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Problem Orientated Medicine for Advanced Practitioners

Mini Series

Session 2: Endocrine Challenges - How to Stop Hormones Catching You Out

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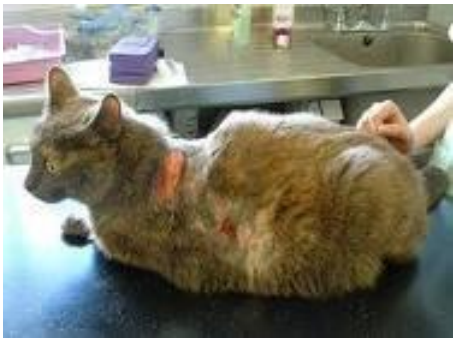

Problem Orientated Medicine

During this session we will explore how use of the problem orientated approach and application of test in an appropriate way can lead to robust diagnosis in difficult endocrine cases. All background information is in the notes and we will work through the cases together

The Endocrine System

Problem orientated approach to medicine depends on identifying WHAT the problem is WHERE it is occurring and WHY. Use of the pneumonic VITAMIN D ie vascular, infectious/inflammatory, toxic, anomalous, metabolic, inflammatory, neoplastic or developmental can aid in generating a list for why. Endocrine disease by the its nature, ie due to hormonal imbalance (a hormone – a substance usually peptide or steroid produced by one tissue and conveyed by the body to another with possible actions on multiple sites) can cause multiple problems, at many sites. Use of the **WHY?** Question can help to confirm diagnostic thinking and identify complicating factors.

In this session we will discuss some of the hormonal conditions commonly encountered, with the aim of exploring how these may trip us up, and how using a problem based case approach can therefore aid diagnosis. As advanced or experienced practitioners it is unlikely that many endocrine conditions will present to us with their classic text book symptoms. All information is in the notes

Hypothyroidism

Review of Synthesis and control

Thyroglobulin is synthesised within the thyroid gland and secreted intot he colloid. Oxidised iodine is bound to thyroglobulin tyrosine residues to produce T3 and T4 which are released into the blood stream. Both extra and intra thyroid regulation occurs. TSH secreted by the pituitary under negative feedback control of T3 (and to a lesser extent T4) increased production of thyroid hormones. TRH produced within the hypothalamus increases TSH production and is under both negative feedback and positive higher neuronal control. T4 is the major secretary product it is highly protein bound, by thyroxine binding globulin (in the dog but not the cat) and albumin. Only free hormone is biologically active and the protein bound hormone acts as a reservoir. Thyroid hormones enter cells mediated by transporter proteins

Canine Hypothyroidism

Hypothyroidism may be primary, secondary or tertiary. Primary hypothyroidism is the most common cause in dogs.

Potential established causes of hypothyroidism in the dog are listed below (ref Feldman and Nelson 4th Edition)

Primary Hypothyroidism

Lymphocytic thyroiditis

Ideopathic atrophy

Neoplastic destruction

Iodine deficiency

Iatrogenic eg radioiodine, or sulphonamide administration

Congenital Neoplasial

Thyroid gland dysgenesis

Secondary Hypothyroidism

Pituitary malformation

Pituitary destruction

Iatrogenic - drugs especially corticosteroids

Tertiaty Hypothyroidism

Primary hypothyroidism

Acquired primary hypothyroidism either due to lymphocytic thyroidits or atrophy (this may be an end result of atrophy) is the most common cause of thyroid disease in the dog. Lymphocytic thyroiditis is an immune mediated process with involvement of humoural and cell mediated immunity, the initiating factors are poorly understood. There is undoubtedly a genetic component given the prevalence in certain breeds.

Lymphocytic thyroititis has an autoimmune component and is sometimes there fore associated with other immune mediated endocrinopathies, associations with diabetes mellitus and hypoadrenocorticism have been demonstrated in dogs.

Clinical signs of hypothyroidism may follow destruction of up to 80% of the gland by an infiltrative tumour either primary or metastatic. Primary tumours are usually unilateral therefore rarely, only approx 10% will signs of hypothyroidism be associated. This can be complicated by the effects of neoplasia on thyroid function tests.

Secondary hypothyroidism

Potential causes are pituitary malformation, destruction of suppression. In dogs the former two are uncommon and the third very common eg glucocorticoids. TSH concentrations are minimal or undetectable although the assay available is not sensitive to very low concentrations and distinguishing between low normal and low values is not reliable. Pituitary malformation has been reported in the GSD as a result of a simple autosomal recessive mutation leading to combined pituitary hormone deficiency and dwarfism. Pituitary cysts have also been reported. Although uncommon pituitary destruction by tumours is reported this is often associated with other pituitary endocrinopthaies. Pituitary thyrotrope suppression may occur due to concurrent illness, drugs eg corticosteroids or malnutrition.

1. Cases

Tertiaty hypothyroidism

This is assumed to be rare in dogs and only sporadic case reports exist.

