ADRENALS

The body contains two adrenal glands, with one lying close to each kidney. The adrenal glands are part of the endocrine system and help to produce several hormones. Glucocorticoids are released by the adrenal glands and are regulated by adrenocorticotropic hormone (ACTH) from the pituitary gland. The term corticosteroids is applied to hormones of the glucocorticoid class (those that affect glucose) that are released from the adrenals.

The most important corticosteroids produced are cortisol and corticosterone. They help increase blood glucose levels by reducing glucose uptake in the cells, aid in gluconeogenesis and help to convert fatty acids back to glucose. When there is an excessive amount of corticosteroids the inflammatory and immune process can be reduced which can lead to poor healing. This process is known as hyperadrenocorticism (Cushing's Syndrome/Disease). A decrease in production is known as hypoadrenocorticism (Addison's Disease).

The adrenals also produce aldosterone, a mineralocorticoid (affects "minerals" also known as electrolytes) which regulates acid/base function of the kidney. It also helps to control the excretion of sodium, chloride and potassium.

Lastly the adrenal glands are responsible for producing both male and female sex hormones and while they produce seemingly insignificant quantities, it may explain why some animals still display some level of sexual behavior even after being neutered.

The body regulates cortisol through a negative feedback loop. When cortisol is needed due to a stressful situation in the body, the hypothalamus signals the pituitary gland to release ACTH. This signals the adrenal glands to produce cortisol. As cortisol levels rise in the body it causes the hypothalamus to decrease its signal to the pituitary gland. This causes less ACTH to be produced which therefore decreases the release of cortisol.

ADRENAL INSUFFICIENCY

The production of mineralocorticoids and/or corticosteroids become decreased. The cause of the decrease can be from bacteria or parasitic agents (histoplasma, cryptococcus) causing inflammation in the adrenals, haemorrhage (Waterhouse-Friederichsen syndrome due to massive sepsis), neoplasia, iatrogenic causes or may be idiopathic. Most dogs diagnosed with hypoadrenocorticism are young to middle aged females (mean 4–5 years). Certain breeds seem to have a higher risk: Standard Poodles, West Highland Terriers, Bearded Collies, Great Danes, Portuguese Water dogs, Labrador retrievers, Rottweilers, and Wheaton Terriers.

Roughly 90% of the adrenal function is compromised once clinical signs finally become evident. As the mineralocorticoids are decreased the sodium, chloride and potassium levels within the body become unregulated. The kidneys no longer secrete appropriate amounts of potassium which leads to hyperkalaemia. The renal tubules do not reabsorb sodium and chloride as well resulting in both being excreted rapidly in the urine. Aldosterone has a direct effect on the extracellular fluid because of a direct relationship with how much sodium is reabsorbed or excreted. Conversely, in the patients with hypoadrenocorticism extracellular fluid volume will decrease as sodium decreases, thus causing the patient to become dehydrated. Any small change in sodium, even by a few milliequivalents on blood work, will stimulate thirst and water intake.

The hyperkalaemia will often cause ECG changes resulting in high-peaked T waves and bradycardia. It can also cause abdominal pain, weakness (due to the cardiac effects), diarrhoea and in severe cases flaccid paralysis of the limbs, respiratory paralysis, circulatory and cardiac failure.

As the sodium decreases the pet will become depressed, lethargic and cerebral oedema may occur. Seizures and coma may occur though these signs are often a reflection of how fast the sodium declined rather than the actual concentration. If the sodium decreases slow enough the pet may have few clinical signs.

As the corticosteroid levels decrease gluconeogenesis may not occur which can result in a mild to moderate hypoglycaemia leading to more lethargy of the pet.

