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Popular Article

Hypothyroidism In Dogs: Causes, Pathophysiology, Clinical Signs, Diagnosis and Treatment

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Introduction

Thyroid gland is responsible for active thyroid hormones production, thyroxine (T_4) and triiodothyronine (T_3), under the influence of thyrotropin (TSH) control from the pituitary gland and release of thyrotropin-releasing hormone (TRH) from the hypothalamus. Hypothyroidism may, therefore, arise from a defect in any of these areas. Hypothyroidism is a common endocrinopathy in dogs, caused by a deficiency in the hormone synthesis by thyroid; it is more often observed in medium to large sized pure breeds, occurring preferentially between 3 to 8 years old. Some breeds as Doberman, Golden Retriever, Irish Setter, Airedale Terrier and Beagle seem to be predisposed (Beaver and Haug, 2003; Dixon, 2009).

Causes of Canine Hypothyroidism

Hypothyroidism may result from dysfunction of any part of the hypothalamicpituitary-thyroid axis and may be acquired (most common) or congenital. Most cases of acquired canine hypothyroidism are attributable to primary hypothyroidism and are caused by lymphocytic thyroiditis or idiopathic thyroid atrophy. More rarely, primary hypothyroidism may be caused by bilateral thyroid neoplasia or invasion of the thyroid by metastatic neoplasia. Secondary hypothyroidism (deficiency of thyrotropin) has been rarely described in dogs. Causes of acquired secondary hypothyroidism include pituitary malformations and pituitary neoplasia. Tertiary hypothyroidism (deficiency of thyrotropinreleasing hormone [TRH]) has yet to be documented in

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the dog. Reported causes of congenital primary hypothyroidism include iodine deficiency, thyroid dysgenesis, and dyshormonogenesis (Chastain *et al.*, 1983). Congenital hypothyroidism with goiter attributable to thyroid peroxidase deficiency was reported as an autosomal recessive trait in Toy Fox Terriers. Secondary congenital hypothyroidism attributable to apparent isolated thyrotropin or TRH deficiency was reported in a family of young Giant Schnauzers and in a young Boxer (Fyffe *et al.*, 2003). Congenital secondary hypothyroidism is also a feature of panhypopituitarism. Iatrogenic causes of hypothyroidism include ^{131}I treatment, administration of antithyroid drugs, and surgical thyroidectomy; however, because of the presence of accessory thyroid tissue, permanent hypothyroidism after thyroidectomy is rare. Because most clinical consequences of hypothyroidism result from the effects of decreased production of the thyroid hormones T_4 and triiodothyronine (T_3) on all organs of the body, clinical signs of hypothyroidism are usually similar independent of the underlying cause of thyroid dysfunction. In some forms of hypothyroidism, however, (congenital hypothyroidism, secondary hypothyroidism, and hypothyroidism attributable to thyroid neoplasia), additional clinical signs, such as a goiter, growth retardation, other signs of pituitary dysfunction, or clinical signs caused by the presence of a cervical mass, may be recognized. Although thyroiditis may cause thyroid pain in human beings, this is not frequently recognized in dogs with thyroiditis.

Pathophysiology

Thyroid hormones (T_4 and T_3) are iodine-containing amino acids synthesized in the thyroid gland. All circulating T_4 is derived from the thyroid gland, but only 20% of T_3 is. The remainder of T_3 is derived from extrathyroidal enzymatic 5'-deiodination of T_4 (Scott-Moncrieff, 2007). In the blood, more than 99% of T_4 and T_3 are bound to plasma proteins, with T_4 more highly bound than T_3. Only free hormone enters cells to produce a biologic effect or a negative feedback effect on the pituitary and hypothalamus. T_3 enters cells more rapidly, has a more rapid onset of action, and is three to five times more potent than T_4. Thyroid hormones bind to receptors in the nuclei; the hormone receptor complex then binds to DNA and influences the expression of a variety of genes coding for regulatory enzymes. Thyroid hormones have a wide variety of physiologic effects, which accounts for the profound clinical effects of thyroid hormone deficiency on the body. Thyroid hormones increase the metabolic rate and oxygen consumption of most tissues, with the exception of the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary. Thyroid hormones have positive inotropic and chronotropic effects on the heart. They increase the number and affinity of β-