Clinical presentation

Incidence of clinical signs in 162 Adult dogs with hypothyroidism (Vet Clin N America 31: 935, 2001)

Clinical sign	Percentage
Dermatologic	88
Obesity	49
Lethargy	48
Weakness	12
Neurologic	
Facial paralysis	4
Peripheral Vestibular	3
Polyneuropathy	2
Cardiovascular	10

Other reported signs include siesures, disorientation, myoedema and larangeal paralysis, corneal ocular lipis deposits, GI oesophageal dysmotility and constipation.

Myoesdematous Coma - Case

A rare presentation of extreme hypothyroidism, characteristic include profound weakness, hypothermia and bradycardia with a decreased level of consciousness. Non pitting oedema of the skin may be present. Hypoglycaemia and hyponatraemia may also be seen

Clinicopathological abnormalities

Many changes are non specific but add weight to diagnostic suspicion

Haematology – mild to moderate normocytic normochromic anaemaia of unknown aeitiology

Biochemistry, fasting hypercholesterolaemia is present in 75% of cases, mild hypercalcaemia is sometimes reported.

Diagnostic Imaging

Ultrasonography Thr thyroid glands are readily identifiable and this may be of use in differentiated cases of hypothyroidism from non thyroidal illness. Ultrasonography is of use in identifying thyroid neoplasia

Thyroid function tests

Baseline Serum Total Thyroxin Concentration

Many labs now use chemiluminescence assays which studies suggest are as reliable as the previously used radioimmunoassay which was considered gold standard. T4 is a relatively stable molecule and storage of up to 8 days in a plastic tube has been shown to make no difference to results. Although many factors affect the level of T4 in the blood the only factor which directly effects

levels measured within the assay is anti T4 antibodies, these occur in lymphocytic thyroiditis and are present in approx 2% of dogs with hypothyroidism. There is overlap between the lower level of T4 in normal dogs, **dogs** that are euthyroid sick and hypothyroid dogs. If a lab has its lower level set too high sensitivity is sacrificed to specificity. Breed variations have also been demonstrated, sighthounds in particular may have a lower normal T4

Baseline serum free T4

The gold standard test is equilibrium dialysis however this method is expensive and time consuming therefore most commercial laboratories with perform a modified method it is important to perform an assay validated in the dog. Serum anti T4 measurements do not effect fT4. Any results need to be interpreted with clinical signs and the presence or not of non thyroidal illness considered. Reference range for sight hounds is also lower for fT4

Baseline TSH

All available assays have poor sensitivity for demonstration of spontaneous secondary hypothyroidism. Serum TSH concentratons should always be interpreted in light of T4 and fT4

Interpretation of Basal thyroid hormone levels and TSH concentrations

	Normal T4 fT4	Decreased of borderline T4, fT4
Normal TSH	Normal Dog	Hypothyroid early, normal variation of euthyroid
	Throid test further only if VERY strong suspicion supported by other clinical findings	Consider thyroid Ab, provocative testing or tx trial
Increased TSH	Early sub clinical disease or recovery from non thyroidal illness	Hypothyroid
	Retest 1-3 months of ATAb	Lifelong therapy with L-T4

TSH stimulation test

This test is performed to distinguish borderline cases from those that are euthyroid sick. It is very expensive to perform and as with any thyroid function test FT4, concurrent illness, anti thyroid antibodies should be taken into account

TRH stimulation test

This test is used in human medicine to distinguish secondary from primary hypothyroidism it has no such functionin dogs and minimal use for distinguishing hypothyroidism from non thyroidal illness comrared to TSH, T4 ratios due to the relatively small rise in T4 in response to TSH. Its most valuable function is in the assessment of hypopituitarism

Tests for lymphocytic throiditis

Antithyroglobulin antibodies – commercial assay available

Serum thyroid hormone autoantibodies –

Factors Effecting thyroid gland function tests

Age – progressive decline in T4 concentrations with age in dogs

Body size – greater in small cf large dogs

Breed – greyhounds have lower T4 and fT4, conditioned sled dogs have lower T4 but not fT4

Gender and reproductive status – gender alone has no effect but T4 may be higher in dioestrous females

Diurnal rhythm and random fluctuations

Concurrent illness – **Euthyroid sick** syndrome, most severe systemic illness and inadequate calorie intake will result in decreased T4, and this may be a physiological adaption to decreased energy availability. T4 and to a lesser extent fT4 concentrations are lower in severe illness and the degree of suppression depends on the severity of illness. TSH is more variably effected in some cases of severe illness it may be impossible to distinguish thyroidal from non thyroidal effects on thyroid function tests

Diabetes Mellitus - Hypothyroidism can be a cause of insulin resistance due to the presence of increased concentrations of IGF-1 and GH. In addition hypothyroidism may cause increase in fructosmaine due to decreased metabolic rate. Therefore a diagnosis of hypothyroidism in the presence of DM may be difficult and it is better to wait for a degree of diabetic stability before completing TFT. If thyroid disease is identified and treated in a diabetic patient, glucose should be monitored carefully once thyroid supplementation starts as insulin sensitivity will rapidly increase.