OVERPRODUCTION

With hyperadrenocorticism the production of mineralocorticoids, corticosteroids and/or sex hormones becomes increased. The most common cause of the increase is due to a corticotroph adenoma or hyperplasia of the pituitary gland. The corticotroph are the cells of the anterior lobe of the pituitary gland that produce
adrenocorticotropic hormone (ACTH) and is known as pituitary-dependent hyperadrenocorticism (PDH). This accounts for 85-90% of all dogs with Cushing's Disease. The adenoma of the pituitary gland causes bilateral adrenal cortical hypertrophy and hyperplasia. While not as common it can occur in cats. Functional adrenal gland neoplasia (most commonly due to a pheochromocytoma) is rare and accounts for only 10-15% of the cases. Tumors of the adrenal gland causing hyperadrenocorticism are known as adrenal tumor hyperadrenocorticism (ATH). Rarely Cushing's can occur due to an iatrogenic cause from the excessive use of glucocorticoids.

Poodles, dachshunds, beagles, German shepherds, and many terrier breeds are predisposed to developing Cushing's though no genetic link has been found at this time. A familial predisposition is particularly noted in the Dachshund. The median age of dogs with pituitary-dependent hyper-adrenocorticism is 10 years. Dogs with adrenal tumors causing Cushing's Disease tend to have a median age of 11.3 years. Females are slightly more predisposed than males (60% vs. 40%). While there are no studies proving a correlation between weight and developing Cushing's Disease roughly 75% of dogs will weigh less than 9 lb (20 kg).

HYPOADRENOCORTICISM
SIGN/SYMPOTOMS

Hypoadrenocorticism may occur acutely or chronically. If the pet has time to get use to the shifting electrolytes and decrease in hormones then they typically present with more non-descript signs: weight loss, hypothermia, shivering, weakness, anorexia, lethargy, vomiting, polyuria and polydipsia. Some patients will also have weight loss, diarrhoea and melena. Cats typically experience lethargy, anorexia, vomiting, weight loss, polyuria and polydipsia. When the body does not have a chance to get use to the decreases in hormones the pet typically presents with severe dehydration, hypovolemic shock, and bradycardia.

Upon presentation pets are usually depressed and at least mildly dehydrated. Pets that experience an acute onset of hypoadrenocorticism will often present with signs of hypovolemic shock: pale/tacky oral membranes, decreased capillary refill time, weak pulses, bradycardia, shaking, collapse, seizures or coma. These patients require emergency treatment.

DIAGNOSIS

A complete blood count (CBC), blood chemistry panel, electrolyte panel, blood gas and ACTH stimulation test are all necessary if Addison's is suspected.

Typically a mild anaemia may be present, but may be masked by dehydration. The CBC is typically normal. On a blood chemistry a hyponatremia, hyperkalaemia and a sodium/potassium ratio less than 27:1 is usually present. Azotemia, hypocalcaemia and hypoglycaemia are present in about 30% of pets. Pets may also experience metabolic acidosis and have a urine specific gravity < 1.030.

Definite diagnosis requires the adrenocorticotropic hormone (ACTH) stimulation test. ACTH is a hormone produced in the pituitary gland that stimulates the adrenal glands to release cortisol and aldosterone. During the test, a small amount of synthetic ACTH (cosyntropin, cortrosyn) is injected either IM or IV, and the amount of cortisol the adrenals produce in response is measured. In pets with hypoadrenocorticism, both the pre- and post- ACTH cortisol concentrations are usually less than 1 µg/dL, with some references stating that under 2.5 µg/dL is diagnostic.

TREATMENT

An adrenal crisis is an acute medical emergency and requires the staff to work quickly in order for the patient to have the best chance of survival. Patients may present weak, ataxic, shaking, non-responsive and in shock. Dealing with the Addisonian crisis requires treating the patient's shock. Focus should be on treatment the hypotension and hypovolemia.

A short, large gauge intravenous (IV) catheter should be placed and fluid therapy started. Since the patient is usually hypotensive and vasconstricted blood should removed from the IV catheter once it is placed as subsequent venipuncture may prove challenging. If hypoadrenocorticism is suspected then 0.9% sodium chloride (NaCl) should be considered choice because it offers a higher amount of sodium and lower amount of potassium compared to other isotonic crystalloids (Lactated Ringer's solution (LRS), Normosol-R (Norm-R)). Any balanced isotonic crystalloid is an acceptable fluid choice in most Addison's disease patients.

