Review Article

Recent Advances in Diagnostic Procedure for Endocrine Disorders in Dogs and Cats

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Abstract

There are 5 most common endocrine disorders affecting dogs and cats of different age groups. The organs affected are adrenals, thyroid and endocrine pancreas. The disease state of these organs is generally brought about by very similar pathomechanism leading to hormone overproduction or underproduction. Pituitary induced bilateral adrenocortical hyperplasia also known as pituitary dependent Cushing's disease (PDH) accounts for 85% of all cases in dogs. There are two important hormone assay tests that can be done for the diagnosis and confirmation of Cushing's syndrome viz. ACTH stimulation test and Low-dose dexamethasone suppression test (LDDST). ACTH stimulation test sensitivity is 85-95% for PDH but 60% for ADH. Majority of HAC cases are PDH. However, sensitivity for LDDST test is about 85-100% for ADH but lower in PDH. ACTH-stimulation test is the only diagnostic and is very reliable test for hypoadrenocorticism (Adisson's disease). Hyperthyroidism is the most common feline endocrinopathy, affecting around 10% of older cats. Feline hyperthyroidism is usually easily diagnosed by the demonstration of elevated total thyroxine (tT4) or free thyroxine (fT4) concentration. Primary hypothyroidism occurs commonly in dogs and is usually associated with thyroid atrophy or lymphocytic thyroiditis. Serum concentration of fT4 is the most sensitive and specific single test for diagnosis of hypothyroidism. The combination of TT4 and canine specific c-TSH data also allow a more reliable evaluation of a dog's thyroid status. Diabetes mellitus is now considered as one of the most common endocrinological disorders in dogs with estimated prevalence between 0.3-1.3 percent of the canine population. The most common form of DM in dogs is type 1 and it has been demonstrated that the majority of diabetic cats (80 to 90%) suffer from diabetes mellitus (DM), similar to type II in humans. The use of glycosylated haemoglobin (HbA1c) levels for the assessment of long term control of DM can be used in dogs and cats but warrant further validation.

Key words: Hyperadrenocortcism (HAC), Pituitary Dependent HAC (PDH), Adrenal Dependent HAC (ADH), Hypoadrenocorticism, Hyperthyroidism, Hypothyroidism, Diabetes Mellitus (DM), HbA1c.

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Introduction

The purpose of this article is to provide the veterinary physicians with the broader view of a recent diagnostic procedure in the most commonly encounter endocrine disorders in dogs and cats. There are 5 most common endocrine disorders affecting dogs and cats of different age groups. The organs affected are adrenals, thyroid and endocrine pancreas. Most of the overproduction endocrine diseases are due to neoplasia, most commonly functional adenomas. The presentation of this disorder is one of a chronic slowly progressing disease associated with specific breed and gender in older patients. Hormone underproduction tends to be caused by immune associated process striking much younger patients. There is stronger genetic link with family, breed, gender and species predisposition. The presentation of underproduction disorder is middle-aged to older patients, with a reasonably rapid onset, progressive disease that has strong breed and gender associations having a few other "striking" abnormalities on routine laboratory profiles. Again, such clusters, when associated with a few "classical" clinical signs, greatly facilitate the choice and interpretation of diagnostic tests.

Hyperadrenocorticism (HAC) or Cushing's syndrome

Pituitary induced bilateral adrenocortical hyperplasia also known as pituitary dependent Cushing's disease (PDH) accounts for 85% of all cases in dogs. It may be due to ACTH secreting adenomas or over secretion of corticotrophin releasing factor (CRF) by the hypothalamus. Adrenal tumors consist of either functional adenomas or adrenocarcinomas of adrenal cortex. This comprises 15% cases of all cases of Cushing syndrome in dogs. Endogenous Cushing's disease is commonly reported in Poodles, Dachshunds and Terriers. The average reported age is 8 years, but can range 3-12 years. There is no particular sex predilection. About 85% of HACs are due to benign functional adenoma of the pituitary and neoplasia of one of the adrenal glands. Half of those are adenocarcinomas. Approximately 85% of cases are pituitary dependent HAC and 15% of cases are adrenal dependent HAC. PDH is predominant in small breed dogs but their prevalence is much lower. ADH is more prevalent in larger dog breeds weighing more than 20kg. The disease, though recognized in the cat, is rare but often concurrent with diabetes mellitus.

