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Feline hyperadrenocorticism — where are we now?

M Hoenig

Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia, Athens, GA 30602, USA

The first case of a cat with hyperadrenocorticism was descibed 26 years ago (Elliott et al 2000). Fewer than 100 cases have been reported worldwide since that time making hyperadrenocorticism in the cat a rare endocrine disorder. Because of the infrequent occurrence of this disease, a systematic approach to diagnosis and treatment has been difficult.

Etiology

Similarly to the dog, most cases of hyperadrenocorticism in the cat are caused by the excessive secretion of adrenocorticotropic hormone (ACTH) from the pars intermedia or pars distalis of the pituitary gland which stimulates the adrenal glands to secrete an excessive amount of cortisol (pituitary-dependent hyperadrenocorticism; PDH) (Duesberg et al 1995, Duesberg & Peterson 1997, Meij et al 2001, Zerbe et al 1987). About 20% to 25% of cats have adrenocortical tumours (AT) which secrete excessive amounts of cortisol in an autonomous fashion (Duesberg et al 1995, Duesberg & Peterson 1997, Meijer et al 1978). The cats that have been described with hyperadrenocorticism were mostly middle-aged and older cats (Duesberg et al 1995). While a female sex predilection has been documented by some (Duesberg & Peterson 1997), this has not been seen uniformly (Duesberg et al 1995, Goossens et al 1995, Meijer et al 1978, Stewart 1994). There is no breed predilection.

Clinical signs

The most frequently observed clinical signs are polyuria, polydipsia, and polyphagia which develop in over 75% of cases (Duesberg et al 1995, Duesberg & Peterson 1997, Goossens et al 1995, Meyers & Bruyette 1994, Nelson et al 1988, Watson & Herrtage 1998). These signs are also consistent with diabetes mellitus which is seen in over 80% of cases. In fact, diabetes is often the reason why owners present their pets, and it is not until insulin resistance is detected by the veterinarian that diagnostic tests for hyperadrenocorticism are performed. Polyuria, polydipsia and polyphagia can, however, also occur without or prior to progression to overt diabetes mellitus (Watson & Herrtage 1998). It should also be noted that not all diabetic Cushingoid cats are insulin-resistant. Other frequently recognised clinical signs include skin problems especially thin and fragile skin, hair loss, pyoderma, and susceptibility to bruising (Duesberg & Peterson 1997, Myers & Bruyette 1994, Schwedes & Mitotane 1997, Stewart 1994, White et al 1987). Obesity and pot-bellied appearance, infections, muscle wasting and hepatomegaly have also been documented (Duesberg & Peterson 1997, Myers & Bruyette 1994). Interestingly, Cushingoid cats have not been reported to develop calcinosis cutis.

Diagnostic tests

Routine laboratory examination may not be very specific for the disease (Duesberg & Peterson

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1997). For example: stress leukograms are seen inconsistently in Cushingoid cats. Cats also are not believed to have the cortisol-inducible isoform of alkaline phosphatase. Both of these findings are helpful, although nonspecific markers of hyperadrenocorticism in the dog. Most routine clinicopathological changes might therefore be merely an indicator of concurrent diabetes mellitus. It is therefore important to perform other tests.

Imaging techniques

Radiography of the abdomen may reveal large adrenocortical neoplasms (AT), but hyperplastic adrenal glands (PDH) are usually too small to be detectable (Widmer & Guptill 1995). The most common finding on abdominal radiography is hepatomegaly (Duesberg et al 1995, Meijer et al 1978, Moore et al 2000, Myers & Bruyette 1994, Nelson et al 1988, Schwedes 1997, Widmeer & Guptill 1995). Calcification of the adrenal gland can be seen in normal cats and is not diagnostic for an adrenal tumour.

Ultrasonography has been shown to be a good method to examine the size and shape of the adrenal glands when performed by an experienced evaluator (Widmer & Guptill 1995). With PDH both adrenal glands may be large and more hypoechoic than normal glands. If nodular hyperplasia is present, they may even be lumpy and irregular. A unilaterally enlarged and irregular adrenal gland indicates the presence of an adrenal tumour, especially if the contralateral gland is atrophied. Bilateral tumours are extremely rare.

Computed tomography and magnetic resonance imaging can be used to identify adrenomegaly as well as pituitary lesions (Elliott et al 2000, Mauldin & Burk 1990, Meij et al 2001). Neither of these tests should be used as the sole diagnostic tool; however, they might be helpful in defining the origin of the disease after pituitary-adrenal function tests have been performed.

Endocrine testing

Urinary cortisol:creatinine ratio:

Although cats excrete only a small fraction of their glucocorticoids in the urine, it was possible to show that Cushingoid cats had an increase in the urinary cortisol:creatinine ratio compared to healthy cats (Goossens et al 1995). However, elevations have also been seen in cats with non-adrenal illness (Henry et al 1996) making this only useful as a screening test. If positive, the diagnosis of hyperadrenocorticism must be confirmed with other tests.

