ACUTE PRIMARY HYPOADRENOCORTICISM IN A YOUNG MALE BASSET HOUND:

A CASE REPORT

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INTRODUCTION

Hypoadrenocorticism, also known as Addison's disease, is a rare illness with no known natural recovery.[7] It is reported in 0.36 to 0.5% of canines, and even more uncommonly in the feline patient.[4] Clinical disease is apparent when over 85% of the adrenal cortex, the outside layer of the adrenal gland, is abolished.[7] This results in almost complete absence of glucocorticoids and mineralocorticoids, which are essential for the body to function.[7] In 1855, Thomas Addison first discovered the disease in humans.[4] He noted atrophy of adrenal glands during autopsies and suspected this adrenal atrophy as the cause of death.[4] Hypoadrenocorticism was first described in canines in 1953, but was not fully understood or studied until the 1970's and 1980's.[4] The purpose of this report is to describe the presentation, diagnostic plan, treatment, and outcome in a canine patient that presented in acute Addisonian crisis.

HISTORY AND PRESENTATION

Tucker, a one-and-a-half-year-old male neutered Basset Hound, presented to MSU-CVM Internal Medicine department for vomiting, inappetence, and lethargy on October 27th, 2016. He was referred for a gastrointestinal work up after having a history of intermittent vomiting and drinking copious amount of water. On October 17th, 10 days prior to admission, Tucker began vomiting constantly. He presented October 21st, four days later, to his referring veterinarian, but his vomiting seemed to resolve, so he was discharged and received his annual vaccinations. That weekend he began to vomit again and became acutely inappetent. On October 26th, Tucker was taken back to his referring veterinarian and was given intravenous fluids, maropitant citrate, and

ampicillin/sulbactam injectable. His lethargy did not resolve overnight, so a complete blood count, chemistry, urinalysis, and abdominal radiographs were obtained the next day. Most notably on chemistry were altered electrolytes and elevated kidney values. Abdominal radiographs revealed gas bubbles within a mid-abdominal loop of bowel. Due to the deteriorating condition of Tucker and a potential intussusception or foreign body, he was referred to MSU-CVM for further care.

On initial examination, Tucker was lethargic and dull. His vital parameters revealed a moderately elevated heart rate (156 bpm). His mucous membranes were brick red with a brisk refill time of less than one second. His abdomen was tense upon palpation and firm popliteal lymph nodes were noted. Tucker was estimated to be approximately 7% dehydrated and in hypovolemic shock. His systolic blood pressure upon presentation was 50 mmHg, so he was given multiple fluid boluses until his blood pressure returned into normal range.

Blood work from the referring veterinarian was not available until Tucker's arrival. His complete blood count revealed a mild neutrophilia 16.27 K/ul (2.0-12.0 K/ul). His chemistry revealed an elevated BUN 84 mg/dL (7-27 mg/dL), creatinine 2.6 mg/dL (0.5-1.8 mg/dL), phosphorus 12.6 mg/dL (2.5-6.8 mg/dL), and potassium 8.3 mmol/L (3.5-5.8 mmol/L). His chemistry also revealed a decreased sodium 131 mmol/L (144-160 mmol/L) and chloride 99 mmol/L (109-122 mmol/L).

Based on his clinical picture and blood work, Addisonian crisis was extremely suspicious as a diagnosis. Tucker was administered an anti-inflammatory dose of dexamethasone shortly after arrival. An ACTH stimulation test was performed, revealing a baseline cortisol of less than 1 ug/dL and a post-stimulation cortisol of less than 1

ug/dL, which is indicative of hypoadrenocorticism. Once stabilized, Tucker had an abdominal ultrasound performed that revealed bilaterally small adrenal glands and enlarged abdominal lymph nodes, most consistent with reactive lymph nodes due to recent vomiting.

Tucker was monitored for additional signs of circulatory shock and stabilized in ICU with intravenous fluids, gastroprotectants and antiemetics (ondansetron, pantoprazole, Cerenia), and steroids (dexamethasone). He received his first Desoxycorticosterone pivalate injection the next day, October 28th. He was then transitioned over to oral medications once his appetite returned. Tucker had a small amount of diarrhea on October 29thand was initiated on oral antibiotic therapy (metronidazole). At the time of discharge, he had a good appetite with a small amount of loose stool and was instructed to recheck electrolytes in two weeks.