Clinical Signs

It is slowly, progressively developing disorder. Major signalment includes, bilateral alopecia, pigmentation of skin, poor hair re-growth, Polyuria and Polydipsia, urinary "incontinence" in a "house-trained" pet. Appetite is usually good and even "very good". Cats are generally polyphagic with weight loss. A dog shows lethargy and disinclination to exercise. Loss of muscle mass, "Obesity" with "pot-bellied" pendulous abdomen Nervous signs like circling, ataxia, blindness etc. in 8-13% dogs with PDH. Cushing's disease is also associated with hypercoagulable state in both dogs and human.

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General Biochemistry and Haematology Profile

Serum of the affected animals is often "lipemic". There will be hypercholesterolemia and/or hypertriglyceridemia. The serum non-specific enzymes *viz.* ALT and ALP activity will increase. This elevated activity is generally seen in dogs and not in cats. Urinary tract infections are very common in this condition with urine specific gravity 1.007 to 1.013. As regards to haematology polycythemia, lymphopenia, eosinopenia with and/or mild/moderate thrombocytosis is reported in some cases. Sporadic marginal/mild hyperglycaemia and mild glycosuria may be observed in some cats.

Specific Hormone Assays

Hormone assay can be done if clinical signs along with biochemistry and haematology reports as mentioned in A and B above are consistent. There are two important hormone assay tests can be done for the diagnosis and confirmation of Cushing's syndrome (Edward, 2009; Carmel, 2008)

ACTH Stimulation Test

To conduct this test first collect basal plasma cortisol sample and then inject corticotropin (5 µg/kg) i.v. or i.m. route. After an hour later, take second (post stimulation) sample. Sensitivity 85-95% for PDH but 60% for ADH. Majority of HAC cases are PDH (Hans, 2010).

Interpretation of the ACTH Stimulation Test

Typical pituitary induced Cushing's dog will hyper secrete cortisol to the level in excess of 170 microgram/dl following ACTH injection. A very low to minimal response may be due to prior glucocoticoids treatments or the presence of an adrenal tumour.

Low-Dose Dexamethasone Suppression Test (LDDST)

Inject 0.01mg/kg dexamethasone phosphate i.m. or i.v and collect blood sample 8 hours later for cortisol estimation. In the normal dog dexamethasone will suppress pituitary ACTH secretion by negative feedback inhibition and thereby suppress adrenocortical cortisol secretion. The test is 90- 95% reliable for diagnosis of endogenous hypercorticism. Sensitivity for this test is about 85-100% for ADH, but lower in PDH (up to 40% false negatives). Suppressed cortisol levels to <1µg /dl rule out endogenous Cushing's syndrome. No suppression indicates Cushing's, but doesn't differentiate adrenal tumour from pituitary induced adrenal hyperplasia.

Urine Cortisol/Creatinine Ratio (UC/C ratio)

To calculate the ratio Urine cortisol is measured by radioimmunoassay (RIA) and urine creatinine measured by Jaffe's reaction. These values are expressed in µmol/L and all ratio values expressed as 10^{-6}. Test results

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more than $10x10^{-6}$ suggest Cushing's syndrome and test results less than $10x10^{-6}$ rules out Cushing's syndrome. But the ratio will be high in virtually all dogs with polyuria and polydipsia and most dogs with other non-adrenal diseases. So, if we select our cases on the basis of classical clinical signs then this test become redundant.

Single Basal Cortisol Assay

It estimation is generally not recommended. This is time consuming, not specific and relatively expensive as cortisol is produced/ released by the adrenal in a pulsed manner and thus, the basal level varies enormously.

Hypoadrenocorticism (Addison 's disease)

This condition is rare as compared with Hyperadrenocorticism. Generally a disease of younger to middle-aged dogs (3-8 years) but can occur in older dogs. Females outnumber males strikingly (2:1).

