Diagnosing thyroid disease in the dog- How do I go about it?

Introduction
Dogs can suffer from hypo- or hyperthyroidism but the latter is extremely rare, while the former is considered one of the most common endocrinopathies in this species. Unfortunately, it is also one of the more over-diagnosed disorders in veterinary practice. This is related to the variation in clinical presentation with few pathognomonic features and the over reliance on total T4 concentration for diagnosing the condition. Hypothyroidism is caused by a deficiency of the active thyroid hormones (T4 and T3). T4 is the predominate hormone secreted by the thyroid and is converted peripherally to the biologically active hormone T3. Thyroid hormones regulate the metabolic rate of most organ systems. Clinical signs are therefore variable, vague and non-specific. Diagnosis depends on a combination of clinical signs, clinicopathological abnormalities and thyroid function tests. The real challenge is in accurately diagnosing hypothyroidism. This presentation will focus on the diagnosis of hypothyroidism and will not discuss the diagnosis of hyperthyroidism.

1- Aetiology of hypothyroidism

A. Primary hypothyroidism:

Primary hypothyroidism accounts for over 90% of cases, due to lymphocytic thyroiditis (50% of cases) or idiopathic atrophy (40-45% of cases). In a small number of cases it results from neoplastic destruction of the thyroid tissue.

- Lymphocytic thyroiditis: This is the most common form and results from immune mediated destruction of the thyroid gland. Antithyroglobulin antibodies are often present in the plasma. A genetic predisposition has been recognised in certain breeds, including borzoi, beagle, great Dane and cocker spaniel.

- Idiopathic atrophy: The cause is unknown. It is a degenerative disorder and on histopathology inflammatory infiltrates are not found. Some workers suggest that it may be the end stage of lymphocytic thyroiditis.

- Neoplastic destruction: canine thyroid tumours are usually hormonally inactive. Hypothyroidism follows total destruction of the gland by tumour invasion, surgery or radiation.

B. Secondary hypothyroidism:

This results from impaired TSH secretion from the pituitary gland. It accounts for less than 5% of cases of hypothyroidism. It can result from congenital malformations of the pituitary axis (GSD), pituitary destruction or the administration of certain medications (glucocorticoids).

C. Tertiary hypothyroidism:
Tertiary hypothyroidism results from a lack of TRH. It has only once been convincingly diagnosed in a dog as a result of a destructive tumour.

D. Miscellaneous causes:

- Congenital defects (thyroid dysgenesis, dyshormonogenesis)
- Iodine deficiency

2- Signalment and clinical signs

Some breeds are known to be predisposed to hypothyroidism: boxers, dachshunds, Dobermanns, golden retrievers, great Danes, Irish setters, miniature schnauzers, poodles and spaniel breeds (especially cocker). However, almost any breed can develop hypothyroidism. The disease is most common in middle aged and elderly dogs (onset of signs 4-6 years) but occasionally occurs in animals as young as 2 years. The mean age at diagnosis is 7 years. Large breed dogs tend to develop signs at an earlier age than small breed dogs.

The general signs associated with hypothyroidism are secondary to decreased metabolic rate: lethargy, exercise intolerance, cold intolerance and increased weight without polyphagia.

The more specific abnormalities are:

- **Dermatologic**:

  * scaling and scurfing: hyperkeratosis
  * alopecia: thyroid hormones are necessary for the initiation of the anagen phase of the hair follicle cycle. Hypothyroidism results in persistence of the telogen growth phase; hairs become easily epilated and eventually alopecia results. This commonly begins in areas of friction such as the neck in animals who wear a neck collar and on the tail resulting in the typical rat-tail appearance. Eventually, it results in bilaterally symmetric truncal alopecia with the head and extremities spared. However dorsal nasal alopecia is reported as a feature of hypothyroidism in retrievers and also occurs in other breeds.

- **Reproductive**:

  Female dogs have irregular oestrus intervals, and may develop gynecomastia and galactorrhea.
  Male dogs are not reported to have any reproductive abnormalities.

- **Cardiovascular**:

  Thyroid hormones have a direct positive inotropic effect on the myocardium. In addition they stimulate myocardial hypertrophy and increase the responsiveness of the heart to adrenergic stimulation. Their absence has the
potential to impair cardiac function: arrhythmias and bradycardia may develop. Hypercholesterolaemia may also lead to the development of atherosclerosis, although this is rare in dogs. The most widely reported cardiac disease linked to hypothyroidism in dogs is dilated cardiomyopathy. However it now clear that there is no causal relationship between the development of cardiomyopathy and hypothyroidism at least in Dobermanns where it has been most extensively studied.

- **Ocular.**

  Corneal lipidosis occurs in a small number of hypothyroid dogs.

- **Neuromuscular.**

  The pathological basis for most central or generalised neuromuscular abnormalities is thought to be reduced axonal transport due to failure of the sodium-potassium ATPase pump. The most common abnormalities documented are weakness, peripheral polyneuropathy (lower motorneuron disease), facial nerve paralysis.

  For the congenital forms (cretinism), clinical signs are different: dwarfism, inappetence, lethargy, delayed dental eruption, alopecia or juvenile hair coat and epiphyseal dysgenesis all occur.

3- **Laboratory abnormalities:**

The most common biochemical and haematological abnormalities encountered in hypothyroidism are hyperlipidemia and anaemia.

**Triglyceride and cholesterol:**

Hypercholesterolaemia occurs in up to 80% of affected dogs. Hypertriglyceridaemia is present in a similar proportion of cases. Hyperlipidaemia is not specific to hypothyroidism and occurs in other endocrine disorders, such as diabetes mellitus and hyperadrenocorticism, however the magnitude of the cholesterol increase in hypothyroidism is typically greater.

