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Recent approaches in diagnosis and management of canine hypothyroidism: A review

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Abstract

Hypothyroidism is the most frequently diagnosed endocrinopathy in dogs characterised by diminished production of the thyroid hormones i.e. thyroxine (T4) and thyronine (T3) and is of three types: primary hypothyroidism (>95 percent), secondary hypothyroidism and tertiary hypothyroidism. In adult dog, the most consistent clinical signs of hypothyroidism are due to decreased cellular metabolism and dermatological manifestations. Additional clinical signs may affect the neuromuscular system, gastrointestinal system and reproductive system. The presence of appropriate clinical signs is imperative, especially when relying on baseline thyroid hormone concentrations for the diagnosis. Identification of mild non-regenerative anaemia on the complete blood count and an increased serum cholesterol concentration on a serum biochemistry panel adds further support for hypothyroidism. Low serum T4, free T4 and increased serum TSH concentrations in a dog with appropriate clinical signs and clinic-pathological abnormalities strongly support the diagnosis of hypothyroidism, especially if systemic illness is not present. Initial treatment of choice, regardless of the underlying cause of hypothyroidism is synthetic L-T4 sodium. The recommended initial dose for healthy hypothyroid dog is 0.02 mg/kg PO every 12 hours. The plasma half-life of L-T4 sodium in dogs ranges from 9 to 14 hours and depends on the dosage and frequency of administration, with higher dosages and more frequent administration associated with a shorter half-life of L-T4 sodium. With appropriate therapy, all of the clinical signs and clinic-pathological abnormalities associated with hypothyroidism should resolve.

Keywords: Canine, Hypothyroidism, Synthetic L-T4 sodium, Thyroxine, Thyronine.

Introduction

Hypothyroidism is the most frequently diagnosed endocrinopathy in dogs. The disease is characterised by diminished production of the thyroid hormones thyroxine (T4) and thyronine (T3). Thyroid hormones influence large number of metabolic processes in the body and, in the event of disorders in hormone production, symptoms can arise from a number of organ systems. In addition to the most commonly occurring symptoms such as dermatological changes and signs of general metabolic disturbances, a number of neurological manifestations have been reported to occur in hypothyroidism in dogs. Neurological symptoms of hypothyroidism can originate from the central and peripheral nervous systems as well as from the muscles.

Thyroid Hormone

Thyroxine (T4) and 3, 5, 3'-triiodothyronine (T3) are iodine-containing amino acids. Thyroid hormone synthesis requires iodine and is dependent upon ingestion of adequate iodide from the diet. Iodide is actively transported from the extracellular fluid into the thyroid follicular cell by the sodium-iodine symporter (NIS), where it is rapidly oxidized by thyroid peroxidase (TPO) into a reactive intermediate. At the apical membrane, iodine is incorporated into the tyrosine residues of Tg^[1]. TPO also catalyzes the coupling of the non-biologically active iodinated tyrosine residues (monoiodotyrosine [MIT], and diiodotyrosine [DIT]) to form the biologically active iodothyronines-T4 and T3. These iodination reactions are referred to as organification.

Hypothyroidism Classification

Hypothyroidism is the most common thyroid disorder in dogs and may be acquired or congenital. Hypothyroidism is classified as primary if it is due to an abnormality at the level of

the thyroid gland, secondary if it is due to decreased TSH secretion and tertiary if it is due to TRH deficiency.

(A) Acquired Hypothyroidism

(1) Primary Hypothyroidism

It is the most common cause of naturally occurring thyroid failure in the adult dog, accounting for more than 95% of cases. Two histologic forms of primary hypothyroidism are recognized in dogs- lymphocytic thyroiditis and idiopathic atrophy. Other much more rare causes of primary hypothyroidism include iodine deficiency, goitrogen ingestion, congenital hypothyroidism, thyroid gland destruction by neoplasia, drug therapy, surgical

Stage 1	Stage 2	Stage 3	Stage 4
Subclinical Thyroiditis	Antibody Positive Subclinical Hypothyroidism	Antibody Positive Overt Hypothyroidism	Non-Inflammatory Atrophic Hypothyroidism
Focal lymphocytic thyroid gland infiltration.	Loss of greater than 60% to 70% of thyroid mass.	Most functional thyroid tissue is destroyed.	Replacement of thyroid tissue by fibrous and adipose tissue.
Positive Tg and Thyroid hormone autoantibody test.	Compensatory increase in TSH, which stimulates the thyroid gland to maintain normal T4 concentrations.	Decreased serum thyroid hormone concentrations and Increased TSH concentration.	Disappearance of inflammatory cell and circulating antibodies.