Hyperadrenocorticism Studies suggest that 40-50% of patients with hyperadrenocorticism have low T4 however fT4 is usually maintained within normal ranges

Drugs any drug should be suspected of influencing thyroid function tests

Glucocorticoids – as in hyperadrenocorticism lowering of T4 is seen, the mechanism may be due to suppression of the pituitary and TSH.

Anticonvulsants – cause decrease in both T4 and fT4, the mechanism is unproven but may be due to increased hepatic metabolism of these hormones. TSH usually increases secondary to decrease in T4 and fT4 but rarely into the level consistent with hypothyroidism

Sulphonamide interfere with thyroid hormone synthesis and T4 , fT4 and T3 are affected with an increase in TSH

Non steroidal anti-inflammatory drugs – decrease T4, fT4 and TSH in man

Diagnosis of a previously treated dog

Thyroid supplements should be withdrawn for a minimum of 4 and ideally 6-8 weeks prior to performing thyroid function tests

Treatment

Synthetic T4 – The ideal dose and frequency varies between patients due to variation in absorbtion of T4. A dose of 0.02mg/kg every 24 hours normalises TSH concentrations in most dogs. Response to treatment is monitored clinically 6-8 weeks after starting treatment together with evaluation of T4 and TSH. T4 should be in or just above the normal range, TSH should be normal.

Cushing's Syndrome Review and Difficult cases

In 1932 Harvey Cushing described a series of 8 patients with a disorder @as the result of pituitary basophilism'. Six of these had small basophilic pituitary adenomas. Other forms of disease and the term Cushing's syndrome describes, pituitary dependent hyperadrenocorticism, autonomous secretion of cortisol by an adrenocortical tumour., iatrogenic disease resultant from exogenous glucocorticoid therapy, secretion of ACTH from an ectopic site, pituitary hyperplasia due to excessive CRH (as yet undescribed in dogs).

Regulation of Glucocorticoid Secretion

CRH secreted by the hypothalamus stimulates the anterior pituitary to secrete ACTH this acts on the adrenal cortices to produce cortisol. Cortisol has a negative feedback on ACTH and CRH production. Dogs and man have two distinct areas of the pituitary the anterior lobe (pars distalis) and the posterior lobe (pars nervosa). In contrast to man dogs have a third distinct area the pars intermedia which produces both MSH and ACTH. In contrast to the pars distalis control of ACTH secretion from this area is under the control of dopamine from the hypothalamus rather than CRH

Steroids

Cortisol , corticosterone and aldosterone are produced by the adrenal cortex. The outer layer the zona glomerulosa ,of the cortex produces aldosterone. The inner and middle zonas fasiculata and reticularis produce cortisol and coricosterone.

Pathophysiology

Pituitary Dependent Hyperadrenocorticism

In dogs with pituitary dependent HAC ACTH is secreted in a constant manner leading to overproduction of cortisol and therefore signs of Cushing's syndrome due to the effect of cortisol. 85% of cushing's patients are reported to have pituitary disease with between 20-100% of these reported as tumours vs pituitary hyperplasi dependent on study. 80% arise in the pars distalis the remainder being found i the pars intermedia, within this latter group a certain proportion are non suspressable by dexamethasone. Tumours may be either macro (>10mm) or micro adenomas (<10mm), carcinomas are rare. Pituitary dependent hyperadrenocorticism occurs due to somatic mutation of a single corticotroph leading to clonal expansion, in man most such tumours are monoclonal

Adrenal dependent hyperadrenocorticism

Adrenocortical adenomas and carcinomas occur and these autologously secrete cortisol type hormones without the control of ACTH. Negative feedback ensures ACTH production decreases and there is atrophy of the contralateral gland. It should be noted however that bilateral tumours have been reported

Ectopic Adrenocorticotrophic Hormone Syndrome

In man ectopic secretion of ACTH has been reported in a number of tumours including small cell tumours of the lungs and neuroendocrine tumours. There are three reports within the literature . The most convincing of these was an 8 year old GSD reported by Galec et al, with a pancreatic/hepatic mass

Review of signalment and history

HAC is a disease of middle aged to older dogs. Most published articles on hyperadrenocorticism clinical signs are now over 10 years old it is likely that due to increased education diagnosis is made earlier upon subtler clinical signs. Table below shows common and less common manifestations. It is likely that hyperadrenocorticism is overdiagnosed, based on false positive results of screening tests. Only pursue a diagnosis of hyperadrenocorticism if more than one clinical sign is present. Signs not associated with HAC is a reason not to pursue this as a diagnosis, coughing, sneezing, vomiting diarrhoea are not associated with hyperadrenocorticism. Seizures, dullness, poor appetite will only be associated with HAC if there is a pituitary macroadenoma. In addition if an ACTH test is performed in an ill animal looking for a diagnosis of hypoadrenocorticism this patient DOES NOT have Cushing's if the test comes back with high values.