PATHOPHYSIOLOGY

The adrenal cortex consists of three layers: the zona glomerulosa, the zona fasciculata, and the zona reticularis. The cortex secretes glucocorticoids and mineralocorticoids, which are necessary for several body functions.[3] Glucocorticoids have many effects throughout the body system, which is why they are important for homeostasis.[3] They help to maintain blood pressure, encourage gluconeogenesis, and enhance catabolism of protein and fat.[3] In addition, they are essential for digestion and absorption of nutrients.[3] Mineralocorticoids help to secrete potassium and absorb sodium in multiple organ systems.[3] Therefore, destruction of the adrenal cortex is life threatening. All three cortical layers secrete glucocorticoids, most importantly cortisol,

but only the zona glomerulosa, the outermost layer of the cortex, secretes mineralocorticoids and contains aldosterone synthase.[3] Aldosterone is vital to the body as it is important sodium, potassium, and body water homeostasis.[7] It is a key factor in the renal regulation of sodium and water resorption and potassium excretion.[7] Not only does aldosterone target the kidneys, but also the mucosa of the intestine, salivary glands, and sweat glands.[7]

Aldosterone secretion is controlled by the renin-angiotensin system, which is associated with the juxtaglomerular apparatus of the kidney. Juxtaglomerular cells act as very small pressure transducers.[3] When there is decreased renal blood flow, decreased glomerular filtration rate, or hypotension caused by decreased volume such as hemorrhage or diuretics, juxtaglomerular cells make and secrete renin, which in turn converts angiotensinogen to angiotensin I.[3,12] Angiotensin I is then converted into angiotensin II by angiotensin converting enzyme in the lungs.[3,12] Angiotensin II acts as a vasoconstrictor and is the main stimulant, along with high potassium levels, for the secretion of aldosterone.[12] Aldosterone secretion is suppressed by sodium retention due to a large amount of aldosterone, which under normal circumstances maintains a normotensive state.[12] With adrenal insufficiency, aldosterone is not secreted. Consequently, sodium and chloride cannot be conserved, and potassium cannot be excreted.[4]

Canine hypoadrenocorticism can be divided into primary and secondary categories. Over 95% of cases are primary, which are generally caused by immune-mediated destruction of the adrenal cortices.[3,12] Other types of primary hypoadrenocorticism are caused by bilateral adrenal neoplasia, fungal diseases,

coagulopathy, infarction, and iatrogenic destruction due to treatment of hyperadrenocorticism with mitotane or trilostane.[3,12] It can also be caused by abruptly stopping chronic glucocorticoid therapy.[3,12] Primary hypoadrenocorticism can be further classified as typical or atypical. Typical refers to the classic presentation with destruction of glucocorticoids along with mineralocorticoids, causing electrolyte abnormalities. Up to 30% of dogs with primary hypoadrenocorticism can have normal electrolyte levels, and have been referred as atypical in character.[3] However, currently it is more commonly thought that these canines are being diagnosed before complete destruction of the zona glomerulosa.[3] Secondary hypoadrenocorticism is due to reduced excretion of ACTH from the pituitary gland, and is much less common.[3] Loss of ACTH causes atrophy of the zona fasciculata and the zona reticularis, and eventually results in lack of glucocorticoids.[3, 12]

Most commonly affected breeds are crossbred canines; however, there are certain overrepresentations of breeds and some with a genetic predisposition in certain family lines.[2] Breeds with an increased risk include the Airedale Terrier, Basset Hound, Bearded Collie, Great Dane, Nova Scotia duck tolling retriever, Portuguese water dog, Rottweiler, Saint Bernard, Springer Spaniel, Standard Poodle, West Highland White Terrier, and Wheaten Terrier.[3] Standard poodles represent 10% of affected canines.[2] Portuguese water dogs and bearded collies are also predisposed.[2] Specific lines of Pomeranians, Nova Scotia duck tolling retrievers, soft-coated wheaten terriers, and Leonbergers have been reported to have familial hypoadrenocorticism.[2] A study performed on Portuguese water dogs established that the more inbred the canine, the more likely they were to have hypoadrenocorticism.[10] Another study showed that the Portuguese water dog inherits the disease through autosomal recessive genes.[10] Further research is still needed to

understand the overlap between genetics, breed disposition, and genetic susceptibility.[2] Approximately 70% of affected dogs are female, but no female prevalence has been reported in Standard poodles, Nova Scotia duck tolling retrievers, Bearded collies, or Portuguese water dogs.[3] The average age of onset is approximately 4 years with a large range of 4 months to 14 years[11]. The Nova Scotia duck tolling retriever has a slightly shorter median age of onset 3 years, and this breed has 10 times greater chance of suffering hypoadrenocorticism than other breeds.[6]

DIAGNOSTIC APPROACH AND CONSIDERATIONS

Clinical signs can vary wary from acutely ill to waxing and waning symptoms.[3] History of gastrointestinal upset such as vomiting, and diarrhea, lethargy, weakness, shaking, and abdominal pain can be observed in primary or secondary hypoadrenocorticism and involve glucocorticoid deficiency.[3] Symptoms such as polyuria, polydipsia, hypovolemic shock, and dehydration involve mineralocorticoid deficiency, indicating typical primary hypoadrenocorticism.[3] These signs are typically more pronounced.