Patients with severe hyperkalaemia (severe bradycardia, ECG abnormalities), should be given regular insulin and dextrose to help decrease serum potassium levels. Calcium gluconate can also be given. While it does not decrease serum potassium levels it does protect the heart against the effects of hyperkalaemia. Typically these treatments are not needed as serum potassium is usually lowered fast enough through the dilution effects from the IV fluids.
Bicarbonate therapy is usually not necessary as the metabolic acidosis is usually mild. However, if the bicarbonate level remains less than 12 mEq/L even after fluid resuscitation, the bicarbonate administration should be considered.

If the patient is stable or after they are stabilized the focus should shift to providing glucocorticoid replacement. All glucocorticoids react with the ACTH stimulation test except dexamethasone. Ideally blood for the ACTH test should be performed before glucocorticoids are given. If the patient is not stable before the ACTH test can be completed then dexamethasone sodium phosphate should be given IV. Dexamethasone is long acting, about thirty times more potent than hydrocortisone, but offers no mineralocorticoid activity.

If the pet is stable enough for the ACTH test to be completed then prednisolone sodium succinate is the glucocorticoid of choice. Prednisolone is a glucocorticoid that has some mineralocorticoid activity. Some suggest hydrocortisone sodium succinate be administered instead of prednisolone because of its combination of mineralocorticoid and glucocorticoid activities. Hydrocortisone has only 25% of the glucocorticoid potency of prednisolone, but offers more mineralocorticoid effects than prednisolone.

Other treatments should be tailored to the pet's condition. Patient may need to be started on dextrose supplementation if they are hypoglycaemic. Antibiotics should be considered in patients with severe melena or hemorrhagic diarrhoea. Antiemetics can be administered to help combat nausea and vomiting. Colloids may need to be administered in patients with hypoalbuminemia and hypotension.

**NURSING CARE**

Patients should be monitored for signs that they are not responding to the glucocorticoid therapy. This may include weakness, lethargy, anorexia, vomiting, ataxia, hypotension and/or tachy- or bradycardia. Physical exam parameters (heart rate, pulse, respiratory rate, effort, mucous membranes, capillary refill time) and blood pressure should be checked every 2-6 hours depending on how critical the pet is. If the patient was experiencing ECG abnormalities then they should be placed on continuous ECG monitoring or have periodic ECG checks minimally every hour or two.

- Pets should be weighed twice a day to monitor rehydration. Urine output should also be monitored to ensure the kidneys are functioning properly as well as for fluid therapy. Due to the severity of dehydration urine output may be lower than volume input because until the pet is adequately hydrated.
- Blood pressure is extremely important in hypoadrenocorticism patients and should be monitored minimally every 4-6 hours. Normalization of blood pressure, defined by a of MAP of 80-120 mmHg or systolic between 110-160 mmHg, is goal.
- Electrolytes, renal function and glucose should be all monitored regularly to assess the response to the glucocorticoid therapy.

Lastly it is important that patients must be given appropriate nutrition. Nurses need to tempt patients to eat and alert the veterinarian if the patient is nauseas or experiencing vomiting.

**LONG TERM CARE**

With diligent monitoring by the owner and appropriate medication hypoadrenocorticism has a good prognosis. Therapy is required for life and dosage may need to be altered throughout the pets lifetime.

Patients will need to be given both mineralocorticoid and glucocorticoid supplements the rest of their lives. Oral prednisone or prednisolone is the glucocorticoid treatment of choice in both dogs and cats. In the United States the options for mineralocorticoid therapy are fludrocortisone acetate or doxycorticosterone pivalate (DOCP). If available, the most economical option is DOCP (Percorten®-V, Novartis) which requires the pet to have an injection every 21-30 days. It does not have any glucocorticoid activity. Almost all dogs on DOCP require prednisone at least every other day. Both DOCP and fludrocortisone should be tapered to effect.

