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Hypercortisolism - a Rare Feline Endocrinopathy

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Introduction

Cortisol is an important hormone secreted by zona fasciculata of adrenal cortex, its key functions include stress response, suppression of insulin secretion, regulation of inflammation, immune response and metabolism etc. Feline Hypercortisolism is a rare endocrine disorder seen in middle aged to older cats. When there is excess concentration of this steroid hormone, severe physiological and biochemical changes occur, thus referred by a broad term "Cushing syndrome".

Key words: Cortisol, Diabetes Mellitus, ACTH, Malignancy, Trilostane.

Synonyms: Hyperadrenocorticism (HAC), Feline Cushing syndrome (FCS) and Feline Cushing Disease (FDH).

Aetiology (Amalendu Chakrabarti, 2007)

i. In pituitary tumours and pituitary hyperplasia which cause excessive synthesis and secretion of ACTH with adrenocortical hyperplasia. [Pituitary dependent hyperadrenocorticism (PDH)].
ii. In hypothalamic disorder there is an excess corticotrophin releasing hormone secretion causes adrenocortical hyperplasia
iii. Excessive adrenal cortisol secretion as a result of adrenocortical carcinoma and adenoma which are relatively common
iv. Iatrogenic causes due to excessive ACTH administration or excessive gluco-corticoid medication.

Epidemiology

The incidence of the syndrome in cats, much less frequently diagnosed than in dogs, probably is similar to that in humans (E C Feldman *et al*., 1994). HAC usually affects middle-aged to older cats, with the majority having concurrent diabetes mellitus that may be considered difficult to regulate (Andrew Bugbee *et al*. J Am Anim Hosp Assoc. 2023). Currently connection to the genes & heredity is not yet established in cats.

There does appear to be a slight breed predilection in Siamese, Persians, Abyssinians, and

domestic long hairs but a majority of cats that have been affected are domestic shorthairs with a trend towards females being affected more than males (Jessica Gaskins, 2012).

Predisposing factors: Age, Sex, Steroids use [corticosteroid medication or hormones - progesterone like drugs (to control breeding cycle in females)].

Types

Common;

1) Pituitary Dependent Hypercortisolism (PDH),
2) Adrenal Dependent Hypercortisolism (ADH),
3) Iatrogenic Hypercortisolism,

Rare;

4) Ectopic Cushing syndrome (theoretically possible, malignant & neuroendocrine tumours may metastasize to different tissues and produce ACTH/CRH, such cases are recorded in humans and dogs but information about ectopic cushing syndrome in cats is currently lacking).
5) Abnormal adrenal receptors sensitivity and interaction (food dependent hypercortisolism – FDH), by gastric inhibitory polypeptide. Information regarding FDH in cats is scarce.
6) Atypical Hypercortisolism (signs appears as of cushingoid cat but diagnostic results are in normal range, this type of hypercortisolism is not well understood)

Pathophysiology

Naturally occurring Hypercortisolism –

According to Feldman EC *et al*., 2000; Naturally occurring feline hyperadrenocorticism (in approximately 80% of cats) is usually caused by an autonomously functioning pituitary tumour that, in turn results in adrenocortical hyperplasia and about 20% of cats have a functioning adrenocortical tumour.

1) *Pituitary Dependent Hypercortisolism*; due to micro/macro tumours (usually an adenoma), these tumours cause adrenocortical hyperplasia and increased cortisol secretion, in some cases pituitary enlargement.
    a) Micro tumours – common in occurrence, they are minute and secrete excess ACTH than normal, which in turn stimulate adrenal gland to produce more cortisol. Over secretion of ACTH (in frequency and amplitude) will expose the animal to excess level of cortisol chronically than normal (levels can be within normal range) and shows clinical signs. However, the amount of hormone is not so high to cause severe brain damage.
    b) Macro tumours – usually rare in occurrence, along with over production of cortisol there is severe enlargement of pituitary gland and cause brain damage. Some animals may show neurological signs like behavioural changes, pacing, diabetes insipidus, apoplexy (pituitary) etc.

Alpha-melanocyte-stimulating hormone levels will also have elevated in some pituitary tumours.

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2) *Adrenal Dependent Hypercortisolism*; (Pituitary independent) Tumours lead to excess synthesis of corticoid hormones, their excess quantity will supress CRF and ACTH secretion and concentration, it also leads to atrophy of non-cancerous cells of adrenal gland. (50% with adrenal tumours are adenoma and 50% carcinoma).

Iatrogenic Hypercortisolism – when the cats underwent chronic un-tapered corticosteroid therapy (may be for allergic or immune mediated diseases), their excess concentration in blood will produce cushingoid signs in cats and they will also supress natural cortisol secretion from adrenal gland. Cases of clinically significant iatrogenic HAC are documented in cats and may be under-recognised. Most reports involve cats treated with long-term or high dose corticosteroids (Lara A Boland *et al*., 2017).