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adrenergic receptors, enhance the response to catecholamines, and increase the proportion of α-myosin heavy chain. Thyroid hormones have catabolic effects on muscle and adipose tissue, stimulate erythropoiesis, and regulate cholesterol synthesis and degradation. Thyroid hormones are also essential for the normal growth and development of the neurologic and skeletal systems (Graham *et al.,* 2007; Mooney, 2011)

Clinical Signs

Because thyroid hormones influence the function of many organs, hypothyroidism should be considered in the differential diagnosis of a wide range of problems. The most common clinical signs of hypothyroidism are those related to a decrease in the metabolic rate and dermatologic changes. Less common but well-documented clinical manifestations include neurologic abnormalities, effects on the cardiovascular system, effects on the female reproductive system, and the constellation of clinical signs seen in congenital hypothyroidism. Clinical manifestations that have been attributed to hypothyroidism but for which there is still no strong evidence of a causal association include behavioral changes, male infertility, ocular disorders, coagulopathy and gastrointestinal dysfunction (Scott-Moncrieff, 2007).

a. Decreased Metabolic Rate

Because thyroid hormones increase the metabolic rate and oxygen consumption of most tissues, a deficiency of thyroid hormone results in signs of a decreased metabolic rate. Clinical signs attributable to decreased metabolic rate include lethargy, weakness, mental dullness, weight gain or obesity unwillingness to exercise, and cold intolerance (Panciera, 1994)

b. Dermatologic Abnormalities

Thyroid hormones are extremely important in maintenance of normal cutaneous function, and dermatologic abnormalities are reported in 60% to 80% of hypothyroid dogs (Panciera, 1994). Signs of decreased metabolic rate in conjunction with dermatologic abnormalities should increase the clinical suspicion of hypothyroidism; Thyroid hormones are thought to be necessary for initiation of the anagen phase of hair growth; therefore, hypothyroid dogs may have alopecia or failure of hair regrowth after clipping. Alopecia is usually bilaterally symmetric (Fig. 1) and is first evident in areas of wear, such as the lateral trunk, ventral thorax, and tail. The head and extremities tend to be spared. The hair may be brittle and easily epilated, the coat may appear dull or faded in color, and loss of undercoat or primary guard hairs may result in a coarse appearance or a puppy-like hair coat. In some

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breeds, hair retention rather than hair loss may predominate. Breed-related differences in hair cycle and follicular morphology may influence the clinical features of hypothyroidism. Other common findings in hypothyroid dogs include dry scaly skin, seborrhea (sicca or oleosa), and superficial pyoderma. Hyperkeratosis, hyperpigmentation, comedone formation, hypertrichosis, ceruminous otitis, poor wound healing, and increased bruising have also been reported. These changes may be related to decreased protein synthesis, decreased mitotic activity, and decreased oxygen consumption of the skin, which result in epidermal atrophy, sebaceous gland atrophy, and abnormal keratinization. Alterations in cutaneous fatty acid concentrations may also play a role (Campbell and Davis, 1990). Hypothyroidism is believed to predispose to recurrent bacterial infections of the skin, and pyoderma has been reported in 10% to 23% of hypothyroid dogs (Panciera, 1994; Doliger *et al.*, 1995)

Malassezia infections and demodicosis have also been reported in hypothyroid dogs. Pruritus may occur if concurrent infection is present. Myxedema (cutaneous mucinosis) is a rare dermatologic manifestation of hypothyroidism characterized by nonpitting thickening of the skin, especially of the eyelids, cheeks, and forehead. It is caused by deposition of hyaluronic acid in the dermis, which occurs because thyroid hormone deficiency decreases catabolism of glycosaminoglycans (Doliger *et al.*, 1995)

c. Reproductive Abnormalities

Female reproductive abnormalities attributed to hypothyroidism include prolonged interestrous interval, silent estrus, failure to cycle, spontaneous abortion, small or low birth weight litters, uterine inertia, and weak or stillborn puppies; however, the evidence for this association is weak. Inappropriate galactorrhea has been reported in sexually intact hypothyroid bitches. Hyperprolactinemia was documented in one hypothyroid bitch with primary hypothyroidism. Male reproductive problems attributed to hypothyroidism include low libido, testicular atrophy, hypospermia, and azoospermia (Cortese *et al.*, 1997).