Common	Not Common	Uncommon
Polyurea	Lethargy	Bruising
Polyphagia	Hyperpigmentation	thromboemboli
Panting	Comedones	Ligament rupture
Abdominal distention	Pyoderma	Thin skin
Endocrine alopecia	Thin skin	Calcinosis cutis
Hepatomegaly	Poor hair regrowth	Pseudomyotonia
Muscle weakness	Urine dribbling	Testicular atrophy
Muscle wasting	Insulin resistant DM	Persistent anoestrous
hypertension		

Unusual presentations

Myotonia - rarely dogs with HAC will develop a myotonia with persistent muscle contraction after cessation of voluntary effort. A stilted hindlimb gait is seen, and muscle enlargement. These signs are seen in conjunction with other signs of hyperadrenocorticism

Facial paralysis can be seen intermitantly in dogs with hyperadrenocorticism, the association is anecdotal

Blindness – due either to SARD (sudden acquired retinal degeneration syndrome), a non inflammatory degeneration with loss of photoreceptors or central blindness due to compression of the optic chiasm by a pituitary macroadenoma

Acute weakness due to a rupture of an adrenal tumour. This results in an acute retroperitoneal bleed and is very painful.

Haematological, serum chemical urine and imaging findings in HAC

Test	Abnormality
Complete blood count	**Mature leucocytosis** **Neutrophilia** **Lymphopaenia** **Eosinopaenia** **Mild erythrocytosis**
Serum chemistry	**Increased ALP, into several thousand** **Mild ALT elevation** **Hypercholesterolaemia** **Hypertriglyceridaemia** **Hyperglycaemia** **Increased bile acids – 30% increase** **Decreased BUN –due to urine loss in PU**
Urinalysis	**USG <1.015 often less 1.008** **Proteinurea, UPC <5** **UTI with inactive sediment**
Imaging	**Hepatomegally** **Excellent Abdominal contrast** **Osteoporosis** **Calcinosis cutis** **Adrenal calcification** **Calcified trachea** **Enlarged adrenal/s**
Blood pressure	**Hypertension**
Thyroid testing	**Low T4**

Screening tests, in HAC confirming a diagnosis

A diagnosis and decision to treat a patient for Hyperadrenocorticism cannot be based soley on any screening test. The positive and negative predictive values for a test increase with the prevelance of disease in that population. Therefore selecting the right patient to test will increase diagnostic accuracy. Screening tests for HAC are the ACTH stimulation test

Sensitivity and Specificity

It is important to consider the specific and sensitivity of diagnostic testing, especially in non classical cases of HAC or where there is concurrent disease present. Sensitivity describes the number of animals with a disease who are correctly identified by a test, eg the LDDST has a 95% sensitivity therefore only 5% of dogs with HAC will have a false negative LDDST, the ACTH stimulation test 86% specificity therefore 14 % of dogs without HAC have a false positive result. More than one test may be required, however if a negative result is obtained in more than one test it is worth pausing to reconsider your disgnosis

Specific considerations

Dogs with known disease, especially diabetes mellitus. The likelihood of a false positive on HAC screening tests increases with the severity of non adrenal illness, and some have positive results on all screening tests. It is worth trying to control the non adrenal illness prior to definitive screening.

Phenobarbitone therapy - Case

Phenobarbitone therapy may cause PU/PD and increase in ALP. Occasional dogs treated with phenobarbitone fail to suppress on the LDDST no such effect is seen with the ACTH stimulation test.

Patients suspected of HAC treated with HAC should be swapped to another anticonvulsant if possible. An ACTH rather than LDDST should be used in patients on phenobarbitone

Urine Cortisol to Createnine ration

Very high sensitivity but low specificity

ACTH stimulation test – This test asses adrenal reserve, it is the gold standard for testing iatrogenic HAC, and the only test recommended for monitoring response to therapy. Its advantages are that it is quick, safe simples but it does have a lower sensitivity than the LDDT

Interpretation – It is essential to look at absolute values both pre and post stimulation. The sensitivity of the ACTH test is 57-95 %, for adrenal disease this is 57-63% and PDH 80-83%. Specificity ranges from 59-93%. All increase to the upper end of the range with population selection. Occasional dogs suspected of HAC have an ACTH stimulation test below the reference range, the most likely cause of this is glucocorticoid administration, either systemic or topical . Other drugs causing this effect include progestergens and ketokonazol. Very rarely adrenal tumours have low cortisol production due to production of intermediates.

Low-Dose Dexamethasone Suppression Test

This demonstrates decreased hypothalamic-pituitary adrenal axis sensitivity to negative glucocorticoid feedback. The tests sensitivity is high and in 40% of cases it will differentiate adrenal from pituitary disease. It is less specific than the ACTH test and takes 8 hours

Interpretation –lack of suppression on a LDDST is consistent with a diagnosis of HAC, in normal dogs plasma cortisol is below the lab ref range at 4 and 8 hours post administration of dex. HAC patients show escape of cortisol at 8 hours. If the 4 hr sample is less than 50% of base and escape is seen at 8 hours and or 8 hour samples is 50% of base this is suggestive of pituitary disease. Occasionally an inverse pattern with loss of control at 4 hours and suppression at 8 hours is seen . This is suspicious but not diagnostic of HAC. Sensitivity of the LDDST is approx 95 % but specificity ranges from 44-73% with increasing false positives with increasing severity of non adrenal illness.