Co-morbidities & Complications: Diabetes Mellitus [(about 70% of cats) most common, usually type 2 D.M] Urinary tract infection, pancreatitis, Chronic kidney disease, opportunistic bacterial and fungal infections, hypertension, diabetes insipidus etc.

Clinical Signs – usually milder in initial stages but progressively condition becomes worse.

General signs include polyuria, polydipsia, polyphagia, increased weight gain, distension of abdomen / pot belly appearance, non-healing wounds, decreased activity and lethargy, increased intra-abdominal fat, dyspnoea, signs of concurrent diseases may be evident (Diabetes mellitus, UTI etc.) which are difficult to control.

Systemic signs*;* not all cats will show systemic changes, it depends upon the duration, level and type of exposure to excessive cortisol levels.

- Cardiovascular system - Systemic hypertension, increased risk of heart failure, blood clotting (into limbs, lungs, brain) & thromboembolism, vascular invasion of metastatic tumours.
- Nervous system – Pituitary apoplexy, in the cases of macro pituitary tumours they compress other adjacent structures, lead to neurological signs like seizures, appetite changes, behavioural changes, difficulty in maintaining thermo-homeostasis, stupor etc. Sudden blindness due to systemic hypertension (detachment of retina).
- Integumentary system – Skin atrophy where skin becomes fragile and thin (also called **fragile skin syndrome**), can be torn and bleed even with minimum friction. Grooming injuries, bruising, recurrence of epidermoid cysts, poor skin and hair coat condition, alopecia, comodones & hyperpigmentation (in some cases) is commonly noticed in affected cats. Decreased skin immunity can lead to secondary bacterial and fungal infections. Curling of ear tips is seen in later stages.
- Urogenital system – increased risk of UTI, increased sexual desire, gonadal atrophy etc.
- Digestive system – severe inflammation of pancreas, hepatomegaly, some animals may show recurrent vomiting & diarrhoea.
- Musculoskeletal system – Muscle weakness, plantigrade stance, Spinal muscles atrophy, osteoporosis etc.
- Immunity – decreased Immunity, makes the animal prone to opportunistic infections (skin, urogenital & respiratory tracts), diminished wound healing tendency.

Clinical pathology – general laboratory findings (not consistent in every case);

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- CBC: Anaemia, leucocytosis, lymphopenia, neutrophilia, eosinopenia.
- Biochemistry panel: elevated glucose and cholesterol levels, increased Blood Urinary Nitrogen (BUN), Alkaline phosphatase/ALP (about 30-40% cats) and Alanine aminotransferase/ALT. Elevated other liver enzymes (in D.M & lipidosis), rise in inflammatory markers, signs of prolonged and chronic infections seen in serum of cushingoid cat. Creatinine rise is seen when concurrently suffering with CKD.
- Urinalysis: hyposthenuria (Usually > 1.020), proteinuria & glucosuria.

Diagnosis

Tentative diagnosis can be done by

- History: regarding feeding, urination, drinking pattern, weight gain, dermopathy etc.
- Clinical signs and general clinical examination,
- Basic laboratory tests (CBC, biochemistry panel and urinalysis).

Confirmatory diagnosis (requires multiple diagnostic tests, as no single test can confirm the type of cushing disease).

Tests for hypercortisolism: ACTH Stimulation Test (to rule out Iatrogenic hyperadrenocorticism), Urine Cortisol to Creatinine ratio, low dose dexamethasone suppression test (LDDST).

Tests for differentiation between ADH and PDH: Ultrasonography (Abdominal), CT scan (Abdominal & head scan), MRI scan, endogenous ACTH levels, high dose dexamethasone suppression test (HDDST), LDDST (in some cases), Combined UCCR and low dose oral dexamethasone suppression test.

***Random serum cortisol level*:** Usually high and persistent.

ACTH *Stimulation Test*: to test the ability of adrenal gland to produce cortisol on ACTH dosing. It is useful to find out if the cat has Iatrogenic hyperadrenocorticism and also to arrive base line in therapeutic monitoring. If suspecting adrenal tumours, this test should not be used.

1) Collect the blood to test base line cortisol level prior to ACTH administration.
2) Administer 5 µg/kg of ACTH or Tetracosactide intravenously.
3) Recollect the sample after one hour to 1 ½ hour, centrifuge and re-evaluate cortisol level.
4) Heavy rise in cortisol level is noted in hypercortisolism cases, but in iatrogenic hyperadrenocorticism the level of cortisol is same or below the baseline level.
5) This test has high chances of false positives.

