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HYPOTHYROIDISM IN DOGS: A DIAGNOSTIC CHALLENGE

Hypothyroidism is the clinical syndrome resulting from deficient production of thyroid hormones. In about 95% of cases of adult onset it is a primary thyroid disorder and in 5% or less it is due to thyrotropin (TSH) deficiency.

Primary hypothyroidism

Pathogenesis

In the spontaneous form a progressive autoimmune process leads to lymphocytic infiltration and disappearance of thyroid follicles. So-called idiopathic forms, in which there is thyroid atrophy without inflammatory infiltrate, are also thought to be the end result of an autoimmune disorder.[1] The immune-mediated destruction is a slow process and clinical manifestations of thyroid hormone deficiency only become evident after destruction of >75% of the thyroid follicles. Although they may not be of great pathogenetic importance, autoantibodies against thyroglobulin (Tg) may serve as markers of autoimmune thyroiditis.[2] Circulating antibodies against Tg are detected in over 50% of hypothyroid dogs. Antibodies against Tg form a heterogeneous group directed at several epitopes. When an epitope includes a hormonogenic site, an antibody can be directed against a fragment that contains T4 or T3. These Tg antibodies occasionally interfere with immunoassays used to measure the plasma concentrations of thyroid hormones, especially T3. Depending on the type of assay, antibodies recognizing epitopes of a thyroid hormone may cause either falsely elevated or lowered values.

Clinical manifestations

Thyroiditis usually remains unnoticed, although very rarely transient signs of hyperthyroidism (mainly characterized by polyuria) have been observed. This is probably due to release of thyroid hormone into the circulation during an acute phase of destructive thyroiditis. Eventually most dogs with thyroiditis probably develop signs of thyroid hormone deficiency.

Acquired primary hypothyroidism is mainly a condition of young-adult and middle-aged dogs. Although dogs of large breeds may be affected more frequently than those of small breeds, there is no pronounced breed predisposition. The incidence is equally distributed between males and females. [3] Thyroid hormones influence the function of almost all tissues of the body and thus the classical clinical picture of overt hypothyroidism involves manifestations from nearly all organ systems (Table 1). The time required for clinically appreciable effects differs considerably: lethargy may be noticed within a few months but skin changes can take almost a year. [4] Central to the clinical signs is usually a history of slowing of mental and physical activities. Most hypothyroid dogs have some degree of mental dullness, lethargy, and disinclination to exercise. These signs are gradual in onset, often subtle, and sometimes unrecognized by the owner until after treatment has been started. Among the observable changes in the hair and skin are alopecia (often with pigmentation), thick folding of the skin, and a puffy facial appearance. The thickening and puffiness are evidence of cutaneous mucinosis or myxedema, which is accumulation in the dermis of glycosaminoglycans and hyaluronic acid with associated edema. [5] Occasionally, hypothyroidism is associated with secondary skin infections, including Malassezia infections. [6,7]

Table 1 Clinical manifestations of primary hypothyroidism in adult dogs.

System	Common	Less common or rare
Metabolism	Weight gain Appetite unchanged or reduced Cold intolerance	Low body temperature
Skin and Hair	Coat coarse and scanty Nonpruritic truncal alopecia starting over points of wear Mucopolysaccharide thickening of skin (myxedema)	Hyperpigmentation Secondary pyoderma Seborrhea
Cardiovascular	Bradycardia, weak peripheral pulse and apex beat Low voltage ECG	Poor peripheral circulation Cool skin
Reproductive and Endocrine	Persistent anestrus Loss of libido Testicular atrophy	Gynecomastia Galactorrhea Polyglandular deficiency (Schmidt's syndrome)
Neuromuscular	Lethargy and somnolence Stiff gait	Vestibular ataxia Head tilt Facial nerve paralysis Lameness
Gastrointestinal		Diarrhea
Hematological	Nonregenerative anemia	
Biochemical	Hypercholesterolemia Hypertriglyceridemia Mild hyperglycemia	Elevated creatinine kinase Hyponatremia Hyperkalemia

Table 1 lists the clinical manifestations by organ system. Changes in a single organ system sometimes dominate to the extent of obscuring the causative disease. [8] Rarely, a hypothyroid dog is presented as an emergency in a comatose state. Routine laboratory examinations can reveal several hematological and biochemical abnormalities (Table 1). Both the nonregenerative anemia and the hyperglycemia are usually mild.

Differential diagnosis

Because the presenting symptoms of hypothyroidism can vary widely, a common pitfall in diagnosis is simply to overlook the possibility that the presented problems could be due to hypothyroidism. For example, it is not uncommon for dogs with hypothyroidism to be presented for attention to cardiopulmonology (lethargy misinterpreted as exercise intolerance) or orthopedics (locomotor disturbance). Lethargy, the most common sign of hypothyroidism, may be mistaken for metabolic (hepatoencephalopathy) or cerebrocortical disease (encephalitis, hydrocephalus). The atrophy of the skin and its adnexa must take into consideration such conditions as estrogen excess and hypercortisolism.

