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ADRENAL DISEASE (HYPERADRENOCORTICISM)

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OVERVIEW

Adrenal Disease is one of the most common ferret conditions seen in clinical practice. The disease is a result of a tumor or hyperplasia (overgrowth) affecting one or both adrenal glands. Although this condition can occur at any age, it is most common in ferrets over three years old. There are many theories as to the cause of this condition (genetic, environmental, diet, early reproductive sterilization); however, the underlying etiology is still unknown. Increasing evidence points both to early neuter and abnormal/artificial light cycles. In the case of neuter, the sterilization procedure removes the source of sex hormones (estrogens and testosterone), which in turn removes the natural inhibition of the continuous stimulation from the pituitary gland on the adrenal glands, which subsequently produce an excess of the sex hormones. In the ferret, the length of daylight regulates sex hormone production via the pineal gland in the brain. Abnormal light cycles result in a similar constant stimulation as sterilization.

Due to the perpetual stimulation from the pituitary gland in the ferret's brain, the affected adrenal gland produces an excess of sex steroid hormones: estrogen, testosterone, and their precursors. Chronic high levels of these hormones causes the myriad of clinical signs present with this disease. This chronic debilitating disease can greatly affect the ferret's quality of life. Although the growth of the diseased adrenal is usually benign (adenoma or hyperplasia), malignancy (carcinoma) is present in about 25% of the cases.

CLINICAL SIGNS

As a ferret owner or veterinarian, it is important to become familiar with the common clinical signs associated with adrenal disease in the ferret. Some of the symptoms that occur are classic clinical signs and, when present, are highly suggestive, almost diagnostic, of this condition.

It is important to note that although hair loss is the most common and most obvious clinical sign, this disease is not simply cosmetic. This chronic debilitating condition can last for months or years, greatly affecting the ferret's quality of life. Some ferrets may live with this disease for years while others may become incapacitated and/or develop life-threatening complications from this illness within months. We know that ferrets are very stoic animals and, unfortunately for them, they hide their illnesses well.

Alopecia

This is the most common clinical sign that occurs with this condition. The hair loss can occur anywhere on the ferret's body but usually first occurs on the tail, at the base of the tail, tops of the rear feet, and over the shoulder blades. Initially, the hair loss may be subtle, occurring on other parts of the trunk such as the chest. The hair loss is generally bilaterally symmetrical and can initially grow back only to be lost again within a few months. Along with the hair loss, the texture of the skin frequently changes. The skin may be dry and flaky or become thin and have a wrinkled appearance.

Swollen Vulva

In about half of the female ferrets with adrenal disease, high estrogen levels will cause the vulva to swell (vulvar hyperplasia). This occurs normally during the heat period in intact jills and regresses after breeding. In spayed ferrets with adrenal disease, the swelling is not normal and will not resolve until the disease is controlled and excess hormone levels are resolved. Swelling may occur overnight; it may be mild or the vulva may become severely enlarged. A vaginal discharge and infection may accompany the swelling. This is an important clinical sign, because if the estrogen level becomes too high, it may cause life-threatening, but uncommon, bone marrow suppression.

Return-to-Male Sexual Behavior/Aggression

Return-to-male sexual behavior describes neutered male ferrets that begin mounting other ferrets or scent mark territory. The other ferrets may be male or female, intact or neutered. Aggression may be part of this clinical picture. Some of the aggression, which is likely androgen driven (somewhat like "steroid rage"), is most commonly toward other ferrets, but it may be toward people. These ferrets have never previously displayed aggression and suddenly become hostile. This clinical sign is often associated with a high incidence of adrenal carcinomas. Spayed females may also display behaviors seen in intact jills in season.

Straining to Urinate

This usually occurs in male ferrets and is a result of prostate enlargement secondary to elevated androgen levels. A persistent bladder or prostate infection may accompany the straining. Adrenal disease is by far the most common cause of straining to urinate in the ferret. When this sign is present, the prepuce is usually red and inflamed. The straining may be due to a partial or life-threatening complete urinary obstruction. Treat ferrets with this clinical sign quickly since the condition is very painful and complete urinary blockage will rapidly lead to renal failure.