Classic biochemistry changes in the Addisonian patient varies, but generally include hyponatremia, hyperkalemia, and azotemia.[12] A hallmark finding is a sodium: potassium ratio <27, but this does not definitively rule in or out hypoadrenocorticism.[4] Hyponatremia and hyperkalemia are due to aldosterone deficiency.[12] Since aldosterone helps with the reabsorption of sodium and water, patients with hypoadrenocorticism are frequently dehydrated or hypotensive.[12] Because aldosterone encourages the excretion of potassium and hydrogen ions in the distal renal tubule, patients suffer not only from

hyperkalemia but also from acidosis due to the reabsorption of hydrogen ions reabsorption.[12] In total, these disturbances lead to dehydration, hyponatremia, hyperkalemia, and metabolic acidosis.[12] Due to decreased renal perfusion and glomerular filtration rate, prerenal azotemia is commonly seen.[12] Due to the hyponatremia, urine specific gravities are often decreased and cannot be used to fully determine renal function.[12] Therefore many Addisonian patients have a low specific gravity, despite being dehydrated.[4] Other chemistry findings include hypochloremia, hypophosphatemia, and hypercalcemia.[3] Hypocholesterolemia, hypoglycemia, and elevated liver enzymes have also been reported.[3] Most notably, hypoglycemia can occur because of the decreased gluconeogenesis caused by the lack of glucocorticoids.[3]

Classic hematologic findings include a nonregenerative, normocytic normochromic anemia, along with an eosinophilia, neutrophilia, and lymphocytosis.[3] The anemia is generally mild to moderate with a hematocrit range of 20-35%.[3] This is attributed to a decrease in red cell production because of a deficiency in cortisol.[3] Gastrointestinal bleeding can also attribute to this anemia.[3] A hallmark finding on a complete blood count is an absence of a stress leukogram, which would typically be present in a normal ill patient.[3] This is due to the lack of cortisol being produced by the adrenals.[3]

Electrocardiography findings are due to hyperkalemia, and can cause the heart to become bradycardic and eventually end in cardiac arrest if not treated.[3] The plasma potassium determines the severity of electrocardiogram changes.[3] Mild hyperkalemia at a level of 6.0 to 7.0 mEg/L causes the T waves to peak and to shorten the QT interval.[3] The PR interval prolongs and the QRS complex widens over 7.0 mEq/L. At 7.5 to 8.0 mEq/L,

loss of the P wave occurs, and over 10 mEq/L ventricular fibrillation or asystole can occur.[3] Once the hyperkalemia is treated, the abnormalities present on the ECG should correct themselves.[3]

The gold standard of definitive diagnosis of hypoadrenocorticism in the dog is the adrenocorticotrophic hormone (ACTH) stimulation test.[4] Serum cortisol concentrations are measured before and after administering ACTH. A baseline sample is acquired before giving ACTH, and a second blood sample is acquired 1 to 2 hours after, depending on the formulation of ACTH used.[8] This demonstrates the ability of the zona fasciculata and the zona reticularis to produce cortisol when stimulated.[8] The most common formulation of ACTH for testing is a synthetic form, 1-24-corticotropin (cosyntropin).[4] Other formulations include corticotropic gel preparations from purified porcine pituitary.[8] Synthetic ACTH only contains the active amino acids (1-24), while the purified contains all 39 amino acids.[8] A previously suggested dosage for this product is 250ug/dog, or one vial.[4] A 2008 study by Lathan, et al. determined that giving 5ug/kg of ACTH will accurately diagnose hypoadrenocorticism affected dogs from normal dogs.[9] This can decrease costs for the owner. Basal cortisol concentrations are an excellent screening test for hypoadrenocorticism, but cannot definitively diagnose it.[1] It is an excellent method to exclude hypoadrenocorticism, and can be done with a concentration of greater than 2.0 ug/dL.[3]

While there is no reported difference in plasma cortisol levels when administering synthetic ACTH IV or IM in normal dog, IM absorption may be delayed in acutely dehydrated dogs presenting in Addisonian crisis, and IV injection is the route of choice.[11] Cosyntropin is able be stored in small aliquots in the freezer for up to 6 months and still

be effective, making it an ideal drug for private practice.[5] A single baseline cortisol is not definitive to confirm hypoadrenocorticism due to the fluctuation of levels throughout the day and well as the fact that it does not take into account adrenocortical reserves.[4] ACTH stimulation tests are also the gold standard of diagnosing secondary hypoadrenocorticism, but if the disease is due to iatrogenic causes such as administration of exogenous corticosteroids, the test may have to be delayed until the adrenal axis can recover.[3] This can vary from 48 hours to 8 weeks depending on the glucocorticoid and length of time administered.[3]