d. Neurologic Abnormalities

The most common neurologic manifestations of hypothyroidism relate to the peripheral nervous system, but central nervous system dysfunction has also been reported. The cause of neurologic dysfunction in hypothyroidism is poorly understood. ATP deficiency leading to impaired sodium/potassium (Na/K) pump activity may cause slowing of axonal transport and peripheral nerve dysfunction. In people, a mononeuropathy has been reported because of compression by mucinous

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deposits in and around affected nerves; however, this has yet to be reported in dogs. Central nervous system signs may occur because of atherosclerotic vascular disease, changes in neuronal metabolism, and abnormalities of neuronal excitability attributable to abnormal neurotransmitter release and reuptake. There may also be failure of local thyroid hormone transport within the brain. Peripheral neuropathy is the best documented neurologic manifestation of hypothyroidism (Jaggy *et al*., 1994; Higgins *et al.*, 2003). Older large or giant breed dogs are most commonly affected, and dogs typically present with exercise intolerance, generalized weakness, ataxia, and quadriparesis or paralysis. Most commonly, all four limbs are affected; however, in some dogs, clinical signs progress from the hind limbs to the forelimbs or affect the hind limbs alone.

e. Cardiovascular Abnormalities

Abnormalities of the cardiovascular system, such as sinus bradycardia, weak apex beat, low QRS voltages, and inverted T waves, occur in hypothyroid dogs. Reduced left ventricular pump function has also been documented (Panciera, 1994). Hypothyroidism alone rarely causes clinically significant myocardial failure in dogs; however, dilated cardiomyopathy and hypothyroidism may occur concurrently (Hess *et al*, 2003). Atherosclerosis probably occurs because of hypercholesterolemia and is a rare complication of canine hypothyroidism, but it can potentially lead to other manifestations of cardiovascular disease, such as impaired left ventricular function and atrial fibrillation.

f. Ophthalmologic Abnormalities

Ocular changes reported in canine hypothyroidism include corneal lipidosis, corneal ulceration, keratoconjunctivitis sicca (Fig.2), uveitis, lipid effusion into the aqueous humor, secondary glaucoma, lipemia retinalis, and retinal detachment (Kern and Riis, 1980).

Diagnosis

If the history and clinical signs are suggestive of hypothyroidism, subsequent diagnostic evaluation is necessary. Routine serum biochemistry and haematology profiles are an important part of the diagnostic work-up.

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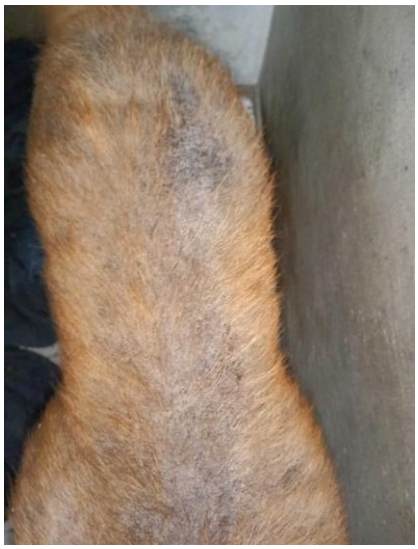

Fig.1: Dog showing bilateral symmetrical alopecia

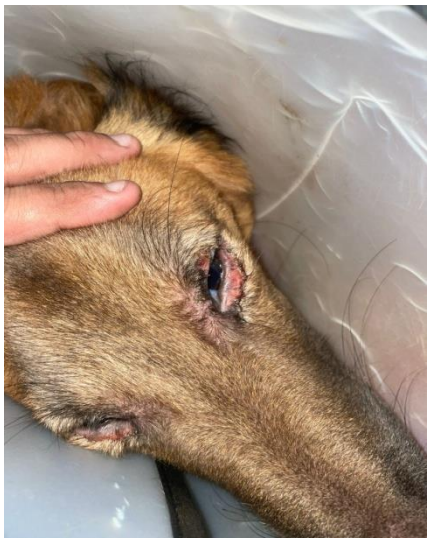

Fig.2: Dog showing keratoconjunctivitis Sicca

Biochemistry

Due to decreased lipid metabolism in affected dogs, the classic serum biochemistry abnormality in hypothyroidism is fasting hypercholesterolaemia, occurring in 75% of cases. The higher the level of cholesterol, the more likely that the diagnosis is hypothyroidism rather than non-thyroidal illness. Hypertriglyceridaemia also occurs in a large number of dogs with hypothyroidism. Other biochemical changes (occur less commonly) like Hypercholesterolaemia, Hypertriglyceridaemia, Hyperlipidaemia, Increased aspartate aminotransferase (AST), Increased alanine aminotransferase (ALT), Increased alkaline phosphatase (ALP), Increased creatine kinase (CK) and Increased fructosamine.

