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Primary Hypothyroidism in Dogs: **A Diagnostic Challenge**

Introduction

- Hypothyroidism, one of the most common endocrinopathies in dogs, is the clinical syndrome resulting from deficient production of thyroid hormones.
- In about 95% of cases hypothyroidism is a primary disorder of the thyroid gland and in about 5% or less it is due to thyrotropin (TSH) deficiency (i.e. central hypothyroidism).
- Spontaneous primary hypothyroidism is usually caused by a progressive autoimmune process leading to lymphocytic infiltration and disappearance of thyroid follicles. The idiopathic form, characterized by thyroid atrophy without inflammatory infiltrate, is also thought to be the end-result of an autoimmune disorder.
- Acquired primary hypothyroidism is mainly a condition of young-adult and middle-aged dogs. Dogs of large breeds are affected more than those of small breeds. Boxer dogs, Alaskan malamutes, Dobermann pinschers, Nova Scotia Duck Tolling Retriever and certain terrier breeds seem to be predisposed. The incidence is equally distributed between males and females.
- Thyroid hormones influence the function of all tissues of the body and thus the classical clinical picture of overt hypothyroidism involves manifestations from nearly all organ systems. 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.
- Gain of body weight despite unchanged or reduced appetite, cold intolerance and low body temperature are commonly seen in hypothyroid dogs.
- Among the observable changes in the hair and skin are alopecia (often with pigmentation), thick folding of the skin, and a puffy facial appearance. Occasionally, hypothyroidism is associated with secondary skin infections, including Malassezia infection.
- Cardiovascular changes may include bradycardia, weak peripheral pulse and apex beat.
- Persistent anoestrus, anovulatory oestrous cycle and loss of libido and testicular atrophy may be signs of the reproductive system.
- Neuromuscular signs may include lethargy, a stiff gait, lameness, vestibular ataxia, head tilt, and facial nerve paralysis.
- Routine laboratory examinations can reveal several hematological and biochemical abnormalities, such as (non-regenerative) anemia, hypercholesterolemia, hypertriglyceridemia, (mild) hyperglycemia, (mildly) elevated kidney values, elevated creatinine kinase, hyponatremia and hyperkalaemia. Possible consequences of severe hyperlipidemia include neurological signs due to atherosclerosis and thromboembolic events.

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Endocrine diagnosis

- The first step in a dog with clinical signs and clinicopathological findings consistent with hypothyroidism is determination of the basal plasma concentrations of both thyroid hormone and TSH.
- As a measure of thyroid function, thyroxine (T_4) has to be preferred over thyronine (T_3), because T_4 is produced exclusively by the thyroid gland, while T_3 in plasma is largely derived from peripheral conversion of T_4 in T_3.
- In most dogs with hypothyroidism, circulating concentrations of total T_4 (TT_4) and free T_4 (fT_4) are markedly below their respective reference ranges. The circulating fT_4 concentration is more specific than the plasma TT_4 concentration but less sensitive. Moreover, several canine free T_4 assays are not reliable; equilibrium dialysis is the preferred method to determine the free T_4 concentration.
- An important reason why diagnosing canine hypothyroidism is challenging is that the plasma TT_4 concentration can also be decreased in dogs without a thyroid disorder because of drugs or illness (i.e. non-thyroidal illness (NTI)). Consequently, the finding of a low basal plasma thyroid hormone concentration is of little diagnostic value. A basal plasma thyroid hormone concentration within the reference range makes hypothyroidism unlikely.
- A low plasma TT_4 concentration combined with a high plasma TSH concentration, in a dog with clinical signs of hypothyroidism, is compatible with primary hypothyroidism. Dogs with untreated hypoadrenocorticism may also have an elevated plasma TSH concentration.
- About 30% of hypothyroid dogs have a plasma TSH concentration within the reference range. Consequently, a low plasma TT_4 concentration in combination with a plasma TSH concentration within the reference range does not distinguish between hypothyroidism and NTI. To overcome this problem, other tests for diagnosing hypothyroidism are required.
- A low plasma TT_4 (or fT_4) concentration insufficiently responsive to stimulation with (recombinant human) TSH, in a dog with clinical signs of hypothyroidism, confirms hypothyroidism, but the high costs of the TSH formulation prevent it from being a realistic diagnostic option in veterinary practice and this test is carried out almost exclusively in reference centers.
- Euthyroid dogs regularly don't show a significant rise in the plasma TT_4 concentration after TRH administration. Consequently, the TRH stimulation test with measurement of TT_4 has been discarded as diagnostic test for canine hypothyroidism.
- Autoantibodies against thyroglobulin (TgAA) may serve as markers of autoimmune thyroiditis. However, circulating antibodies against Tg are detected in over 50% of dogs with primary hypothyroidism, i.e. certainly not in all hypothyroid dogs. Moreover, detection of Tg autoantibodies does not prove that the dog has or will develop hypothyroidism.
- Autoantibodies against Tg can be directed against a fragment that contains T_4 or T_3. These Tg antibodies occasionally interfere with immunoassays used to measure the plasma concentrations of thyroid hormones. Depending on the type of assay, antibodies recognizing epitopes of a thyroid hormone (T_4AA) may cause either falsely elevated or lowered values.