**HYPERADRENOCORTICISM**

**SIGNS/SYMPTOMS**

Hyperadrenocorticism is a chronic disease process. Signs/symptoms occur because of the long term high doses of the naturally occurring corticosteroids. While signs rarely, if ever, cause an emergency for the pet, they do play a role in decreasing the quality of life.
Appetite is often increased as a result of either the increase in corticosteroids or the damage caused directly to the hypothalamic appetite center as in the case caused by neoplasia. Owners will often report their pets as ravenous and pets who normally do not ingest foreign material or raid garbage cans may start doing so. Approximately 80-85% of pets will display polyuria and polydipsia. This often leads to pets having accidents in the house which frequently prompts the owner to bring them in for a veterinary consult.

Pets will develop muscle weakness due to the high cortisol levels which, in turn, weakens the muscle of the abdomen until they start to atrophy. This results in abdominal distension, curving of the spine (lordosis) and muscle trembling. The liver will increase in size due to the increase deposits of lipid and glycogen into the liver which adds to the increase in abdominal size and distension.

Pets with Cushing's will often be poor healers and have skin disease. Cushing's should be suspected in pets that have poor hair growth, balding, thin skin and pyoderma. The skin disease is often a result of the catabolic action of excessive cortisol which causes certain proteins, such as collagen and elastin, to be molecularly changed.

While rare, cats will often develop the same symptoms as dogs. However, only 10% of dogs with Cushing's disease develop diabetes mellitus while 80% of cats will develop diabetes mellitus.

Approximately 80% of dogs will develop hypertension. Despite treatment approximately 40% remain hypertensive despite adequate control Cushing's disease. If the hypertension is significant treatment should be considered.

Rarely pets will develop respiratory changes which can include tachypnea and even more rare, pulmonary thromboembolism. The thought is that the increase in abdominal fat, generalized weakened muscles (including respiratory muscles) and enlarged liver can all lead to respiratory disturbances. Pulmonary thromboembolism may occur due to the decrease level of antithrombin III and the increase of several other factors and fibrinogen.

**DIAGNOSIS**

A sterile urine culture should be obtained and submitted to a laboratory for a urinalysis and culture. Most commonly dogs with Cushing's disease have a lower urine specific gravity of less than 1.020. The exact cause of the dilution is unknown, but it is suspected it's due to cortisol's effect on the antidiuretic hormone. Approximately 50% of dogs will have a urinary tract infection.

A urine cortisol and creatinine ratio (UC:CR) has been found to be a good screening test for dogs because it requires just a free catch urine. Stress can cause false elevations in urine cortisol levels so owners are often instructed to catch samples at home. Because there are numerous other diseases that can cause elevations in UC:CR it is more important to note that a negative test can be good in helping to rule hyperadrenocorticism out. An elevated test will need further testing to diagnose the cause of the elevation.

The most common tests that truly diagnosis hyperadrenocorticism are the ACTH stimulation test and the low dose dexamethasone suppression test (LDDST). Neither test is 100% specific and therefore incorrect diagnoses can occur when running either test. It is important, therefore, that the test results are looked at with the full diagnostic picture.

The LDDST (sensitivity 95%) is based on the negative feedback system between the pituitary and adrenal glands. In normal dogs, the administration of dexamethasone will cause the pituitary gland to decrease its secretion of ACTH which, in turn decreases the release of cortisol. In pets with Cushing's, there will be no change in the level of cortisol after the administration of dexamethasone. To perform an initial blood sample is taken as a baseline. Dexamethasone is administered at a usual dose of 0.01 mg/kg of IV. Post administration samples are drawn at 4 and 8 hours, though many references suggest that just an 8 hour post is necessary. Obtaining a 4 hour allows for more information. The LDDST test will not be accurate in where iatrogenic hyperadrenocorticism is the cause may be falsely positive or negative. The LDDST is the test of choice for diagnosing feline hyperadrenocorticism thought the test is performed using a higher dose of dexamethasone (0.1 mg/kg IV).