(b) Idiopathic Atrophy

It is characterized microscopically by progressive reduction in the size of the thyroid follicles, and replacement of the degenerating follicles with adipose tissue. The parathyroid glands are not affected, and variable numbers of parafollicular cells remain. Idiopathic thyroid atrophy may be either a primary degenerative disorder [3], or an end stage of lymphocytic thyroiditis as evident by initial degenerative thyroidal parenchymal changes, which progressed to progressively worsening inflammation, subsequent fibrosis, and thyroid gland destruction.

(c) Neoplastic Destruction

Clinical signs of hypothyroidism may develop following destruction of more than 80% of the normal thyroid gland by an infiltrative tumour. Tumours may arise from the thyroid gland or unlike for may metastasize to or invade the thyroid gland from adjacent tissues. Interpretation of thyroid hormone concentrations in dogs with thyroid tumours is complicated by the effects of concurrent illness on serum thyroid hormone concentration [4].

(d) Miscellaneous Causes

Acquired primary hypothyroidism may rarely result from ingestion of goitrogens, administration of anti-thyroid medications (e.g., propylthiouracil and methimazole), and chronic use of high doses of potentiated sulfonamides. A palpable goiter may develop in dogs treated chronically with potentiated sulfonamides [5].

(2) Secondary Hypothyroidism

Secondary hypothyroidism results from failure of pituitary thyrotrophs to develop due to pituitary malformation or acquired dysfunction of the pituitary thyrotrophs causing impaired secretion of TSH. Deficiency of TSH leads to decreased thyroid hormone synthesis and secretion and thyroid gland hypoplasia [6].

Potential causes of secondary hypothyroidism include congenital malformations of the pituitary gland, pituitary destruction, and pituitary suppression. In the dog, secondary hypothyroidism caused by naturally acquired defects in

thyroidectomy, and treatment with radioactive iodine.

(a) Lymphocytic Thyroiditis

Lymphocytic thyroiditis is an immune-mediated disorder, where both humoral and cell mediated immunity play a role in pathogenesis. The major thyroid antigens that initiate an immune response in the thyroid gland are Tg and TPO. Lymphocytic thyroiditis is characterized histologically by diffuse infiltration of lymphocytes, plasma cells, and macrophages into the thyroid gland, resulting in progressive destruction of follicles and secondary fibrosis. [2] Have proposed four stages in the development of lymphocytic thyroiditis in dogs.

pituitary thyrotroph function or destruction of pituitary thyrotrophs (e.g., pituitary neoplasia) is uncommon.

(3) Tertiary Hypothyroidism

Tertiary hypothyroidism is defined as a deficiency in the secretion of TRH by peptidergic neurons in the supraoptic and paraventricular nuclei of the hypothalamus. Lack of TRH secretion causes deficiency of TSH secretion and follicular atrophy of the thyroid gland. Neurologic signs and additional pituitary dysfunction may be present, depending on the cause. Tertiary hypothyroidism is assumed to be rare in dogs.

(B) Congenital Hypothyroidism

Congenital hypothyroidism is rare in dogs. Unfortunately, congenital hypothyroidism frequently results in early puppy death, and the cause of death is rarely documented. A defect anywhere in the hypothalamic-pituitary-thyroid axis or of the thyroid hormone receptor can result in congenital hypothyroidism. Congenital hypothyroidism with goiter (CHG) develops if the hypothalamic-pituitary-thyroid axis is intact; TSH binds appropriately with its receptor, but there is an intra-thyroidal defect in thyroid hormone synthesis (dysshormonogenesis). Increased serum TSH concentrations result in development of thyroid hyperplasia and a goitre.

Clinical Features of Hypothyroidism in the Adult Dog

General Metabolic Signs

Most adult dogs with acquired hypothyroidism have clinical signs that result from a generalized decrease in metabolic rate. Clinical signs due to the decreased metabolic rate include mental dullness, lethargy, exercise intolerance or unwillingness to exercise, cold intolerance, and a propensity to gain weight without a corresponding increase in appetite or food intake.