Haematology

Mild normochromic, normocytic, non-regenerative anaemia is the only consistent haematological abnormality, occurring in upto 50% of dogs with hypothyroidism. The reason for this is multifactorial–there is decreased oxygen consumption, which leads to decreased erythropoietin (EPO) production, and reduced tissue responsiveness to EPO leads to reduced red blood cell production. The leucocyte count is typically normal in hypothyroid dogs, unless there is concurrent infection.

Thyroid function tests

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The serum T_4 determination is still the most commonly run test for initial thyroid evaluation. A normal value (1.5-4.3 µ/dl, 20-55 nmol/L) essentially rules out hypothyroidism. A very low T_4 level in conjunction with appropriate clinical signs and the absence of confounding factors is usually sufficient for making the diagnosis of hypothyroidism.

The serum T_3 determination (normal 0.7-2.3 nmol/L, 45-150 ng/dl) is commonly run but it is not as diagnostic as T_4 measurement. It is not uncommon to find normal T_3 concentrations in dogs with hypothyroidism.

The thyroid stimulating hormone (TSH) response test is used to identify hypothyroidism when the T_4 results are questionable. A reduced or no response to TSH is expected in hypothyroidism. It is important to consider that although the test will distinguish many borderline situations, the results are not always clear in dogs with non-thyroid illness or those treated with certain drugs.

However, post TSH T_4 levels greater than 45 nmol/L rule out hypothyroidism while levels less than 15 nmol/L indicate a need for replacement therapy. On the negative side, the commercial availability of TSH is unreliable and it is relatively expensive.

The free T_4 level represents the fraction of total hormone available for target cell entry. It comprises less than 1% of total T_4. The equilibrium dialysis technique is the preferred method with normal values ranging from 12-33 pmol/L (Nachreiner, MSU).

Treatment

Primary hypothyroidism is initially treated with Synthetic thyroxine (levothyroxine Sodium) at a dosage of 22 µg/kg (0.1 mg/10 pounds) every 12 hours. This same dose can be decreased to once daily treatment after the first month. The dose for treatment of hypothyroid dogs is 5-6 times higher than the dose used in hypothyroid humans because of poorer gastrointestinal absorption and a shorter serum half-life of T_4 in dogs compared to humans. Periodic blood level monitoring should be done 4-7 hours post-thyroxine administration, and the treatment should be adjusted accordingly. Improved mentation and activity levels should become apparent over the first 2-7 day period. Skin and neurological improvement should occur after 1-3 months of treatment. Reproductive abnormalities might hopefully improve over a 3-10 month period. Sodium liothyronine (synthetic T_3 Cytomel) is not the initial thyroid hormone supplement of choice. While liothyronine will raise the T_3 level, it will also lower the T_4 level through negative feedback inhibition. Synthetic T_3 therapy is indicated

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when levothyroxine treatment fails to achieve a desired clinical response in a confirmed hypothyroid dog. This can arise if there is impaired thyroxine absorption from the bowel.

Summary

The thyroid gland is an essential gland in the body that produces several hormones, including triiodothyronine (T_3) and thyroxine (T_4), all of which are necessary for normal metabolic functions in the body. While canine hypothyroidism can result from various potential causes, it is typically considered an acquired disease of middle-aged to older dogs, and mostly arises due to irreversible, acquired thyroid gland disease. Few cases are reversible or result from congenital, hypothalamic, pituitary or nutritional conditions. This condition, therefore, represents a diagnostic challenge since it can manifest in a wide range of medical problems, often mimicking other conditions. Don't rely on T_4 alone to diagnose hypothyroidism, a normal or low TSH does not rule out hypothyroidism. FT4ED testing (Free T_4 by Equilibrium Dialysis) is an ideal test to confirm hypothyroidism – Low Total T_4 combined wíth low FT4ED has a diagnostic accuracy > 95% in hypothyroidism.

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