Much like diagnosing hypoadrenocorticism, the ACTH stimulation test can be performed to diagnose hyperadrenocorticism. If sample results come back with the post-ACTH 18–22 μg/dL it is possibly Cushing's. Samples with post-ACTH >22 μg/dL are consistent with Cushing's. Studies have shown this test to be between 73-95% sensitive.

Even after blood tests it may be necessary to perform a high-dose dexamethasone suppression (0.1mg/kg IV), endogenous ACTH concentration and/or abdominal ultrasound to discriminate between PDH and ATH. Abdominal ultrasonography is very beneficial in helping to determine the cause of hyperadrenocorticism. In one study of 71 dogs with adrenal tumors approximately 86% of the cases were diagnosed correctly. Computer tomography is better at diagnosing and evaluating adrenal glands, but it is not 100% accurate either due to the size of the tumor and/or adrenal glands.
TREATMENT

Ultimately treatment is based on the cause of the hyperadrenocorticism. Pets that are treated appropriately live long productive lives. Ultimately the treatment is based on the severity of the disease, cost/affordability and owner compliance.

Mitotane (Lysodren) is the most common treatment for hyperadrenocorticism in dogs. It is a derivative of an insecticide and works by causing necrosis in two out of the three layers of the adrenal glands that release glucocorticoids. Mitotane can be used to treat either PDH or ATH. There are two phases: Induction and Maintenance. After the initial induction phase ACTH levels are rechecked to see how the pet is responding to the medication. Pet owners should watch for signs of anorexia, diarrhea, vomiting, lethargy and weakness. These signs occur due to the rapid decrease in serum cortisol levels. Owner should contact their veterinarian immediately if they notice these signs. Approximately 25% of dogs may exhibit signs. Adverse effects of mitotane include GI upset, hepatotoxicity, CNS toxicity, and development of transient or permanent decrease in cortisol production.

For pets with PDH an adrenalectomy may be considered if they did not respond well to medical management. Post surgery replacement glucocorticoid and mineralocorticoid therapy is begun and continued lifelong. A pet with an adrenal tumor may require surgery unless it is nonresectable. Adrenalectomy is the preferred treatment of ATH because it offers a potential cure. On average survival times have ranged from 2 months to more than 3 years. If complete surgical resection of a solitary pheochromocytoma is performed a cure may be achieved. Mitotane may be used in patients with ATH in lieu of surgery or until surgery is performed. Pets with other underlying disorders (clotting disorders, diabetes) are not surgical candidates. Pets undergoing an adrenalectomy need preoperative work up that includes bloodwork and radiographs. Corticosteroids should be administered before and after surgery and if both adrenals were removed then glucocorticoids and mineralocorticoids will need to be administered for the life of the pet. Post operatively the pet needs to be closely monitored with particular attention to electrolytes (sodium and potassium) occuring.

Trilostane, a synthetic inactive steroid, has also been successfully used to treat hyperadrenocorticism by blocking the production of cortisol, aldosterone and sex hormones. There is less literature and studies regarding trilostane and therefore, it is not used as commonly as mitotane. That being said it is thought to be comparable to mitotane with regards to efficacy. An initial dose is usually given and recheck ACTH levels are performed. The pets response to decreasing cortisol levels are monitored the same as when giving mitotane. ketoconazole is an antifungal agent that works to decrease cortisol levels by inhibiting the enzymes needed for glucocorticoid synthesis. Unlike mitotane and trilostane, ketoconazole may cause a change in coat color. Rare reported side effects include transient decreases in cortisol levels, GI upset, and hepatotoxicity. It is administered indefinitely unless side effects are noted or it is not considered effective.

CONCLUSION

As a veterinary technician it is important to understand signs, testing and treatment options for adrenal disease. Often times owners dismiss may signs as "old age" or "they are just a little off" not realizing the can help improve their pet's quality of life. Ultimately if owners are diligent pets with adrenal disease can live long productive lives with treatment. Being able to talk to owners about the disease and treatment will help improve owner compliance and understanding which will help to improve the pet's prognosis.

References Available Upon Request