Clinical Signs

The disease, though recognized in the cat, is relatively uncommon. The onset of the disease is relatively rapid and progressively developing, Dogs may show anorexia, vomiting, diarrhea, weakness, depression, exercises intolerance. Stressful event may precipitate signs. Often "Addison's Crisis" such as severe weakness, bradycardia, arrhythmia and shock is reported.

General Biochemistry and Haematology Profile

Common biochemical changes observed during Addison's crisis are hyperkalemia, hyponatremia, hypercalcemia, hypoglycemia along with mild/moderate azotemia. Lymphocytosis along with eosinophilia also reported in majority of the cases.

Specific Hormone Assays

Hormone assay can be done if clinical signs along with biochemistry and haematologyreports as mentioned in A and B above are consistent. ACTH-stimulation test which is discussed in Cushing syndrome above is the only diagnostic test and is very reliable.

Hyperthyroidism (The Most Common Endocrinopathy of Cats)

Hyperthyroidism is the most common feline endocrinopathy, affecting around 10% of older cats. It is generally caused by benign changes (adenomatous hyperplasia or follicular cell adenoma) to one (30%) or both (70%) thyroid glands, although a small percentage (1-3%) of affected cats are diagnosed with a malignant thyroid carcinoma (Elsa Edery, 2017). Feline hyperthyroidism also called "thyrotoxicosis" is a well-defined common clinical syndrome generally seen in older cats. Hyperthyroidism in cats caused by

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nodular hyperplasia or adenoma is clinically and histologically similar to toxic nodular goiter in humans. Subclinical hyperthyroidism in humans expresses low TSH in conjugation with within reference range thyroid hormones concentrations. Euthyroid old cats as defined by total thyroxine with low TSH are likely to have histological evidence of nodular thyroid disease and such cats could be consider sub clinically hyperthyroid (Jenifer *et al.,* 2007). In most cases, enlargement of thyroid glands is caused by a non-cancerous tumor called an adenoma. Some rare cases of hyperthyroid disease are caused by malignant tumors known as thyroid adenocarcinomas (Shiel & Mooney, 2007; Peterson & Ward, 2007).

Presentation and Clinical Signs

It is almost exclusively a disease of old and geriatric cats (above 8yr). Females seem to outnumber males. Gradual onset and progressive development of the condition. Major clinical signs include weight loss despite good appetite, hyperactive, hyper-excitable, tachycardia, hypertension, polyuria/polydipsia are prominent. In some cases enlargement or nodules of one or both thyroids (normal feline thyroids difficult to find) are noticed. Vomiting and diarrhoea is not uncommon.

General Biochemistry/Haematological Profile

Increased in serum enzyme *viz.* ALT and/or ALP is seen. Polycythemia, leukocytosis and thrombocytosis variably present in affected cats. Azotemia is common, but usually not severe.

Specific Hormone Tests

Feline hyperthyroidism is usually easily diagnosed by the demonstration of elevated total thyroxine (tT4) or free thyroxine (fT4) concentration. (Peterson *et al*., 2001). Total thyroxine (TT4) is the most reliable (91% sensitivity). Free T4 by Chemiluminescence (CLA) not better than TT4. Total triiodothyronine (TT3) sensitivity approximately 70% (not worth using). TSH concentration are not routinely used for the diagnosis of hyperthyroidism in cats due to lack of commercial available specific assay, But TSH concentration can be measured using Chemiluminicent (CLA) Canine TSH assay. This assay has been validated for use in cats (Wakeling *et al.,* 2008).

Interpretation of Hormone Assays

TT4 in range 40-60nmol/L would need very convincing clinical signs.TT4 > 60 nmol/L usually diagnostic, but clinical signs should be reasonably consistent. Euthyroid (as defined by TT4) senior cats with low TSH are likely to have histological evidence of nodular thyroid disease and such cats could be considered to be subclinically hyperthyroid (Jenifer *et al.,* 2007).