Diagnosis

As a measure of thyroid function, T4 has to be preferred over T3 because it is produced exclusively by the thyroid gland while T3 in plasma is largely derived by peripheral conversion. In most dogs with primary hypothyroidism, plasma concentrations of total T4 (TT4) and free T4 (fT4) are below the reference range. However, they can also be decreased in dogs without a thyroid disorder because of drugs or illness. The terms nonthyroidal illness and sick euthyroid syndrome have been introduced for this derangement of thyroid homeostasis. Consequently, the finding of a low basal plasma thyroid hormone concentration is of little diagnostic value. [9,10] For this reason stimulation tests using either TSH or TRH have been advocated. The TRH-stimulation test using measurement of plasma TT4 concentration does not distinguish with sufficient accuracy between dogs with hypothyroidism and those with nonthyroidal illness. [11] Until the end of the last century, primary hypothyroidism in dogs was diagnosed by the finding of a low plasma TT4 (and/or fT4) concentration insufficiently responsive to stimulation with bovine TSH (bTSH) [12,13]

It was expected that introduction of a homologous immunoassays for plasma TSH in dogs would greatly aid and simplify assessment of the canine pituitary-thyroid axis by the paired measurement of T4 and TSH. It was hoped that a single blood sample would suffice to confirm the diagnosis of primary hypothyroidism by revealing a low T4 concentration in the presence of a high TSH concentration. However, using the TSH-stimulation test as the gold standard, it was found that in as many as one-third of dogs

with primary hypothyroidism, plasma TSH concentration was not elevated.[14] Frustration with the limitations of the available endogenous canine TSH assay caused most clinicians to resume using the TSH-stimulation test, [15] albeit now usually employing recombinant human (rh)TSH instead of bTSH. [16-18]

In dogs with clinical signs of hypothyroidism, the combination of a low plasma TT4 and a clearly elevated plasma TSH concentration is diagnostic for primary hypothyroidism. When TT4 is low but TSH is within the reference range, a TSH-stimulation test can be performed. Methods not involving biochemical assessment of the pituitary-thyroid axis—such as a radionuclide scan or thyroid uptake measurement with 99mTcO4-, high-resolution ultrasonography, or even a thyroid biopsy—seem to be reliable for diagnosing primary hypothyroidism in dogs.[19,20] In a study of 99mTcO4- uptake in dogs with primary hypothyroidism and nonthyroidal illness, there was no overlap in thyroid uptake at 45-120 minutes after injection.[19] In high-resolution ultrasonography of the thyroid glands, loss of echogenicity, homogeneity, and fusiform shape are particularly characteristic of primary hypothyroidism. [21,22] Demonstration of circulating antibodies to Tg indicates the presence of thyroiditis but provides no information about thyroid function. As indicated in the section on pathogenesis, the absence of antibodies against Tg does not exclude hypothyroidism. In addition, dogs with antibodies against Tg may have thyroiditis that has not yet resulted in hypothyroidism.

Recently it was found that administration of TRH results in an increased plasma growth hormone (GH) concentration in hypothyroid dogs, whereas in dogs with nonthyroidal illness no increase in plasma GH concentration is found. This observation suggests that a TRH stimulation test with measurement of plasma GH concentration may be a value tool to identify dogs with hypothyroidism.

Central hypothyroidism

In central hypothyroidism the thyroids are not affected primarily but are deprived of stimulation by TSH. Histological examination reveals no loss of follicles but rather the characteristics of inactivity. The condition is rare compared with primary thyroid failure. Spontaneous causes include tumor of the pituitary or adjacent regions and head trauma. [23] The clinical picture is similar to that of primary hypothyroidism, although generally less pronounced. There may be lethargy and alopecia, but thickening of the skin is less pronounced. Not uncommonly, the lesion causing reduced TSH secretion is a hormone-secreting tumor, such as a corticotroph adenoma that is hypersecreting ACTH. The symptoms and signs arising from such a pituitary tumor may precede, accompany, and even obscure the manifestations of pituitary failure. In the presence of an ACTH-secreting tumor, central hypothyroidism may only become manifest after reversal of the associated hypercortisolism. The diagnosis of central hypothyroidism should be based on the demonstration of low concentrations of T4 and TSH in plasma. In secondary hypothyroidism, plasma T4 concentration increases in a TSH-stimulation test, although repeated stimulation may be necessary. A prerequisite for correct interpretation of these tests is the certainty that the low T4 (and TSH) concentrations are not caused by illness or drugs. In addition, diagnostic assessment should include [(1)] the secretion of other pituitary hormone and [(2)] the morphology of the pituitary and adjacent areas by diagnostic imaging.

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