thyroid function tests	
Age	< 3 months ↑ T4 / >6 years ↓ T4
Body size (inversely proportional to BW)	<10kg ↑ T4 / >30kg ↓ T4
Breed	Greyhounds ↓ T4, ↓ fT4, normal TSH
Gender	No effect
Obesity	↑ T4
Strenuous exercise	↑ T4, ↓ TSH, normal TSH
Carprofen	↓ T4, ↓ fT4, normal TSH
Glucocorticoids	↓ T4, ↓ fT4, can ↓ TSH
Fruosemide	↓ T4
Methimazole	↓ T4, ↓ fT4, ↑ TSH
Phenylbutazone	↓ T4
Phenobarbitone	↓ T4, ↓ fT4, ↑ TSH
Potassium bromide	No effect
Penicillin	↓ T4
Cephalexin	No effect
TMPS	↓ T4, ↓ fT4, ↑ TSH
Dietary iodine intake	If excessive ↓ T4, ↓ fT4, ↑ TSH
Thyroid autoantibodies	↓/↑ T4 no effect on fT4 and TSH

Anti-thyroid antibodies can interfere with the actual levels of TT4, creating artificially high results. The presence of antibodies to TT4 or TT3 are seen rarely in dogs with hypothyroidism (T4 auto-antibodies of eight per cent in a study of 11,606 dogs¹) and have no clinical effects other than to make it difficult to measure TT4 accurately.¹⁰ In cases where TT4 appears normal (or elevated) in the face of suggestive clinical signs of hypothyroidism, a suspicion of autoantibodies should be raised and the measurement of TT4/TT3 or anti-thyroglobulin autoantibodies should be considered.

Measurement of TSH has greatly improved the ease of accurately diagnosing hypothyroidism and is suggested along with TT4 as the front-line test for hypothyroidism. In primary hypothyroidism the loss of thyroid tissue leads to

the lack of negative feedback on the pituitary, as a result excessive levels of TSH are produced in the majority of cases. Combining TT4 with TSH measurements will reveal approximately 80 per cent of cases; however TSH can be normal in 20-40 per cent of cases.¹¹ TSH can also be affected by a variety of drugs (for example glucocorticoids decrease TSH and TPMS increase TSH levels) and non-thyroidal illnesses. Inappropriately low TSH levels are expected in secondary or central hypothyroidism, however the currently available TSH assay cannot distinguish normal from low TSH values.

Free T4 (fT4) is the active hormone and represents the proportion of thyroid hormone that is available for tissue uptake. It is less affected by non-thyroidal factors, such as drugs and non-thyroidal illness. As such it is less sensitive but much more specific when compared to TT4.¹² Free T4 needs to be measured by equilibrium dialysis as RIAs underestimate fT4 values; as a result measurement is usually performed at reference laboratories. It is therefore most appropriately used as a second-line test and, in this respect, its poorer sensitivity compared to TT4 is less important (Table 3). Its main use is in cases with low TT4 and normal TSH; in these cases, fT4 will help to differentiate between cases of non-thyroidal illness and genuine hypothyroidism.

Table 3: Sensitivity and specificity of thyroid function tests for the diagnosis of canine hypothyroidism.¹⁰

Test	Total T4	Free T4	TSH	TT4 and TSH
Sensitivity	95%	>80%	75%	75%
Specificity	75%	>90%	80%	>90%

The TSH stimulation test is considered the gold standard in the diagnosis of hypothyroidism, although the development of accurate TSH and fT4 assays has reduced its clinical indications.¹³ Administration of a supra-maximal dose of bovine or human TSH leads to TT4 release, assessing the functional reserve of the thyroid. TSH is currently difficult and expensive to obtain, and hypersensitivity reactions have been reported. TRH is easier to source; however, TRH stimulation tests are harder to interpret as they rely on the stimulation of TSH and are less reliable. A good response to TRH can exclude hypothyroidism, but cannot distinguish non-thyroidal illness.