Dermatologic Signs

Alterations in the skin and hair coat occur in 60% to 80% of hypothyroid dogs and are the most commonly observed abnormalities in dogs with hypothyroidism. Thyroid hormone is necessary to initiate and maintain the anagen, or growing, phase of the hair cycle [7]. With thyroid hormone deficiency,

hair follicles prematurely enter the telogen phase of the hair cycle. Excessive shedding with lack of hair regrowth leads to alopecia. Decreased concentrations of cutaneous fatty acids and prostaglandin E2 in canine hypothyroidism may lead to sebaceous gland atrophy, hyperkeratosis, scale formation, seborrhea sicca, and a dry and lusterless hair coat [8]. In the early stages of hypothyroidism, hair loss is often asymmetric and develops over areas of excessive wear or pressure, such as the caudal thighs, ventral thorax, tail base, and tail (i.e., development of a “rat tail;”). As hypothyroidism becomes more severe or chronic, alopecia becomes more symmetric and truncal, eventually developing into the classic cutaneous finding of bilaterally symmetric, nonpruritic truncal alopecia. Hyperpigmentation is common in hypothyroidism, especially in regions of alopecia and areas of wear, such as the axilla and inguinal regions. In severe cases of hypothyroidism, the hygroscopic glycosaminoglycan, hyaluronic acid may accumulate in the dermis, bind water and result in increased thickness and non-pitting edema of the skin, referred to as myxedema, or cutaneous mucinosis [9]. Myxedema predominantly affects the forehead, eyelids, and lips that contribute to the development of the classic “tragic facial expression” described in hypothyroid dogs.

Reproductive Signs

The classic clinical signs and clinicopathologic abnormalities in hypothyroidism are lack of libido, testicular atrophy, and oligospermia or azoospermia so hypothyroidism appears to be a cause of infertility in male dogs. Additional reproductive abnormalities have been reported as weak or silent estrus cycles, prolonged estrual bleeding, and inappropriate galactorrhea and gynecomastia which may develop following a thyroid hormone deficiency-induced increase in TRH secretion, which in turn stimulates prolactin secretion [10].

Ocular Signs

Corneal ulceration, uveitis, lipid effusion into the aqueous humor, secondary glaucoma, lipemia retinalis, retinal detachment, keratoconjunctivitis sicca (KCS), and Horner’s syndrome have been reported in hypothyroid dogs [11].

Gastrointestinal Signs

Clinical signs related to the gastrointestinal system have been described but are not common in hypothyroid dogs. Constipation may occur, presumably as a result of alterations in electrical control activity and smooth muscle contractile responses in the gastrointestinal tract. Diarrhoea has also been reported with hypothyroidism.

Neurologic Signs

Both the peripheral nervous system and CNS may be affected by hypothyroidism. Diffuse peripheral neuropathy characterized by exercise intolerance, weakness, ataxia, quadriparesis or paralysis, deficits of conscious proprioception, and decreased spinal reflexes has been reported to occur in dogs with hypothyroidism.

Other Neurologic Disorders

- 1) **Laryngeal Paralysis and megaesophagus** [12] may both occur in association with hypothyroidism.
- 2) **Myasthenia gravis** Myasthenia gravis has been identified in dogs with hypothyroidism [13] and is a well-recognized cause of acquired megaesophagus in the dog.
- 3) **Myxedema Coma** is an extremely rare syndrome of

severe hypothyroidism characterized by profound weakness, hypothermia, bradycardia, and a diminished level of consciousness, which can rapidly progress to stupor and then coma [14]. Clinical signs in addition to the more typical clinical signs of hypothyroidism include mental dullness, depression, unresponsiveness, and weakness. Physical findings include profound weakness, hypothermia, non-pitting edema of the skin, face and jowls (myxedema), bradycardia, hypotension; and hypoventilation.

Diagnosis and clinico-pathologic abnormalities of Hypothyroidism

(1) Blood tests of thyroid gland function

Serum T4, both protein-bound and free, comes from the thyroid gland. Therefore tests that measure the serum total and fT4 concentrations, in conjunction with the serum TSH concentration, are currently recommended for the assessment of thyroid gland function in dogs suspected of having hypothyroidism. In contrast, most T3 and rT3 is formed through the deiodination of T4 in extrathyroidal sites-most notably the liver, kidney, and muscle. Serum T3 concentration is a poor gauge of thyroid gland function because of its predominant intracellular location and the minimal amount of T3 secreted by the thyroid gland compared with T4. Thus measurement of serum T3, fT3, or rT3 concentration is not routinely recommended for the assessment of thyroid gland function in dogs.