Differentiating Pituitary Dependent Hyperadrenocorticism and adrenocortical tumour

Prognosis and treatment options vary for adrenal and pituitary disease therefore it is important to differentiate these conditions. A screening test MUST be performed first to establish diagnosis

The high dose dexamethasone suppression test

If a dog does not suppress on a HDDST it has a 50% chance of having pituitary or adrenal disease, and if a patient has not shown differentiation on a LDDST it is unlikely to do so on a HDDST. Approx 75% of dogs with pituitary disease suppress on a HDDST, the remainders either have a large pituitary mass or a mass originating from the pars intermedia

Exogenous ACTH

Measurement of endogenous ACTH is the most accurate biochemical test for differentiating PD~H from adrenal disease, the molecule is highly labile and there is a grey zone between pituitary and adrenal disease where cannot be made

Diagnostic Imaging

Radiography – as mentioned above there are several non specific markers consistent with HAC**,** differentiation can be achieved radiographically as published data suggests 50% of adrenal tumours are calcified.

Abdominal ultrasound – is a more useful differentiation tool than radiography. It is not a diagnostic tool, many adrenal masses, up to 50% are seen incidentally. Small adrenal masses can be seen and bilateral adrenal enlargement in PDH noted. An adrenal lesion of greater than 4cm has a high **correlation** with malignancy

CT and MRI –

Pituitary – Pituitaty imaging (CT and MRI) can provide valauable information regarding treatment and prognosis and should be considered for cases of PDH. Where neurological signs are present pituitary masses are almost always seen, however small masses may not be seen on advanced imaging with or without contrast and their absence does not rule out PDH. A pituitary macroadenoma (>10mm) will require radiation therapy for control of tumour growth, and the number of neurological signs and size of tumour have direct correlations for prognosis and survival. Of a study of 13 dogs (Bertroy 1995,1996), 6 had tumour growth at 1 year, and four developed neurological signs within 1 year. Dogs with small masses at time of diagnosis can be treated medically and ideally followed up with imaging at 1 year, those with masses > 8mm should be offered radiotherapy

Abdominal imaging – CT is an accurate way of assessing adrenal gland morphology and can give valuable information about vascular invasion. Differentiation between adrenal tumour and hyperplasia may be available.

Treatment Options

Differentiating adrenal from pituitary disease is essential to allow full range of options to be given to the client. It should be noted that in some cases conflicting results will make this differentiation difficult in which cases, in which case as pituitary disease is more common this should be undertaken. The drug used in PDH treatment, trilostane is not benign and the degree of disease needs to be considered and discussed with the owner before embarking on treatment.

Adrenalectomy – Although adrenalectomy is the treatment of choice for ADH caused by cortisol secreting adrenal tumours it is technically demanding and carries significant peri and post operative complication risks. A up to 25 % mortality rate has been reported, although this is almost certainly dependent on patient selection, this procedure requires a hospital environment with high level of anaesthesia and 24 hour nursing care. Dogs with tumours of >5cm, with thrombosis, renal or body wall involvement have a considerably worse prognosis

Preoperative considerations – Cushing's patients have several significant preoperative considerations due to the nature of the disease itself. These include hypertension, poor wound healing, immunosuppression and hypercoaguability. Therefore prior to surgery it is suggested that a short course of trolostane (3-4 weeks is considered), an ACTH stimulation test should be performed prior to surgery. In addition hypertension should be assessed and managed, PCR and anti thrombin III should be assessed as patients where the former is high and the latter low can be recognised as having a greater risk of hypercoagulability. Ultrasound or CT to asses invasion and chest x-ray should be carried out. It is recommended the patient is blood typed.

Intra and postoperative management – Suppression of the contralateral gland by autologous secretion of cortisol by an adrenal tumour, puts patients at immediate risk of hypoadrenocorticism. It is not advised that corticosteroids are administered preoperatively due to increased risk of hypertension etc. However once the surgeon has removed the adrenal gland a CRI of dexamethasone should be started (0.5-1mg/kg given over 6 hours) after this time the dose is reduced by 0.02 mg/kg every 24 hours until the patient is no longera t risk of vomiting and oral prednisalone can be given. Pred is given at 0.25 (sometimes up to 0.5)mg/kg bid and dose reduced in small increments every 2 weeks. An alternative is to perform an ACTH stimulation test 6-8 hours post surgery. However it is the authors experience that glucocorticoid therapy is required especially in

patients with larger tumours. Electrolytes should be closely monitored due to the risk of hypoadrenocorticism. If Sodium drops below 135mmol/l it is recommended that short term mineralocorticoid therapy is started.

Postoperative Complications and survival – The most concerning postoperative complication is thromboembolism, careful patient selection and making sure the patient is ambulatory 4hours post operatively decrease the complication. Other complications include pancreatitis, acute renal failure, hypoadrenocorticism and cardiac arrhythmias. Rates of up to 30% have been reported (Schwartz 2008). Median survival was 690 days in this study in dogs who survived the immediate post operative period

Hypophysectomy – Is the treatment of choice in man. A series of 150 dogs undergoing this procedure was published from Utrect in 2005. Although complication occur this appears in experienced hands to be a promising treatment in dogs. It is most effective in patients with early diagnosis without pituitary enlargement .