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Hypothyroidism (The Most Common Endocrinopathy of Dogs)

Primary hypothyroidism occurs commonly in dogs and is usually associated with thyroid atrophy or lymphocytic thyroiditis. Autoimmune thyroiditis is an immune mediated disease that results in gradual destructions of thyroid gland leading to hypothyroidism (Grahum *et al.,* 2007). In over 90% of dogs it is due to primary atrophy of the glands, either focal or more of the follicle (Benjamin *et al.*, 1996). In 95 % cases there will be Immune destruction (lymphocytic and idiopathic) of the thyroid glands. Other forms are rare. Middle-aged to older dogs (4-10 year) are generally affected. A large range of breeds are affected. Mainly relatively large breeds Labradors, Spaniels, Poodles, Dobermans, Daschies, Rotties. Rare in small and "toy" breeds.

Presentation and Clinical Signs

Very few clinical signs until >75% of gland destroyed. There after the condition is rapidly progressive. Lethargy, mental dullness, exercise intolerance, cold intolerance, weight gain. Dermatologic abnormalities are noted in more than 70% of affected dogs. Skin/hair coat abnormalities, dry coat, seborrhea, hyperpigmentation, pyoderma, alopecia especially bilaterally symmetrical and involving areas of friction with classical "rat tail" condition. Small proportion develops dermal myxoedema (tragic face) and even cardiac and CNS myxoedema (accumulation of intracellular mucin leading to non-pitting edema) leading to tragic facial look. Some cases inverted T-waves and bradycardia, weak pulse and reduced myocardial contractibility also reported (Panciera, 1994; Scott-Moncrief, 2007).

General Biochemistry/Haematological Profile

Lipaemia and hypercholesterolemia and/or hypertriglyceridemia are very consistent (80% sensitivity). Mild normocytic, normochromic anaemia is reported. Sometimes increased serum ALP and/or CK activity is observed in some cases.

Specific Hormone Tests

Thyroid Function Test

Measurement of serum total thyroxine (TT4) when clinical signs absent is not recommended because of limited specificity of the test. Many factors such as age, breed, body condition, reproductive stage exercise, non-thyroidal illness and drugs can affect the thyroid hormones concentration. Thyroid function test must be therefore interpreted in the light of clinical findings. T4 concentration is the hormone most frequently used for initial testing of thyroid function because it is widely available, relative inexpensive and results can be obtained quickly. It has high sensitivity (89-98 %) but the specificity is low. Serum concentration of fT4 is the most sensitive and specific single test for diagnosis of hypothyroidism. However, it is more costly, less available and to be done by equilibrium dialysis method (David Panaera, 2017). But T3 and T4

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assay can also be done by Chemilluminicence assay (CLA) and Radioimmunoassy and it is as reliable as other methods of analysis. Canine-specific thyroid stimulating hormone (c-TSH) is a useful adjunct to TT4 to improve specificity.

Interpretation of Hormone Assays

Because non-thyroidal inflammatory diseases causes low TT4 by suppressing production, low serum TT4 is poorly specific for hypothyroidism. The combination of TT4 and canine specific c-TSH data allow a more reliable evaluation of a dog's thyroid status, as in the table, below, based on a few small studies (Ferguson, 2007).

TTT4 nmole/L l/L	TSH ng/ml	Classification
> 24.0	Immaterial	Not hypothyroid
12 to 24	= or <0.5	Euthyroid
12 to 24	>0.5	Suspected Hypothyroid
<12	>0.5	Hypothyroid

Diabetes mellitus (DM)

Diabetes mellitus is now considered as one of the most common endocrinological disorders in dogs with estimated prevalence between 0.3-1.3% of the canine population (Sara & Federico, 2017). Most of the dogs with DM diagnosed between the ages of 5-15 yrs with peak prevalence between 7-9yrs. In canines DM generally due to destruction of pancreatic β-cells by an autoimmune mediated mechanism but has multifactorial pathogenesis. The most common form of DM in dogs is type 1 and its onset is middle aged and older animals. Administration of diabetogenic drugs such as corticosteroids induces insulin resistance and promotes gluconeogenesis can be predispose to the development of DM. It has been demonstrated that the majority of diabetic cats (80 to 90%) suffer from diabetes mellitus (DM), similar to type II in humans. The clinical characteristics of diabetes mellitus type II are presented in obese, adult cats (Rios L& Ward C 2008). This diabetes is often transient or reversible. Obesity is a determinant factor in the pathophysiology of diabetes mellitus type II.