Dexamethasone suppression test (pre and post) [Zoetis & AAHA, 2023]

1) An 8-hour post-dexamethasone concentration <1.1 ug/dL is consistent with pituitary-dependent hyperadrenocorticism (PDH) in patients with previously diagnosed hyperadrenocorticism (HAC).
2) An 8-hour post-dexamethasone concentration >1.4 µg/dL is consistent with adrenal-dependent HAC (adrenal tumor), but PDH cannot be ruled out. Cortisol concentrations between 1.1 and 1.4 ug/dL are considered inconclusive.

High dose Dexamethasone suppression test is more reliable than low dose test, because of variability in

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cat's dexamethasone duration of action. Inject the dose of 0.1 mg/kg of body weight dexamethasone intravenously. This test is should not be performed in cases for severe chronic illness and in severely stressed animal.

***Endogenous* ACTH *levels*:** elevated ACTH levels are seen in PDH and declined in ADH.

***Urinary Cortisol to Creatinine ratio* (UCCR):** elevated in cushingoid cats. It is highly sensitive test with low specificity because stress, hyperthyroidism, steroid therapy can also make the UCCR levels elevated.

UCCR with High Dose Oral Dexamethasone Suppression for Diagnosis and Discrimination (R.V. Barrs, 2018);

Protocol: Home collection of two morning urine samples on consecutive days followed on day two by administration of 0.1 mg/kg oral dexamethasone at 8 am, 4 pm and midnight, then collection of a third urine samples the next morning (day 3). If the UCCR of the first two urine samples (averaged) is within reference range, then HAC is excluded, while an elevated result is consistent with HAC. Suppression occurs if the UCCR of the third urine sample is <50% of baseline and this result is consistent with PDH. Less than 50% suppression means that differentiation between ADH and PDH cannot be determined.

Diagnostic imaging:

***Abdominal Ultrasonography*:** can evince enlarged adrenal glands, abnormal masses, venous thromboembolism (VTE) and vascular involvement of adrenal tumours, increased abdominal fat, hepatomegaly & pancreatitis (if present).

***Thoracic and abdominal radiography*:** when suspecting metastatic tumours and abnormal calcification.

CT and MRI *scan*: Pituitary imaging to rule out PDH (able to discover only macro tumours) and abdominal imaging to rule out ADH, for surgery pre-plan and also when vascular invasion (posterior vena cava) is suspected. Iopamidol of 600 mgI/kg intravenous administration can be used for contrast CT of head (Yayoshi N *et al*., 2022).

Ultrasound guided FNAC of adrenal glands and other abnormal abdominal masses to differentiate tumours. Rule out other endocrine disorders like hypothyroidism & other co-morbidities - Diabetes Mellitus, pancreatitis, CKD etc. by testing for specific diseases.

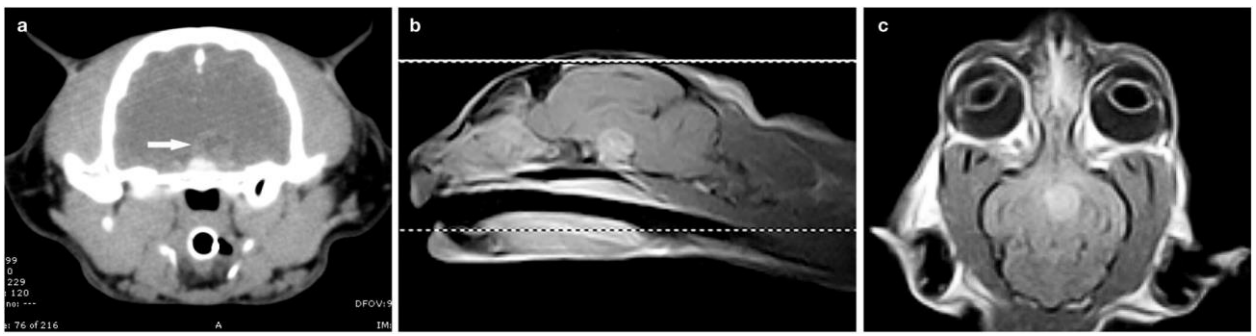

Fig 1 Description: Advanced diagnostic imaging of the cat with PDH

(a) Post-contrast transverse CT showing a heterogeneously enhancing pituitary macroadenoma (arrow).

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The lesion is shown also on sagittal (b) and coronal (c) post-contrast magnetic resonance images. ***Reference:*** From Boland LA, Barrs VR, 2017; Peculiarities of feline hyperadrenocorticism.

Differential diagnosis: endocrine disorders like hypothyroidism, diabetes mellitus, metastatic tumours (with ectopic hormone production).