Medical Managment . Trilostane Treatment Complications and treatment failures

A synthetic steroid analogue that inhibits adrenal enzyme 3B – HSD suppressing production of progesterone and its end products cortisol and aldosterone. Although originally considered a benign treatment acute adrenal necrosis and hypoadrenocorticism have been described.

Twice Daily Dosing – Case chihuahue recently. Bell 2006 demonstrated that control of the hypothalamic pituitary adrenal axis is lost in some dogs and in some individuals only lasts 8-10 hours. Therefore twice daily dosing may be required. Cinical signs related to control are ongoing PU/PD where biological control of the HAC on ACTH stimulation test appears adequate.

Atypical /Occult Hyperadrenocorticism

‘ A syndrome in which a dog appears to have HAC based on clinicopathological findings, history and physical exam, but the LDDST, UC:CR and ACTH stimulation test fall into currently accepted reference ranges’ ACVIM consensus statement 2012

The syndrome is proposed to occur due to diversion of the normal adrenocortical production pathways of cortisol and aldosterone with production of sex hormones as an alternative, and is diagnosed by demonstration of elevation of one or more of these pre and post ACTH stimulation. Conclusive evidence is lacking

Evidence for and against the existence of occuly hyperadrenocorticism as a sex hormone mediated disease

1. **Adreanl Sex hormone and cortisol precursor secretion as a cause of bilaterally symmetrical alopecia**
   Alopeica X occurs in certain plush coated breeds such as the Pomeranian, Chow and Poodle. A bilateral symmetrical endocrine alopecia occurs. It is unknown if this is a separate entity to occult HAC or a cutaneous only expression of the disease.
   a) **Evidence in favour** – Sex hormones are known to cause endocrine alopecia, eg sertoli cell tumours and castration responsive alopecia. In the first report of alopecia X described seven Pomeranians classic HAC was ruled out. Progesterone, 17-hydroxy-progesterone and 11 deoxycortisoldehydrepiandrosterone sulphate DHEAS, androsterone, testosterone and oestrodiol were measured pre and post ACTH, in affected dogs, unaffected Pomeranians and 19 non Pomeranians. Only ACTH stimulated 17 OHP differed between affected and non affected Pomeranians. ACTH stimulated progesterone and DHEAS were significantly higher in Pomeranians of both groups cf controls. Therefore it was suggested the alopecia was due to 17 OHP. In humans with 21

hydroxylase deficiency cortisol is not synthesised and !&OHP accumulates. A partial enzyme defcincy was therefore hypothesised in Chihuahuas

b) **Evidence against**. When female and male Poms were compared in the affected group only females had raised 17OHP. In 276 dogs with alopecia X only 73% had at least one post ACTH sex hormone elevated and there was no consistent pattern. No gene mutations for 17OHP deficiency have been demonstrated.

17 Hydroxyprogesterone, Other sex Hormones and Cortisol Precursors as Causes of Occult Hyperadrenocorticism

a) **Evidence in Favour** Ristic et al, 2002 described 24 dogs with classical clinical and laboratory signs consistent with HAC. Of these 11 had classical responses to ACTH, and 13 normal ACTH results. Of the group of 13, 6 had suggestive LDDST, 4 normal LDDST and remainder had variable to low cortisol making interpretation of LDDST impossible. All subjects, both positive to ACTH and normal had exaggerated 17 OHP concentrations to ACTH. Numerous other studies have reported elevated sex hormones in patients with HAC and sporadic reports exist of Adrenal tumours secreting sex hormones with low cholesterol concentrations

b) **Evidence against** – The hormone most mentioned is 17 OHP and it is difficult to appreciate how this can cause signs of HAC. Chronic progestagen excesses of 60-90 days occur in dioestrous without signs of HAC. In man clinically silent adrenal tumours secreting 17 OHP are recognised. A syndrome in which 17 OHP is not broken down is seen due to enzyme deficiency is recognised but is clinically silent. Therefore the phenotypic expression of the genotypic variant is not understood. A hormone excess alone does not appear enough to cause signs of HAC>

Sex hormone panel testing

a) **Evidence in favour** – testing a panel of hormones in cases of occult HAC is thought to increase sensitivity of testing the most commonly elevated hormone is oestrodiol 40%

b) **Evidence against** - if dogs with non adrenal illness can have variations and excessive ACTH stimulation response it is possible that other hormones will also be altered. Oestradiol has a very wide natural variation

Response to treatment

a) **Evidence in favour** - treatment with drugs that interfere with the hypothalamic adrenal pituitary axis can cause resolution of clinical signs. Eg 3 Alaskan Malamutes with signs of Alopecia X showed hair regrowth when treated with trilostance Leone et al 2005

b) **Evidence against** – treatment does not produce predictable or consistent outcomes

Indications for diagnostic testing

Testing should not be undertaken in any patient that does not have consistent clinical signs and laboratory abnormalities for HAC. All patients should have a ACTH stimulation test and or LDDST. If these are non suggestive and HAC is still suspected an abdominal ultrasound is warranted. An adrenal tumour may be seen as which case hormonal testing is suggested. If there is bilateral adrenal enlargement pituitary imaging and hormonal panel testing are indicated. If signs are mild and the adrenals normal re testing several months later may be required as the patient is in an early stage of disease.