Lethargy

This is a very common clinical sign of ferrets with adrenal gland disease, yet it is not unique to this condition. Although the lethargy may be mild to quite severe, it can come on so gradually that most ferret owners do not think their ferret is lethargic until they see how much more active he/she becomes after the ferret is treated. It is common for owners to mistake the lethargy for "old age." The lethargy may be all the time or as subtle as less time playing with other ferrets.

Muscle Atrophy

Muscle atrophy is common in ferrets with adrenal disease. The muscle loss is usually most prominent over the dorsal pelvis and lateral chest. Although typically mild to moderate, in some cases the muscle atrophy is quite severe.

Pruritis

Itchy skin is not a common clinical sign in ferrets with adrenal disease. However, in some cases, the pruritis is severe and unresponsive to steroids and/or antihistamines. Although the itchiness may be present anywhere on the ferret's body, is frequently on the head, feet, and lateral chest. In severe cases, it may be mistaken for ear mites, fleas, and immune mediated skin disease. Owners may also note excessive grooming.

SURGICAL TREATMENT

Currently, there are two forms of treatment (surgical and medical) available for ferrets with adrenal disease. Of the two options, surgical removal of the affected adrenal gland(s) is still the best treatment for the following reasons:

1. Surgical removal of the diseased adrenal gland offers the best chance for a cure and the longest symptom free survival time.
2. Malignant adrenal tumors occur in 25% of ferrets with hyperadrenocorticism.
3. Not all ferrets will respond to medical treatment.
4. During surgery, the veterinarian will inspect the other organs (including the pancreas) for signs of tumors or concurrent disease and biopsy when indicated.

Since ferret adrenal gland surgery can be technically difficult, it is very important that an experienced ferret surgeon perform the procedure. When the left adrenal gland is affected, surgical removal is often relatively straightforward. In contrast, the right adrenal gland in the ferret is attached to the wall of the vena cava, the largest vein in the body. Aggressive adrenal tumors may invade through the wall into the vessel. The close association with the vena cava makes right adrenal gland removal complicated. Current surgical techniques include excision of the gland, laser, and cryosurgery. With more invasive tumors, it is sometimes necessary to remove a portion of the wall of the vena cava along with the gland. In severely enlarged and invasive right adrenal tumors, surgeons have gone so far as to resect the section of the vena cava attached to the tumor. This is a radical procedure with significant potential for post-operative complications, including acute renal failure and death with fatality rates currently in excess of 25%.

MEDICAL TREATMENT

Several medical protocols exist that use drugs to block the formation of adrenal steroids in the ferret, or block the action of those steroids on target tissues, such as the prostate. Medical therapy may alleviate clinical signs, but it does not stop tumor growth or in any means, cure the disease. Please note that the use of these drugs for adrenal disease is up to the discretion of the veterinarian and the informed client. There is not much long-term data available on the use of these drugs in the ferret and the FDA has not approved these drugs for use in the ferret.

Lupron®

Lupron® decreases the levels of both estrogen and testosterone. It is available as an injectable drug in several forms (short-acting daily injection, 1-month depot, 3-month depot, and 4-month depot). One protocol includes a high dose of Lupron® 4-month depot, which is extremely effective in reversing all of the clinical signs of the disease for four to seven months. The dose is 2 mg/ferret subcutaneously; repeat when clinical signs recur. Others have suggested using lower dosages or shorter acting Lupron® more often. Do not use the short-acting daily form as it is ineffective and may even aggravate the condition.

The drug comes as a powder and diluent, which are mixed together prior to administration. Stability of the 4-month depot form after mixing and freezing appears to be between four and six months.

Currently, a compounding pharmacy will separate the 4-month depot into vials with either 1 or 2 mg of Lupron® and sell the individual dosages to veterinarians (Professional Arts Pharmacy 1-800-832-9285).

A small number of ferrets develop subcutaneous reactions to the injection approximately two to four weeks after administration. A biopsy of the site may reveal inflammation consistent with injection site panniculitis. It is best to leave the swelling alone; it resolves on its own in four to six weeks. Surgical removal of the reaction site also removes the drug. Anti-inflammatory medication may help with resolution and comfort.