Prognosis: highly variable and depends upon the cause and associated co-morbidities but the quality of life can be improved with the treatment,

- In Iatrogenic cases usually prognosis is good (as cats will respond to the treatment),
- In the case of malignancy (of pituitary and adrenal tumours) and with level of metastasis the prognosis is mostly poor and more guarded,
- If the animal is aged or not responding well to medication, the prognosis is poor.
- Cushingoid cats may also suffer with diabetes mellitus or secondary infections, if the diagnosis and therapeutic management is lacking, in such cases prognosis is poor.

Treatment: Identifying the cause of FCS is very important as the treatment protocol and prognosis vary between types;

Medical management:

Trilostane – recommended drug for treating Cushing syndrome in cats. It depresses steroidogenesis by inhibiting 3-β –hydroxysteroid dehydrogenase enzyme and decrease systemic cortisol levels. This drug is well tolerated by cats, potential side-effects include lethargy, anorexia, hyperkalaemia.

According to A.M. Mellett Keith *et al*., 2013; The mean initial dose of Trilostane was 4.3mg/kg once daily and 3.3mg/kg twice daily. The mean final dose of trilostane was 2.7mg/kg once daily and 5.6mg/kg twice daily. Administration frequency changed because of increased ACTH stimulation test results in conjunction with persistent clinical signs. Studies using trilostane in cats have not been performed, necessitating extrapolation.

Mitotane – It is an adrenocorticolytic drug with high potency.

According to clinical study by David Bruyette, 2001; Use of mitotane in cats has been discouraged due to the feline sensitivity to chlorinated hydrocarbons. Two cats with PDH treated with o,p'-DDD (25 mg/kg/day x 25 days, and 25–50 mg/kg/day x 59 days) tolerated the drug without apparent toxicity, but therapy was ineffective in controlling clinical signs in either cat. A cat with PDH treated with mitotane (50 mg/kg/day x one week, then 50 mg/kg/week) developed signs compatible with iatrogenic hypoadrenocorticism after 40 weeks of therapy with o,p'-DDD.

Metyrapone - This medication is an 11-βhydroxylase inhibitor that blocks the conversion of 11-deoxycortisol to cortisol (Jessica Gaskins, 2012). Metyrapone, administered orally at a dosage of 65 mg/kg of body weight, every 12 hours (C A Daley *et al.*, 1993).

Overall, the effectiveness of metyrapone in cats with hyperadrenocorticism is variable and may be transient, so the drug is best used over the short term to prepare for surgical adrenalectomy. However, metyrapone is difficult to obtain, precluding its widespread use for cats with hyperadrenocorticism (W.B. Saunders, 2012).

Ketoconazole – the antifungal that can depress adrenal steroidogenesis. Although ketoconazole has been

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used successfully in both humans and dogs with hyperadrenocorticism, the drug does not reliably suppress adrenocortical function in normal cats or cats with hyperadrenocorticism and may cause serious side effects such as thrombocytopenia. Therefore ketoconazole cannot be recommended for treatment of cats with hyperadrenocorticism (W.B. Saunders, 2012).

Selegiline doesn't work in cats.

Surgical Management:

For pituitary tumours; hypophysectomy is rarely performed (surgical removal of pituitary gland). The microsurgical technique of transsphenoidal hypophysectomy performed with the cats positioned in sternal recumbency enables the treatment of Cushing's disease, independent of skull type, in a safe and effective manner. In cats, special attention should be paid to closure of the soft palate (B P Meij., 2001). Lifelong supplementation of thyroid hormone, glucocorticoids and desmopressin if required (following serum level check-up).

For adrenal tumours; (unilateral/bilateral adrenalectomy – based on tumour location) can be performed when animal is poorly responding to medication, surgery should be only performed once the animal is stabilized. Following adrenalectomy, animal may require supplementation with mineralocorticoids and steroids.

Radiation therapy: stereotactic radiotherapy can decrease size of pituitary mass and supress neurological signs, also improves cat's diabetes mellitus condition clinically.

***Additional requirements*:** varies based on co-morbidities and serum biochemical panel values. For example, Insulin therapy (in diabetes mellitus), Antibiotics and antifungals (for secondary infections), entero-dilaysis therapy (in CKD cases), skin and coat vitalizers (aids in recovering from dermopathy) etc.

Conclusion

Multimodal approach is usually effective. Repeated health check-ups is required to assess clinical improvement by evaluating insulin levels, ACTH Stimulation Test (effectiveness of treatment), assessing dimensions of tumours and lesions, culture and sensitivity testing in UTI & skin infections. Diagnosis and treatment of cushingoid cat is costly as it requires regular testing and monitoring of health. In detail explanation to the owner regarding prognosis and treatment options is very important so they can take correct decision in keeping cat's welfare in mind.

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