ACVIM consensus guidelines

Patients with occult HAC may be 1. Early in disease, in cortisol sensitivity may vary in dogs as in man or a rare form of disease may exist.

Treatment

Is dependent on the form of disease eg adrenal tumour thought to be hormonally active may require surgery (Eadie McCredie). Other forms of disease can be treated as for standard HAC

Hypoadrenocorticism, treatment pitfalls and atypical disease

The presence of 'suprarenal glands' had long been recognised by anatomists however it was not until Thomas Addison 1855, described a disease associated with their dysfunction was their importance recognised. The syndrome was associated with anaemia lethargy vomiting , and patients rapidly died. PM noted TB destruction of the glands of atrophy. In the 1930 a crude extract of the adrenal cortex was shown to maintain life in adreanectomised cats, Loeb demonstrated Sodium deficiency as a major component of disease at this time. By 1942 DOCA, desoxycortisone acetate was shown to be of benefit in treatment of adrenal insufficiency by Thorn et al. By the 1950s the majot hormones of the adrenal gland glucocorticoids, mineralocorticoids and aldosterone were recognised. By the 1980s small series of naturally occurring Addisons syndrome were recognised in dogs.

Regulation and action of mineralocorticoid synthesis

This is regulated by the renin angiotensin system and serum potassium concentration. Increase in potassium and angiotensin II, markedly increase aldosterone concentration. Increased angiotensin synthesis is stimulated by decreased extracellular fluid volume sensed by the juxtaglomerular apparatus. Renin is realeased and angiotensin converted to angiotensin II primarlily in the lungs. Plasma potassium has a direct positive effect on aldosterone production. A total absence of ACTH decreases aldosterone secretion, but has no effect on controlling the rate of production.

Aldosterone causes secretion of potassium and absorption of potassium from the kidney, sweat glands, salivary glands and intestinal epithelia cells and is therefore essential in maintaining body salt. The main site of action is the distal convoluted tubule (Pose 2001)

Consequences of deficiency –

Hyponatraemia and hypochloraemia – NaCl loss causes a loss of body water and decrease in extracellular volume, therefore decreased glomerular filtration rate and prerenal azotaemia. Mild aldosterone deficiency may be alleviated by increased salt intake although where salt loss is extreme eg vomiting severe salt deficient occurs and decrease in extracellular fluid

Hyperkalaemia – causes decreased myocardial excitability and an increase in the myocardial refractory period and slowed conduction . Hypoxia secondary to hypovolaemia and poor tissue perfusion contributes to poor myocardial dysfunction

Acidosis – due to impaired reabsorbtion of bicarbonate and chloride

Polyurea and polydipsea

Consequences of glucocorticoid deficiency – hypotension, hypoglycaemia, anorexia and vomiting diarrhoea weight loss and muscle weakness

Glucocorticoid Deficiency Versus Mineralocorticoid Deficincy

The majority of dogs have both mineralocorticoid and glucocorticoid deficiency although disgnosis is made on measurement of cortisol response to ACTH. Aldosterone is less commonly measured and is assumed from the electrolyte abnormalities documented. Approx 30% of patients with hypoaldosteronism have normal electrolytes. It has been assumed that these 'atypical cases' had normal aldosterone concentrations due to sparing of the zona glomerulosa in some individuals with immune mediated disease. However this is unlikely the case in all patients and low aldosterone has been demonstrated in dogs with normal electrolytes leading to the supposition that other mechanisms than aldosterone alone may be involved in maintenance of electrolyte concentration

Primary Adrenocortical Failure

The process is gradual with clinical signs rarely seen until 90% of glands are destroyed. The most common cause is immune mediated destruction, athough in some parts of the world, granulomatous destruction due to TN remains common. Large series in dogs have not been published but the most common cause appears to e lymphplasmacytic inflammation

Polyglandular autoimmune syndromes

In man hypoadrenocorticism is associated with other immune mediated endocrinopathies

Type 1 – Hypoparathyroidism, and chronic mucocutaneous candidiasis

Type 2 -thyroiditis, insulin dependent diabetes mellitus - this occurs rarely in dogs

Secondary adrenocortical failure

Reduced ACTH will cause reduced glucocorticoid synthesis, therefore in man and more rarely in dogs tumours of the hypothalamus or pituitary are described as causing hypoadrenocorticism

Iatrogenic Secondary Hypoadrenocorticism

Suppression of ACTH is seen with all corticosteroid related drugs from topical preparation to oral drugs and intravenous preparations. The more potent the preparation the longer the hypothalamic, pituitary adrenal axis will take to recover . Prednisalone is thought to be 5 times as potent as cortisone and dexamethasone fifty times as potent. Recovery of the axis for testing ranges from 48 hours with a single dose of pred to 4-6 weeks with a depot injection, 4 weeks is recommended after lengthy topical uses. If dexamethasone has been administered an ACTH stimulation test can be performed with 24-48 hours as dex does not interfere with the cortisol assay.

