Canine Hypothyroidism: What is the Best Test?

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Hypothyroidism is the most common canine endocrinopathy (population prevalence 0.2-0.8%), 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 understand the changes seen at each of those steps and help us to choose the most appropriate test for our patients.

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). Secondary hypothyroidism is seen uncommonly (<5% of cases) and results from decreased TSH production usually as a result of pituitary neoplasia. Tertiary hypothyroidism as a result of reduced 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 (see table below).

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 7 years. One study showed onset of clinical signs at 2-3 years in 22%, 4-6 years in 33% and 7-9 years old in 22% of cases. 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 different breeds. Most dogs with hypothyroidism have reduced activity and mental states, resulting in

exercise intolerance and lethargy. Weight gain is seen in 48% of cases as a result of up to a 15% reduction in calorie expenditure. Their reduced metabolism makes hypothyroidism dogs intolerant of cold temperatures.

The vast majority of dogs with hypothyroidism have dermatological signs (>80% of cases) and vary depending on the duration and the severity of the disease. Thyroid hormones are needed to initiate the anagen phase of hair growth, so there 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. This usually spares the head and limbs, and is usually non pruritic. Dorsal nasal alopecia is seen in some breeds, especially Retrievers. Hyperpigmentation and comedones, with seborrhoea or dry, scaly skin is commonly seen. Bacterial or *Malazzesia* dermatitis is also common. Breed related differences are also noted with artic breeds usually losing the primary hairs, leaving a coarse woolly appearance to the remaining hair. Increased hair coat (hyertrichosis) is sometimes seen in Boxers and Irish Setters.

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 EMG changes are seen but clinical signs usually improve within 3 months of treatment. Peripheral vestibular syndrome and fascial 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.

Thyroxine has inotropic and chronotropic effects, thus dogs with hypothyroidism commonly present with bradycardia (35% of cases) and a reduced apex beat; however clinical signs rarely result directly from cardiac dysfunction. Atrial fibrillation has been reported rarely, however more commonly encountered ECG changes include reduced R waves (50% of cases), 1st degree 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 in the myocardium.

Gastrointestinal signs are uncommon in hypothyroidism but constipation has been seen as a result of decrease muscular activity. Diarrhoea is also reported presumably as a result of decreased gastrointestinal motility and enzyme production. Some dogs with megaoesophagus 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. 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 an increased inter oestrus in females; this is due to the need for thyroxine in normal LH and FSH production. Ocular signs occur rarely, however lipid deposits can develop secondary to hyperlipidaemia and has 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 KCS is unclear.

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's factor (vWF), however these dogs were shown to have underlying concurrent von Willebrand's 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.

Myxoedematous coma is caused by severe hypothyroidism and animal present collapsed, with profound weakness, bradycardia and hypothermia, this can progress rapidly to stupor and coma. 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 TT_4 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% if cardiac failure is present). Aggressive symptomatic management of hypothermia, hypovolaemia and electrolytes 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%) non regenerative (normocytic, normochromic) anaemia in around 30-50% 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 (e.g. pyoderma) and platelet numbers can be increased, but their volume reduced.

Biochemistry commonly reveals hyperlipidaemia (cholesterol >10mmol/l in 75% of cases), as thyroid hormones control all aspects of lipid metabolism; this accumulation predisposes to atherosclerosis. Mild increases in ALT and ALKp may be seen (in around 30% of dogs), possibility in relation to hepatic lipidosis. Elevations in CK and 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 occasionally reveals evidence of glomerular nephritis in association with immune mediated thyroiditis. Fructosamine levels are increased in around 80% of hypothyroid dogs as a result of decreased protein turnover. Levels are usually only mildly elevated and it is usually relatively straight forward to differentiate these elevations from diabetes patients. Fructosamine should therefore be used cautiously for monitoring in hypothyroid dogs with concurrent diabetes mellitus.

Hypothyroidism also leads to reduced levels of growth hormone, leading to dwarfism in congenital hypothyroidism. Increased TRH levels in response to low thyroxine concentrations can stimulate prolactin secretion leading to inappropriate lactation. Thyroxine is also needed for normal LH and FSH secretion.

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 are 100% accurate, with variable sensitive and specific. 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 (TT_4) is the first line test for diagnosing hypothyroidism; as it is cheap, widely available and straight forward 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 (see table below). Normal values make hypothyroidism very unlikely (<5% 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 (e.g. 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.

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 (5.7% for TT3 and 1.7% for TT4) and have no clinical effects other than to make it difficult to measure TT4 accurately. 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.

Total T3 has a lower diagnostic accuracy than TT4, thus the measurement of both TT3 and fT3 is not particularly helpful in the diagnosis of hypothyroidism.

Factors affecting thyroid tests	
Age	< 3months ↑ 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
Frusemide	↓ 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 & TSH

Measurement of TSH has greatly improved the ease of accurately diagnosing hypothyroidism and is suggested along with TT4 as the frontline 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% of cases, however TSH can be normal in 20-40% of cases. TSH can also be affected be 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.

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

Free T4 (fT4) is the metactive 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. fT4 needs to be measured by equilibrium dialysis as RIA's underestimate fT4 values and is a more expensive test 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. Its great use comes in cases with low TT4 and normal TSH, in these cases fT4 will help differentiate between cases of non-thyroidal illness and genuine hypothyroidism.

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. 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. 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 homogenous and isoechoic or hyperechoic compared to the adjacent sternothyroid muscle. Dogs with lymphocytic plasmocytic thyroiditis have decreased echogenicity and a markedly heterogenous appearance, with a rounded cross section and overall decreased volume. CT and MRI allow more detail 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-thryroxine 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.

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

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 allow all clinical signs of disease to resolve. Treatment should then be withdrawn and if clinical signs recur then a diagnosis of hypothyroidism can be confirmed.

TT4 is the monitoring test of choice, with values of 50-60nmol/l suggested 4-6 hours post pill. Levels <35nmol/l are likely associated with suboptimal control, whilst 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 tyroxine to the pituitary will allow TSH levels to fall to normal very quickly. Elevated TSH levels on therapy indicate poor owner compliance or sub-optimal therapy.