TREATMENT AND MANAGEMENT

It is important to treat aggressively when presented with a dog in Addisonian crisis. Generally, they are hypovolemic and dehydrated, with a low blood pressure, extreme electrolyte disturbances, and acid-base abnormalities.[8] Blood pressure, ECG, PCV, and electrolytes should be monitored closely until the patient is stabilized. Fluid therapy is essential as it helps with correcting shock and diuresis of potassium by improving renal blood flow[1]. 0.9% sodium chloride is the ideal crystalloid of choice due to the fact it will decrease hyperkalemia by dilution as well as correct hyponatremia and correct a metabolic acidosis.[8] If a bradyarrhythmia is present due to an extreme hyperkalemia, a 0.2 U/kg of regular insulin can be given and followed with a bolus of dextrose.[8] Insulin will drive the potassium back into cells and will lower the serum level.[8] If presenting in crisis with the above manifestations, dexamethasone at 0.1-2.0 mg/kg IV may be given before completing the ACTH stimulation test as it does not react with the

cortisol assay like prednisone does, while still providing a beneficial source of glucocorticoid that the adrenal cortices are lacking.[1.3]

Maintenance therapy of primary hypoadrenocorticism is life long and vital for survival. It requires consistent supplementation of glucocorticoids and mineralocorticoids such as prednisone and Desoxycorticosterone pivalate (DOCP), respectively.[12] Most veterinarians use prednisone or prednisolone at a dose of 0.1-0.2 mg/kg/d.[12] Physiologic doses (0.22 mg/kg) of prednisone should be given twice daily to begin with, and then tapered down to once daily.[8] If side effects such as polyuria, polydipsia, panting, and increased appetite are apparent, doses can be reduced with careful monitoring or switched to methylprednisone or dexamethasone.[8,12] Those signs are consistent with iatrogenic hyperadrenocorticism.[12] Also, when owners anticipate stress in their Addisonian dog, increased doses of glucocorticoids can be used at 2-10 times normal range to prevent crisis.[12]

Dogs with evidence of electrolyte abnormalities should be treated with mineralocorticoids such as DOCP or fludrocortisone.[3,12] DOCP needs to be given during acute crisis, but generally after the confirmation of diagnosis.[3,12] DOCP, also known as Percorten V, is the only drug approved by the FDA for canine hypoadrenocorticism.[3,12] It can be administered intramuscularly or subcutaneously.[3,12] It is effective within hours of administration at a starting dose of 2.2 mg/kg every 25 days.[3,12] It is recommended to recheck electrolytes every two weeks after the first DOCP injection for 1 to 2 months to monitor the frequency and dosage needed.[8,12] If warranted, the dose can be dropped by 10% each month while monitoring electrolytes.[8] Once stabilized, bloodwork frequency can decrease to two to four times a year.[8] Fludrocortisone (Florinef) is an alternative type

of mineralocorticoid and is given orally.[8] The beginning dose is 0.02 mg/kg once daily, and since it has some glucocorticoid activity, prednisone may not be needed.[8]. Dosage may need to be increased with time due to a possibility that the gastrointestinal tract does not absorb the drug as well as humans, who generally require a lower and constant dosage.[3] Because of this, it is hard to obtain a correct drug dosage for dogs, so it is not as popular among clinicians as DOCP.[8] Long term prognosis is excellent with proper medical management and care. Unfortunately, the monthly cost of DOCP is expensive and is currently approximately $180 for a 25mg/ml 4 ml vial.

CASE OUTCOME

Once stabilized with fluid boluses and dexamethasone, Tucker brightened immediately. Tucker recovered well from his Addisonian crisis and was discharged with transient diarrhea after a five-day hospital stay. The day after diagnosis, he began eating and was placed on DOCP and prednisone for long term maintenance therapy as well as Cerenia, omeprazole, and metronidazole. His transient diarrhea was most likely due to his cortisol deficiency. It resolved with prednisone and metronidazole. He was directed to have his electrolytes rechecked with the referring veterinarian in two weeks and then again in four weeks and to call with any questions.

CONCLUSION

Canine primary hypoadrenocorticism occurs when 85-90% of the adrenal cortices are destroyed, generally by immune-mediated destruction, and the body has a depleted supply of glucocorticoids and mineralocorticoid that are necessary for the body to

function.[12] Left untreated, hypoadrenocorticism in dogs is fatal. Prognosis is generally excellent with correct mineralocorticoid and glucocorticoid therapy.[3] Median survival time for these patients once stabilized are an average of 5 years.[3] Owner compliance and finance are the largest issues with the treatment of this disease.[3] Treatment is generally well tolerated and straightforward, and owners must be made aware that dosages of glucocorticoids must be increased in times of stress. The genetic impact of this disease is not completely understood and is still being studied.

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