ADRENAL GLAND DISEASE (HYPERADRENOCORTICISM)

The pathophysiology of adrenal gland disease in ferrets is significantly different from that in domesticated animals known as Cushing’s disease and therefore it should not be called Cushing’s disease in the ferret. Adrenal gland disease is considered the second most common disease in the ferret after insulinoma. While several different hypotheses regarding the etiology of ferret adrenal disease have been put forward in the literature, it appears that there is a direct link between the early age of neutering and the onset of this disease. The difference between the ferret adrenal disease and the typical Cushing’s presentation and pathophysiology, is the fact that, in the ferret, the adrenal cortex does not produce significant levels of cortisol from the zona fasciculata, and instead the tumor produces a significant increase of the sex steroids produced by the zona reticularis. The sex steroids that are usually elevated are estradiol, 17-hydroxyprogesterone, testosterone and androgestosterone. These hormones can be measured in the blood. The University of Tennessee offers this test. (contact Dr. Jack Oliver at joliver@utk.edu). Besides as a primary diagnostic tool, this test can also be a useful aid in the differentiation between a seasonal shed and the disease.

The primary clinical signs in ferrets are directly related to the increase of these sex steroids in the blood resulting in estrogen toxicity. Enlargement of the vulva in females, prostatic enlargement, prostatitis and cystitis in males, as well as alopecia and pruritus are all extremely common clinical signs. If the elevation of the estrogen precursors are allowed to continue for a prolonged period of time, anemia will often follow and it usually non-regenerative, because the bone marrow undergoes fatty degeneration.

At Tufts University we use abdominal ultrasound exam as the primary tool for the diagnosis of the disease. The clinical signs of the animal have no direct correlation with the size of the gland. It is not an uncommon scenario to be presented with an animal with severe clinical signs and neither of the adrenal glands are physically enlarged or appear abnormal to the naked eye of the surgeon. In this case it is extremely difficult to decide which gland should be surgically removed. An ultrasound exam can evaluate this situation before the animal is presented for the surgical procedure.

In the case where neither of the adrenal glands are enlarged, the owner is advised to start with the medical treatment of the disease and to repeat the ultrasound exam in 3 months. If one of the glands is mildly larger than before, even if still within normal limits, surgical removal of this gland is then recommended. It is important to submit the removed tissue for histopathological evaluation in order to document the pathological nature of the tissue to the client and to differentiate the degree of pathology of the tissue in order to provide the owner with a realistic prognosis of expected recurrence. Histologically the lesion of the adrenal gland can be differentiated as benign hyperplasia, adenoma or carcinoma.

MEDICAL TREATMENT

Medical treatment of the condition can be achieved with monthly injections of Lupron® (leuprolide acetate) at 0.1 mg/animal if less than 1 kg, and 0.2 mg/animal if over 1 kg of bodyweight. The drug is considered a GnRH superagonist and will stop the production of LH and FSH due to negative feedback from persistent stimulation of the hypophysis. This process is call “desensitization.” This treatment should be done monthly for at least three months. It is then potentially possible to reduce the frequency of injections depending on the clinical signs, however, continuation of the monthly injections can be recommended. The advantages of this treatment choice are obvious, it is both non-invasive and relatively inexpensive. Each injection costs the client approximately $30-50. However, there are disadvantages which also need to be explained to the owner before treatment is started. This treatment does not interfere at all with tumor growth. It only affects response to the hormones and does not affect cell growth. In addition, these treatments need to be lifelong, and so in the long run, this option may end up being as expensive as surgical removal of the diseased tissue. It has also been noted that a ‘resistance’ seems to develop over time and higher doses are needed in order to control the clinical signs. In rare cases the adrenal gland will produce hormones independent of LH and FSH regulation, in these cases the lupron treatment is completely ineffective.

The second option for medical treatment is the use of melatonin to suppress the hormone release. Melatonin is a hormone which is normally released during the dark phase of the day by the pineal gland. It directly inhibits GnRH release and therefore suppresses LH and FSH production. The importance of the pineal gland and its influence on gonadal activity has been validated as long as 30 years ago in the ferret. Melatonin treatment is done using a commercially available melatonin implant that can be injected under the skin, similar to a microchip, which will release enough melatonin for three months. The implant can be ordered through Melatek (www.melatek.net or 1-877-MELATEK) and the cost to the owner is similar to the cost for the lupron treatments. Melatonin has been reported to be extremely effective even in cases where lupron treatment did not produce a satisfactory response.
Melatonin also appears to be very safe and can be used in combination with other drugs including lupon.

**SURGICAL APPROACH**

The surgical approach is always a treatment possibility with its goal removal of the pathological gland. Against popular belief, it is possible to remove both adrenal glands at the same time without creating significant hormonal problems. It is best to medicate these animals with dexamethsone (1mg/kg IM) during post-op recovery, and then to continue medication with oral prednisone (1 mg/kg SID PO) for a few weeks. Supplementation with glucocorticoids is usually not needed with unilateral removal of the gland.

The owner should always be informed that it is possible for the disease to recur even if both adrenal glands have been removed. As mentioned above, the excised tissue should be submitted for histopathological evaluation in order to differentiate between hyperplasia, carcinoma and adenoma. This will help in discussions of the long-term prognosis with the owner.

An interesting new surgical approach has been developed in an exotics practice in Italy. Good results are being achieved after alcohol injection into the diseased gland (Selleri, P. pers. comm., 2005). The injection of alcohol into the adrenal and other tumor sites has been used in human medicine and is well published. The treated gland appears to shrink, and this has been documented with abdominal ultrasound examinations. This localized treatment option may provide an exciting new solution to cases where complete excision is not possible. Frequently a tumor of the right adrenal will have invaded significantly into the vena cava making partial resection the only option short of removal of vena cava at this site.

It is important to mention that it is sometimes possible to successfully completely resect the vena cava if it is too badly damaged during removal of the right adrenal gland. Ferrets have many collateral vessels into which blood will be diverted into the vertebral sinuses. Data available indicate that approximately 25% of animals will die during surgery with this aggressive procedure. Survivors must be treated with aggressive fluid therapy for 2-3 days post-op, and renal values should be closely monitored for signs of renal failure due to impaired perfusion.

**SUMMARY**

Adrenal gland disease is one of the easiest diseases to recognize in the ferret due to the striking clinical signs. Care has to be taken not to correlate clinical signs with the physical size of the gland. Only after an appropriate diagnostic workup, should the patient be submitted for surgery. Abdominal ultrasound exams appear to be the most reliable diagnostic tool in order to decide if the disease should be treated medically or surgically.

**References**