**Anaemia:**

A mild normochromic, normocytic anaemia affects 40-50% of hypothyroid dogs. Typically it is mild.

**Creatine Kinase:**

An increase in CK is commonly reported and is thought to be secondary to reduced clearance.

**Liver enzymes:**
30% of hypothyroid dogs have mild increases in liver enzymes (particularly ALP and GGT). This is presumed to result from hepatic lipid deposition.

**Fructosamine:**

Fructosamine values are increased in hypothyroid dogs (to the top end of the range 300 umol/L approximately). This is due to a reduction in protein turnover rather than any change in glycaemic control.

**4- Diagnosis:**

A. **Total Thyroxine T4:**

As for all endocrine testing you need to check with the laboratory what the reference ranges are and that the assay has been validated for dogs (human assays are optimised to measure much higher concentrations than typically seen in dogs). In general, a reference range total T4 supports euthyroidism, but low levels do not confirm it as many factors can influence basal concentrations. A low total T4 indicates the need for further testing. A small number of animals with hypothyroidism have total T4 values within the reference range, as a result of circulating T4 autoantibodies.

*Factors causing low total T4 in euthyroid animals:*
- Non-specific fluctuations.
- Concurrent illness.
- Medications: glucocorticoids, anticonvulsants, propanolol, sulfonamides
- Aging.
- Breed: sighthounds

B. **Endogenous thyrotropin (cTSH):**

When circulating T4 and T3 concentrations are reduced their negative feedback effect on pituitary TSH secretion declines. Circulating cTSH concentration is therefore increased in most dogs with primary hypothyroidism. However, several studies have demonstrated that approximately a quarter of hypothyroid dogs have cTSH concentrations within reference range, precluding the use of this test as a screening test. Furthermore, although the specificity of cTSH measurement is high, elevated values can occur in euthyroid dogs receiving sulphonamide therapy, during the recovery phase of non thyroidal illnesses and in compensating hypothyroidism.

C. **Free T4:**

Free T4 is the biologically active fraction of thyroid hormone and has been shown to be much less affected by non thyroidal factors (medication, concurrent illness,, etc). However both glucocorticoids and phenobarbitone have been shown to lower free T4 concentration in dogs. Greyhounds have low free T4 values regardless of their thyroid status. Although a number of fT4
assays are commercially available, only those that employ a dialysis step are valid in the dog. Determination of $fT4$ by equilibrium dialysis has been shown to be the single best test at diagnosing hypothyroidism but is expensive and usually retained for those cases in which a diagnosis is not achieved with total T4 and cTSH estimations.

D. Thyroglobulin autoantibodies:

Antibodies to thyroglobulin may be produced during the development of lymphocytic thyroiditis. A sensitive and specific assay is available to measure TgAA. A positive TgAA status provides evidence for an active inflammatory process in the thyroid glands but it does not provide any information on thyroid status per se because thyroid dysfunction does not occur until at least 60-70% of the gland is destroyed. Approximately 20% of dogs with positive TgAA status and no other thyroid hormone abnormality, progress to thyroid dysfunction within a year.

Table 1 Features of Total T4, cTSH, Free T4 and TgAA measurement. (Mooney 2008, WSAVA)

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>TT4</td>
<td>Inexpensive, sensitive marker for hypothyroidism, widely available, easily measured.</td>
<td>Lower in elderly dogs and certain breeds Decreased by most NTIs Subnormal at random times</td>
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<tr>
<td>TSH</td>
<td>Easy, not expensive, available</td>
<td>¼ of hypothyroid dogs have TSH values within the reference range (low sensitivity). Always use in combination with TT4</td>
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<tr>
<td>Free T4</td>
<td>Less influenced by non thyroidal illness or drug administration than TT4</td>
<td>The only reliable method includes equilibrium dialysis. Not readily available in all laboratories.</td>
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<tr>
<td>Thyroglobulin autoantibodies (TgAA)</td>
<td>Positive result suggestive of thyroid pathology</td>
<td>Provides no assessment of thyroid functionnal capacity Negative result does not rule out significant thyroid disease</td>
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E. Combining basal analyses:

Combining different tests enables us to overcome some limitations of each individual test. The current recommendation for diagnosis of hypothyroidism is concurrent measurement of total T4 and cTSH concentrations. The combination of a highly sensitive test (TT4) and a highly specific test (cTSH) provides a diagnosis of hypothyroidism in most cases especially if dogs are being tested with a strong clinical suspicion.
The one case scenario that requires further testing is when a total T4 value is below the reference range and cTSH within its reference range. In this situation, if the index of suspicion for hypothyroidism is high, free T4 and TgAA measurements may provide useful information. Free T4 in most cases distinguish genuine hypothyroidism from other causes of hypothyroidism and a positive TgAA status provides evidence of thyroid pathology.

The above tests have largely meant that older stimulation tests (TSH or TRH) are no longer required in the investigation of hypothyroidism.

F. Diagnostic imaging:

Thyroid ultrasonography: ultrasonographic changes observed in hypothyroid dogs were recently described and include a decrease in thyroid volume and a decreased echogenicity compared to normal dogs. Quality of the ultrasonographic equipment and experience of the ultrasonographer may negatively impact accurate measurement of thyroid size and will most likely limit the use of ultrasonography for the diagnosis of hypothyroidism in current veterinary practice.

Thyroid scintigraphy: this is a very useful method for the most accurate evaluation of thyroid function. When available, it can be used to differentiate dogs with the euthyroid sick syndrome from truly hypothyroid dogs. It is only available in a few defined referral centres (including the UVH).