Casodex®

Casodex® blocks androgen (testosterone) binding sites in cells. It is an oral drug available as a 50 mg tablet. Casodex® appears to be just as effective as Lupron® in reversing clinical signs including, straining to urinate, aggression, and return-to-male sexual behavior. Most ferrets start to become more active and play more within one to two weeks after starting Casodex®. This drug may be effective for males and females; it just depends upon which hormone the tumor is producing. Pregnant women should not handle Casodex®. Some pharmacies will compound the tablet into a suspension, including the compounding pharmacy noted above. The dose is 5 mg/kg once a day until all clinical signs resolve, then pulse therapy (one week on and one week off) for life. Do not use this drug with Arimidex®.

Arimidex®

Arimidex® blocks the enzyme that converts testosterone to estrogen. It is available as a 1 mg tablet. Overall, it appears to be less effective than Lupron® or Casodex®, but it may be more helpful for some ferrets with adrenal disease. Pregnant women should not handle Arimidex®. The dose is 0.1 mg/kg once a day until clinical signs resolve, then pulse therapy (one week on and one week off) for life. Do not use this drug with Casodex®.

Casodex and Arimidex are not “front line” drugs. Reserve their use for cases that do not respond to GnRH analogs.

Melatonin

Available in both oral and slow-release implant forms, melatonin inhibits the release of GnRH, thereby suppressing formation of LH and FSH. Ferret sexual activity is highly seasonal and relatively dormant during periods of long darkness (winter). Ferrets normally release their own melatonin during the dark phase of the day; consequently, melatonin plays a role in the normal seasonal drop in hormone production in non-neutered ferrets. The implant (similar to a microchip) releases melatonin for three months. Oral dosing is 0.5 to 1 mg once daily in the evening. Published experimental studies with the oral form have shown consistent improvement or resolution of clinical signs for a period of up to a year. In one study, roughly 66% of the ferrets treated with melatonin began to have hair loss again within eight months of the start of therapy. The same study also showed that adrenal gland size continued to increase over time and that melatonin had no effect on preventing the development of adrenal carcinoma. Additionally, though precursor adrenal hormone levels dropped after four months of therapy, some rose above pretreatment levels by the end of the year of the study. The drug seems well tolerated with minimal side effects.

Deslorelin®

Research on Deslorelin®, a GnRH analog (like Lupron®) in a time-release implant, is currently underway. The FDA has not approved Deslorelin® for general use in the United States, and it is only available on a research basis. Two implant sizes are available; a recently published study of the 3 mg implant indicates that Deslorelin® is quite effective at eliminating clinical signs for over a year. As with Lupron®, Deslorelin® does not decrease adrenal tumor growth in ferrets.

GENERAL INFORMATION AND SUGGESTIONS ABOUT MEDICAL THERAPY

1. Although these drugs can effectively block and/or inhibit the production of the hormones that are elevated in adrenal disease alleviating clinical signs, they do not decrease the size of the adrenal tumor or hyperplasia, nor arrest the advancement of the disease. Therefore, surgery is the treatment of choice; reserve medical treatment for ferrets that are not good surgical candidates.
2. Since these drugs offer palliative treatment, use them at the lowest possible dose effective to reverse the clinical signs.
3. Since the information on these drugs is scarce, changes to the suggested protocol and dosing may occur from time to time.
4. Although these drugs may be effective individually, do not use Casodex® and Arimidex® together since the precursor hormones may build up and the clinical signs may worsen.
5. The clinical signs return-to-male sexual behavior and aggression are associated with a high incidence of adrenal carcinoma. In the ferret, adrenal carcinomas rarely metastasize, but they may be locally aggressive. Therefore, when these clinical signs are present, consider surgery, if possible.
6. If surgery is not an option, consider using Lupron® first in ferrets with adrenal disease. If it is unavailable or ineffective, try Casodex®. If there is no response to Casodex®, use Arimidex®, but wait one to two weeks between Casodex® and Arimidex®.

NOTE: An informative link is available for further information
<http://miamiferret.org/fhc/basics.htm>