Ultrasound evaluation of thyroid gland volume is useful to distinguish hypothyroid animals from those with sick euthyroid syndrome (from non-thyroidal illness); many breed specific reference ranges are now becoming available.¹⁴ In normal dogs, the thyroids are visible as rounded oblong shapes, which are triangular in cross section and have a smooth surface. The echotexture should be homogeneous and isoechoic or hyperechoic compared to the adjacent sternothyroid muscle. Dogs with lymphocytic plasmocytic thyroiditis have decreased echogenicity and a markedly heterogeneous appearance, with a rounded cross section and overall decreased volume. Computed tomography (CT) and magnetic resonance imaging (MRI) allow more

detailed assessment of thyroid size and nuclear scintigraphy assessment of thyroid gland function.

TREATMENT

Treatment of hypothyroidism involves replacement therapy with a synthetic thyroxine preparation (L-thyroxine 0.02-0.04mg/kg in divided daily dosing). Clinical signs start to improve quickly with treatment; however, some signs may take longer to improve (Table 4).

In some cases treatment may be used as a therapeutic trial (although this is discouraged and should only be used as a last resort in cases with a high index of suspicion for hyperthyroidism), however this can be difficult to interpret as the signs of a number of non-thyroidal illnesses will improve with thyroxine supplementation. To truly use treatment as a trial, therapy should be instigated, proven to be at a therapeutic level and all clinical signs of disease allowed to resolve. Treatment should then be withdrawn and, if clinical signs recur, a diagnosis of hypothyroidism can be confirmed.

TT4 is the monitoring test of choice, with values of 50-60nmol/l suggested four to six hours post-pill. Levels <35nmol/l are likely associated with suboptimal control, while levels >100nmol/l are likely to be related to signs of toxicosis. TSH can be used in the monitoring of hypothyroidism to assess the longer-term adequacy of

treatment. With supplementation feedback of thyroxine to the pituitary will allow TSH levels to fall to normal very quickly. Elevated TSH levels on therapy indicate poor owner compliance or suboptimal therapy.⁹

Table 4: Time for clinical signs of hypothyroidism to improve with treatment.

Clinical sign	Time to improvement
Mentation and activity	2-7 days
Lipaemia and clinical pathology	2-4 weeks
Dermatological abnormalities	2-4 months
Neurological abnormalities	1-3 months
Cardiac abnormalities	1-2 months
Reproductive abnormalities	3-10 months

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Reader Questions and Answers

1: WHICH OF THE FOLLOWING STATEMENTS REGARDING HYPOTHYROIDISM IS CORRECT?

- A. Male dogs are more likely to be affected than females
- B. Most will be over 10 years old at first presentation
- C. Congenital hypothyroidism leads to proportional dwarfism
- D. Breed predispositions are reported for Golden Retrievers, Labradors and Doberman Pinschers

2: WHICH OF THE FOLLOWING STATEMENTS REGARDING HYPOTHYROID DOGS IS UNTRUE?

- A. Mild increases in liver enzymes are seen in 30% of cases
- B. Cholesterol is elevated in all dogs
- C. A mild non-regenerative anaemia is commonly reported
- D. Leptocytes in proportion to elevated cholesterol levels

3: WHICH OF THE FOLLOWING STATEMENTS REGARDING THYROID TESTING IS TRUE?

- A. Obesity decreases total T4 levels
- B. Dogs less than 10kg have proportionally lower TT4
- C. Phenobarbitone administration reduces TT4 levels
- D. Glucocorticoids decrease TT4 and fT4 levels

4: WHICH OF THE FOLLOWING STATEMENTS REGARDING TESTING FOR HYPOTHYROIDISM IS UNTRUE?

- A. TSH measurements will be increased in all dogs
- B. TT3 measurements are rarely helpful in diagnosing hypothyroidism
- C. Thyroid autoantibodies are rarely seen in hypothyroid dogs
- D. TSH stimulation tests allow assessment of the functional reserve of the thyroid gland

5: WHAT DURATION OF TREATMENT WOULD YOU EXPECT TO NEED TO GIVE TO SEE DERMATOLOGICAL CHANGES?

- A. Two to seven days
- B. Two to four weeks
- C. Two to four months
- D. Six to 12 months

ANSWERS: 1. D, 2. B, 3. B, 4. A, 5. C