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- Scintigraphy, using radioactive pertechnetate ($^{99}TcO_4^-$), is an excellent method for diagnosing canine hypothyroidism. Unfortunately, this diagnostic option is only available in a few referral centers, since specialist equipment and radiation-isolation facilities are needed.

- High-resolution ultrasonography of the thyroid glands may reveal loss of echogenicity, homogeneity and fusiform shape. However, there is considerable overlap between hypothyroid dogs and dogs with NTI.

- Histologic examination of thyroid tissue is regarded as the definitive test to identify thyroid disease, but taking thyroid biopsies is invasive and the presence of a lesion does not necessarily prove the existence of a functional abnormality.

- The frustration associated with inconclusive test results and the unavailability of additional tests for veterinary practitioners in a dog with clinical signs and clinicopathological findings consistent with hypothyroidism, a very low TT_4 (and fT_4), and a TSH within the reference range, may be a reason to perform “a therapeutic trial” with l-thyroxine and evaluate the therapeutic response after 1-2 months. The majority of these dogs, however, will be dogs with NTI, and owners of these dogs may report a clinical improvement after l-thyroxine administration has started. This may be a placebo effect, but it may also be due to aspecific stimulation of mental and physical activities. Moreover, it may be that the underlying cause of the low plasma T_4 concentration has resolved spontaneously. The end result may be that dogs that do not have hypothyroidism are unnecessarily treated with l-thyroxine (often lifelong).

- This indicates the need for better diagnostic tests that can be applied easily in veterinary practice. The TRH stimulation test with measurement of the plasma concentrations of growth hormone (GH) or TSH may have the potential to distinguish between hypothyroidism and NTI.

- In healthy dogs TRH administration does not result in changes in the plasma GH concentration, whereas in hypothyroid dogs TRH administration induces an increase in plasma GH concentrations. This indicates the potential of the TRH stimulation test with measurement of the plasma GH concentrations to differentiate between hypothyroid dogs and dogs with NTI.

- A more feasible application in clinical practice is the TRH stimulation test with measurement of plasma TSH concentrations. TRH administration usually results in a significant increase in the plasma TSH concentration in dogs with NTI. However, a significant TRH-induced increase in plasma TSH concentration is usually absent in hypothyroid dogs.

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Treatment and prognosis

- Although T_3 is the metabolically active thyroid hormone, it is not the supplement of choice. A primary advantage of providing the "prohormone" T_4 is that the body is given the opportunity to regulate the amount of T_3 generated by normal physiologic mechanisms.

- Oral supplementation with l-thyroxine (liquid or tablets) is started at a dose rate of about 20 µg/kg daily (refer to the datasheet of the product you are prescribing for specific dosing regimen). Plasma T_4 concentration increases following oral administration, with a peak from 3-6 hours after administration, and then declines until the following dose is given. A follow-up examination is made after 6-8 weeks. In adequately dosed dogs, peak plasma concentration of T_4 should be around the upper limit of the reference range for the type of dog. Plasma TSH concentration should not be elevated. Because of the individual variation in intestinal absorption of T_4, further follow-up examinations and adjustments may be needed.

- Canine hypothyroidism is one of the most gratifying diseases to treat, because of the ease and completeness with which it responds to treatment. With appropriate treatment and follow-up examinations every half year, usually all of the alterations associated with hypothyroidism are reversible. The long-term prognosis is excellent.

- The most common reason for a poor or absent response to l-thyroxine therapy is an incorrect diagnosis, i.e. absence of hypothyroidism.

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