1) Complete Blood Count

A normocytic, normochromic, nonregenerative anaemia is identified in dogs. Decreased erythropoietin, decreased erythroid progenitor response to erythropoietin, and lack of a direct effect of thyroid hormone on early hemopoietic pluripotent stem cells may all contribute to the anaemia. Erythrocyte survival time is not affected by hypothyroidism. These cells are believed to develop from increased erythrocyte membrane cholesterol loading, a direct result of the concomitant hypercholesterolemia associated with thyroid deficiency.

Serum Biochemistry Panel

The classic abnormality seen on a screening biochemistry panel is fasting hypercholesterolemia, which is present in approximately 75% of hypothyroid dogs. Thyroid hormones stimulate virtually all aspects of lipid metabolism, including synthesis, mobilization, and degradation. Both the synthesis and degradation of lipids are depressed in hypothyroidism, with degradation affected more than synthesis. The net effect is an accumulation of plasma lipids in hypothyroidism and the potential for development of atherosclerosis [15].

2) Urinalysis

Results of urinalysis are usually normal in dogs with hypothyroidism. In dogs with lymphocytic thyroiditis, concurrent immune-complex glomerulonephritis may result in proteinuria [16].

3) Conventional Radiography

In congenital hypothyroidism, radiographic abnormalities include delayed epiphyseal ossification, epiphyseal dysgenesis (i.e. irregularly formed, fragmented, or stippled epiphyseal centers), most common in the humeral, femoral,

and proximal tibial condyles; short broad skulls; shortened vertebral bodies; and delayed maturation.

4) Ultrasonography

Ultrasound may also be helpful for confirmation of hypothyroidism. The normal thyroid gland is homogenous and well delineated with a hyperechoic capsule. The parenchyma is hyperechoic to the surrounding muscles, and the size is correlated with the size (body surface area) of the dog [17].

5) Nuclear Imaging

Thyroid scintigraphy is useful for evaluating the size, shape, and location of thyroid tissue. Either technetium-99m pertechnetate ($^{99m}\text{TcO}_4$) or iodine-123 (^{123}I) can be used for scintigraphy in dogs is the most commonly used isotope used for thyroid scintigraphy in veterinary medicine because of its low cost, short half-life, and safety. On scintigraphy, normal canine thyroid lobes appear as two uniformly dense, symmetric ovals in the mid-cervical area, although asymmetrical uptake has been reported in some euthyroid dogs

Baseline Serum Total Thyroxine Concentration

Baseline serum T4 concentrations are lower in healthy dogs than in humans (1.0 to 3.5 versus 4.0 to 10.0 $\mu\text{g/dL}$ respectively) because of weaker protein binding in dogs. The serum T4 concentration in healthy dogs ranges between 1.0 and 3.5 $\mu\text{g/dl}$.

Baseline Serum Total Triiodothyronine Concentration

Serum total T3 concentrations are the sum of the protein-bound and free levels circulating in the blood. Almost all commercial laboratories currently use either RIA or chemiluminescent techniques for measuring T3 concentrations in the blood. Most human RIAs for T3 are suitable for use in the dog, because blood concentrations are similar for both species. Using the RIA technique, an approximate normal range for blood T3 concentrations is 0.8 to 2.1 nmol/L .

Baseline Serum Free Thyroxine Concentration

Although the gold standard technique for measurement of fT4 is equilibrium dialysis, this technique is expensive and time consuming and is only performed in research laboratories. In commercial laboratories, canine serum fT4 is measured by one of three methods: modified equilibrium dialysis (MED), analog RIA, or analogue chemiluminescent assay. MED techniques are regarded as the most accurate commercially-available technique for determining serum fT4 concentrations in dogs. fT4 in dogs ranges from 0.52 to 2.7 ng/dl .

Thyrotropin Stimulation Test

The TSH stimulation test evaluates the thyroid gland responsiveness to exogenous TSH administration and is a test of thyroid gland reserve. The TSH stimulation test is indicated in dogs with low basal thyroid hormone concentrations to differentiate hypothyroidism from nonthyroidal illness syndrome (NTIS). The biologic activity of the TSH molecule is not species-specific so human recombinant TSH can be used for the test.