History

Clinical signs are vague and none are pathopneumonic. They will often wax and wane, eg intermittent GI signs. It is important to have a high level of suspicion and also to look for what is not there.

Case

Diagnosis

Clinical Pathology

Common clinicopathological abnormalities observed in dogs suffering from hypoadrenocorticism

Clinpath changes	%affected
Eosinophilea	20
Lack of stress leucogram	92
Lymphocytosis	10
Neutropaenia	32
Nonregenerative anaemia	27
Azotaemia	88
Hypercalcaemia	95
Hyperphosphataemia	68
Hypoalbuminaemia	6-39
Hypocholaraemia	42
Hypoglycaemia	17
Hyponatraemia	81
Increased liver enzymes	30-50
Metabolic acidosis	40
USG >1.030	60

Hyponatraemia and hyperkalaemia

Hyponatraemia and hyperkalaemia are the trademarks of hypoadrenocorticism. Approx 30% of dogs do not have these abnormalities. Patients without the classical abnormalities tend to be older and have a longer duration of disease. Not all will progress to mineralocorticoid deficiency and most that do do so within 1 year.

A diagnosis for hypoadrenocorticism should not e made on electrolyte abnormalities alone and should be confirmed with an ACTH stimulation test. Differntials for hyponatraemia nd hypokalaemia include

1. Renal and urinary tract disorders – acute obstruction or renal failure
2. GI – tricuris vulpis and parvo
3. Acidosis pancreatitis and or trauma
4. Pleural effusion
5. Artifact
6. Lipaemia

Total Calcium and Ionised Calcium total calcium may be raised, ionised can be raised or normal

Radiography – Most untreated dogs will have one or more radiographic feature consistent with hypovolaemia, these include microhepatica, microcardia, small vessesl. A megaoesophagus may be present although this is an unusual feature (1 of 225 dogs in a study reported by Peterson et al 1996)

Abdominal ultrasound Most dogs will have demonstrable changes on ultrasound. Wenger et al 2010 demonstrated that dogs with hypoadrenocorticism, had significantly thinner adrenal glands than normal dogs or those with hyperkalaemia and hyponatraemia for another reason

Electrocardiology. Changes on ECG are due to changes in K as the K raises p waves vanish and eventually a wide broad ventricular rhythm is seen.

Confirming the diagnosis

ACTH stimulation test and basal cortisol

Documentation of a low basal cortisol alone does not confirm a diagnosis of hypoadrenocorticism but it will rule it out. ACTH stimulation test measures adrenal reserve and is the gold standard of diagnosis

Treatment

Acute management

A patient in Addisonisn crisis is in a life threatening condition. Hyperkalemia left untreated will cause fatal cardiac arrhythmia.. The aim of treatment is to treat the signs of shock and confirm the diagnosis with an ACTH stimulation test. Care not to raise Sodium too quickly once initial hypovolaemia is dealt with must be executed.

General outline of treatment

Place an iv catheter

- If in hypovolaemia shock bolus with 0.9% saline
- Continue at a reduced rate for several hours depending on the severity of shock and hyperkalaemia
- Collect samples for haematology, ciochemistry, urine and serum base line cortisol. Start ACTH stimulation test
- Start glucocorticoids after second sample of ACTH stimulation test. Either as dexamethasone CRI, or dex iv. Continue dex until patient is able to eat
- If hyperkalaemia is severe consider insulin and iv glucose.
- If severe acidosis consider sodium bicarbonate infusion. Deficit = 0.3 x BW (Kg) x 24-HCO3
- Give iv glucose if hypoglycaemia

case

Monitor

- Serum electrolytes
- Blood glucose
- Acid-base status
- Blood pressure
- Urine output
- ECG

Long Term Maintenance

We are all comfortable with management of patients with flodrocortisone and pred. However fludrocortisone is no longer on the market and a new drug Zyocotal is available. Much confusion exists about transitioning dogs onto this medication

We are using the same protocol as Glasgow Vet School

Day 1 inject zycortal 2.2mg/kg (however anecdotal evidence from RVS suggests this may be excessive in some dogs, Mitchigan state is working with 1mg/kg). Dose is every 25 -29 days based on electrolyte analysis.

Day 2 Give the dog one half of the usual florinef dose. Start glucocorticoid if not already on this 0.2-0.4mg/kg.

Day 3 Give the dog ¼ of the normal dose of florinef

Day 4 no further florinef

In the USA standard practice is to train owners to inject themselves . It is vital that on starting zyocortol prednisolone is given every day, no attempt at every other day treatment should be made (you are not trying for recovery of the HPA). Prednisolone dose should be increased at times of metabolic stress by 2-4 times.