To assess the pituitary-adrenal axis in cats, the following tests have been used:

ACTH stimulation test:

This test can be used as a screening test to determine if hyperadrenocorticism is present or not.
Protocol: 125 microgram of synthetic ACTH (cosyntropin) are administered intravenously (Duesberg & Peterson 1997, Schoeman et al 2000). As there is greater variability in the time of peak post-ACTH cortisol, blood samples for the determination of plasma cortisol concentrations are taken before and at 60 and 90 min after ACTH administration.

Cats with hyperadrenocorticism (AT or PDH) would be expected to show a high cortisol response at 60 and 90 min after intravenous injection of the ACTH.

It has been shown that cats with non-adrenal illness can show an exaggerated response to ACTH, so false positive results are possible.

Although cats are very resistant to the clinical effects of glucocorticoids, if iatrogenic hyperadrenocorticism is suspected, the ACTH response test is the test of choice, and a diminished cortisol response to ACTH administration would be expected.

Low dose dexamethasone suppression test (LDDST):

This test is performed differently in the cat than in the dog because most cats do not suppress adequately with 0.01 mg/kg bodyweight, the dose that is used in the dog to screen for the presence of hyperadrenocorticism. A ten-fold higher dexamethasone dose is therefore used in the cat.
Protocol: 0.1 mg/kg of dexamethasone is administered intravenously (Duesberg & Peterson 1997). Blood samples are taken before and 4 and 8 h after drug administration for the determination of plasma cortisol concentrations.

Cats with hyperadrenocorticism (AT or PDH) would be expected to show no or inadequate cortisol suppression at 4 and 8 h after dexamethasone administration.

Combined ACTH/dexamethasone suppression test:

This is an infrequently performed test. It offers the advantage that it takes less time than each test performed individually and may give the clinician more confidence in the diagnosis of hyperadrenocorticism if both parts of the test are abnormal.

Protocol: 0.1 mg/kg dexamethasone is injected intravenously after a baseline cortisol sample has been obtained. After 2 h, a post-dexamethasone sample for cortisol measurement is obtained and at that time 125 mg of cosyntropin are injected intravenously. A second sample for the evaluation of cortisol concentrations is taken 1 h after injection of cosyntropin (Duesberg & Peterson 1997).

Cats with hyperadrenocorticism (PDH and AT) would be expected to show no or inadequate suppression at 2 h after dexamethasone and show a high cortisol response 1 h after cosyntropin.

In order to distinguish the origin of the disease, a high dose dexamethasone suppression test can be performed using 1.0 mg/kg intravenously (Duesberg & Peterson 1997). Cats with PDH would be expected to suppress cortisol concentrations 8 h after drug administration, whereas cats with AT would be expected to show no or inadequate suppression.

Alternatively, endogenous ACTH concentrations can be measured (Duesberg & Peterson 1997). Cats with PDH would be expected to have high-normal or high endogenous ACTH concentrations, whereas they would be low or undetectable in cats with AT. Because ACTH is rapidly degraded after collection, special handling requirements need to be observed. They include the use of a protease inhibitor such as aprotinin or benzamidine when blood is collected, rapid separation of plasma and proper storage temperatures (4°C for 1–2 days, −20°C for longer storage).

Some of the imaging techniques are also helpful in the differentiation of PDH vs AT.

Treatment options

Different treatments have been described in the literature. Surgical treatment methods seem to be the most successful. Surgical treatment options include bilateral adrenalectomy (PDH) or excision of the tumour-bearing adrenal gland (AT) (Duesberg et al 1995, Duesberg & Peterson 1997, Moore et al 2000, Nelson 1988, Van Sluijs & Sjollema 1992). While cats undergoing bilateral adrenalectomy require lifelong treatment with mineralo- and glucocorticoids, cats that had a unilateral adrenalectomy only need supportive care until the other (atrophied) gland resumes normal function. The prognosis is guarded because postoperative complications are not uncommon. Most recently, microsurgical transphenoidal hypophysectomy has been reported to be an effective method of treatment for feline PDH (Meij et al 2000). Besides a highly skilled surgeon, this technique also necessitates advanced imaging facilities. It, therefore, remains a highly specialised form of treatment, and the result is a cat with hypopituitarism requiring multiple hormone treatments.

The response to medical treatment has been less consistent. Metyrapone, mitotane (op'DDD) or ketoconazole have been used in a few cases with variable results (Duesberg & Peterson 1997, Moore et al 2000, Myers & Bruyette 1996, Schwedes 1997). These drugs have different mechanisms of action. Metyrapone is a drug which inhibits the action of the enzyme that converts 11-deoxycortisol to cortisol, thereby reducing plasma cortisol concentrations. Mitotane is an adrenocortical cytolytic agent, whereas ketoconazole inhibits the synthesis of cholesterol and therefore the synthesis of hormones from cholesterol such as cortisol (Loose et al 1983) While single cases have responded favourably, the overall success rate has been low.

Radiation treatment has also been performed in a small number of cases with partial success (Mauldin & Burk 1990, Nelson et al 1988).

It is interesting to note that diabetes resolved in about 50% of all treated cases for which long-term follow-up was available. This is very different from the Cushingoid dog where transient diabetes is only seen in a small percentage.

In summary, hyperadrenocorticism in the cat is a complex disease. The low incidence has hampered any systematic approach and has made it difficult to develop guidelines for diagnosis and treatment.

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