Thyrotropin-Releasing Hormone Stimulation Test

The TRH stimulation test evaluates the pituitary gland respon-

siveness to TRH and the thyroid gland responsiveness to TSH secreted in response to TRH administration. Dogs with primary hypothyroidism have a lower change in TSH concentration after TRH administration than the healthy dogs [18]. This finding has been attributed to TRH receptor desensitization due to persistent stimulation of the pituitary thyrotrophs by the negative feedback loop [19]. In dogs, the TRH stimulation test has been used to differentiate between hypothyroidism and the NTIS in dogs with low basal thyroid hormone concentrations.

Tests for Lymphocytic Thyroiditis

During the inflammatory phase of lymphocytic thyroiditis, antibodies are released into the circulation. In dogs, the predominant antibody that arises is directed against Tg. Tg is a large complex protein molecule with several epitopes and antibodies formed against it are heterogenous. The thyroid hormones T3 and T4 are haptens and do not elicit an antibody response unless attached to a larger protein molecule [20]. Thus the Tg autoantibody test is a more sensitive test for lymphocytic thyroiditis than is measurement of anti-T3 and anti-T4 antibodies. Circulating Tg autoantibodies are detected in approximately 50% of hypothyroid dogs [2].

Concurrent illness (Nonthyroidal illness Syndrome)

The nonthyroidal illness syndrome (NTIS, Euthyroid Sick Syndrome) refers to suppression of serum thyroid hormone concentrations that occur in euthyroid patients due to concurrent illness.

Decreased serum thyroid hormone concentrations are believed to be a physiologic adaptation that decreases cellular metabolism during illness. Generally, the magnitude of the change in serum thyroid hormone concentrations is not related to the specific disorder but rather reflects the severity of the illness, with more severe systemic illness resulting in more severe suppression of serum thyroid hormone concentrations [21]. Disorders that are frequently associated with NTIS in dogs include neoplasia, renal disease, hepatic disease, cardiac failure, neurologic disease, inflammatory disorders, and diabetic keto-acidosis.

Treatment

The initial treatment of choice is synthetic L-T4 sodium. The same treatment protocol is used for both a therapeutic trial and definitive therapy. Treatment with L-T4 sodium preserves normal regulation of T4 to T3 de-iodination, which allows physiologic regulation of individual tissue T3 concentrations. The recommended initial dose for otherwise healthy hypothyroid dogs is 0.02 mg/kg by mouth every 12 hours. The dose for treatment of hypothyroid dogs is 10 times higher than the dose used in hypothyroid humans because of poorer gastrointestinal absorption and a shorter serum half-life of T4 in dogs compared to humans.

Response to Levothyroxine Sodium Therapy

Thyroid hormone supplementation should be continued for a minimum of 6 to 8 weeks. So that all of the clinical signs and clinic-pathologic abnormalities associated with hypothyroidism should resolve.

- 1) As evident by an increase in mental alertness and activity usually occurs within the first week of treatment this is an important early indicator that the diagnosis of hypothyroidism was correct.
- 2) Some hair regrowth may be observed during the first

month in dogs with endocrine alopecia, it may take several months for complete regrowth and a marked reduction in hyperpigmentation of the skin to occur. Initially, the hair coat may appear to worsen as hairs in the telogen stage of the hair cycle are shed^[7].

- 3) If obesity is caused by hypothyroidism, it should also begin to improve within 2 months after initiating L-T4 sodium therapy along with adjustments in diet and exercise.
- 4) Improvement in myocardial function is usually evident within 1 to 2 months, but it may take as long as 12 months for complete recovery.
- 5) Neurologic deficits improve rapidly after treatment, but complete resolution may take 2 to 3 months^[22].

Conclusion

The thyroid gland is an essential gland in the body, producing a number of hormones, including T3 and T4 both of which are required for normal metabolism in the body. So it is the most frequently diagnosed and one of the most over diagnosed endocrinopathy in dogs. Don't rely on T4 alone to diagnose hypothyroidism. A normal or low TSH does not rule out hypothyroidism. fT4ED testing is an ideal test to help confirm hypothyroidism – Low Total T4 combined with low fT4ED has a diagnostic accuracy > 95% in hypothyroidism. If non-thyroidal illness is involved, postpone additional thyroid diagnostics until NTI is resolved. Replacement therapy with synthetic L-thyroxine is the most appropriate treatment

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