Clinical Signs

Polyuria and polydipsia, recurring urinary tract infections, polyphagia with weight loss, cataracts in dogs, plantigrade stance in cats are common clinical signs exhibited by both the animals. The icterus observed (possibly due to hepatic lipidosis) in some cats. Dogs presented with sudden onset of visual impairment due to development of diabetic cataract due to accumulation of sorbitol within the lens which draws water. Cats and dogs with diabetic ketoacidosis may show elevated blood glucose concentrations, azotemia and decreased total CO_2 secondary to metabolic acidosis, osmotic diuresis, dehydration, and, in the case of profound hyperosmolarity and coma (Behrend *et al.,* 2018).

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Diagnostic Laboratory Findings

There are no useful hormone tests for the diagnosis of Diabetes mellitus for the general practitioner. A single, one-off hyperglycaemia finding is very sensitive for Diabetes mellitus but very poorly specific. DM is characterized by persistent fasting blood sugar more than 140mg/dl. Concurrent marked/severe glycosuria leads to strong suspicion. Establishing the presence of ketonuria is important in managing the patient. In cats the glycosuria may have to be assessed at home and cases with repeated hyperglycaemia and glycosuria that do not have convincing clinical signs need serum fructosamine (reflects 2-3 week glycemia status in dogs and 1-2 week status in cats). Monitoring dogs on treatment by blood and urine glucose works quite well. Monitoring cats often requires additional serum fructosamine assay due to non-diabetic glycemia. Lipaemia and associated hypercholesterolemia and hypertriglyceridemia are common findings. Increased serum enzymes ALP and ALT are reported in dogs. Surprisingly "high" urine SG due to glucose content is also observed.

HbA1c in Dogs

Diabetes mellitus is common endocrinopathy in pet animals. The available insulin and technical ease of therapy provide the means of increasing the life expectancy of the affected animals. However frequent evaluation of glucose status is required and such testing involves many hurdles to the client and interpretative problem for the physician. A reliable means for monitoring long term control of glucose is to be sought. The method would eliminate confounding factors such as age, sex, diet, exercise, patient excitability etc. The measurement of glycosylated haemoglobin (HbA1c) levels in humans is used to indicate the degree of long term diabetic control. Using an available methods for humans values could be obtain for diabetic dogs. But the normal ranged established in dogs are broad and overlap considerably. So the test is not found to be value for dogs and cats **(**Delack and Stogdale, 1993). The use of glycosylated hemoglobin levels for the assessment of long term control of DM in dogs and cats warrant further validation (Yu and Hui, 2009).

Conclusion

There are 5 most common endocrine disorders affecting dogs and cats of different age groups. Pituitary induced bilateral adrenocortical hyperplasia also known as pituitary dependent Cushing's disease (PDH) accounts for 85% of all Cushing cases in dogs. LDDST is 90- 95% reliable for diagnosis of endogenous hypercorticism. Sensitivity for this test is about 85-100% for ADH, but lower in PDH. Addison's disease is rare as compared with Hyperadrenocorticism. Hyperthyroidism is the most common feline endocrinopathy and is generally caused by benign changes in thyroid glands. Total thyroxine (TT4) is the most reliable (91% sensitivity) test for diagnosis of hyperthyroidism in cats.

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Primary hypothyroidism occurs commonly in dogs and is usually associated with thyroid atrophy or lymphocytic thyroiditis. Serum concentration of fT4 is the most sensitive and specific single test for diagnosis of hypothyroidism. In canines DM generally due to destruction of pancreatic β-cells by an autoimmune mediated mechanism. The most common form of DM in dogs is type 1 and it is type II in cats as in human. The use of HbA1c levels for the assessment of long term control of DM in dogs and cats warrant further validation.

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