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ADRENAL DISEASE IN FERRETS

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Overview

Adrenal Disease (AD) is one of the most common ferret medical conditions seen in clinical practice in the United States. 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 often seen in ferrets over three years of age. There are many theories as to the cause of this condition, (genetic, environmental, diet, and early reproductive sterilization); however, a definitive 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 feedback inhibition of the continuous stimulation from the pituitary gland on the adrenal glands, which subsequently produce an excess of sex hormones. In the ferret, the length of daylight regulates sex hormone production via the pineal gland in the brain. Abnormal (long daylight) light cycles result in a similar constant stimulation as sterilization as the brain "assumes" it is breeding season regardless of the time of the year.

Due to the perpetual stimulation from the pituitary gland in the ferret's brain, the affected adrenal gland(s) produces an excess of sex steroid hormones: estrogen, testosterone, and their chemical precursors. Chronic high levels of these hormones cause the myriad of clinical signs present with AD. 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 signs that occur are classic clinical features 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 is a chronic debilitating condition that 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 the coat 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 flakey or become thin and have a wrinkled appearance.

Swollen Vulva

In about half of the female ferrets with adrenal disease, high estrogen levels produced by the adrenal glands will cause the vulva to swell (vulvar hyperplasia). In intact jills this occurs normally during the heat period as elevated estrogen levels are produced by the ovaries and regresses after breeding. In spayed ferrets with adrenal disease the vulvar hyperplasia is not normal and will not resolve until the disease is controlled and excessive 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. Though uncommon, elevated estrogen levels may cause life-threatening bone marrow suppression.

Estrogen produced by the ovaries during the heat period of intact (unspayed) jills will cause vulvar hyperplasia. Vaginal stimulation during breeding induces ovulation and a concomitant drop in plasma estrogen levels, which leads to regression of the hyperplasia. Differentiating vulvar hyperplasia caused by adrenal disease from normal ovarian (heat) vulvar enlargement in unsprayed female ferrets can be accomplished by inducing ovulation with administration of HCG. If the jill fails to respond it is likely that the hyperplasia is adrenal in origin.

Return-to-Male Sexual Behavior/Aggression

Return-to-male sexual behavior describes neutered male ferrets that begin mounting other ferrets or scent marking 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 directed toward other ferrets, but it may be directed towards 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

Seen in male ferrets it is a result of prostate enlargement and squamous metaplasia in the prostatic tissue 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 the sign is present, the prepuce is usually red and inflamed as well. The straining may be due to a partial or life-threatening complete urinary obstruction. Treat ferret with this clinical sign as an emergency 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, but 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.

Puritis

Itchy skin is another clinical sign in some ferrets with adrenal disease. Tragically for the ferret, the puritis in some cases is severe and unresponsive to steroids and/or antihistamines. Although the itchiness may be present anywhere on the ferret's body, it 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. Signs of self trauma in the form of linear excoriations or crusts from scratching may be seen on the trunk.

Posterior Paresis

Another possibly confusing sign of adrenal disease is evidence of posterior paresis, where in the ferret is weak in the rear legs and no longer able to climb or jump, or there is partial to complete loss of rear leg function. Posterior paresis is not restricted to ferrets with AD and is seen in a host of other conditions including heart disease, insulinoma, and lymphoma.

Surgical Treatment

Currently there are two forms of treatment (surgical and medical) available for ferrets with adrenal disease. Depending on the overall clinical picture, surgical removal of the affected adrenal gland(s) may be the best treatment option for the following reasons:

1. Not all ferrets will respond to medical treatment.
2. Malignant adrenal tumors occur in about 25% of ferrets with AD.
3. During surgical exploration, the veterinarian can inspect the other organs (including the pancreas) for signs of tumors or concurrent disease and secure biopsy samples when indicated.
4. Recent data seems to indicate that a combination of surgical and medical therapies offers the best chance for cure and the longest symptom free survival times. In one study, 25-30% of unilateral adrenalectomy ferrets developed signs of adrenal disease 3-18 months post surgery. This is often a result of development of disease in the contra-lateral gland, in ectopic adrenal tissue or incompletely removed tissue from the initial surgical site which can become hyperplastic or neoplastic.

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 dorso-medial 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 technically difficult. 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 ligate and resect a 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%.

As a way to avoid post-surgical adrenal insufficiency (Addison's disease), many surgeons perform a subtotal adrenalectomy technique in order to retain some functional adrenal tissue. However, many ferrets with what appears to be complete bilateral resection of the adrenal glands do not go on to become Addisonian and do not require replacement therapy.

Medical Treatment

Several medical protocols exist using drugs to block the formation of adrenal steroids, block the action of those steroids on target tissues, such as the prostate, or inhibit the chronic stimulation of the adrenal glands by the pituitary. Medical therapy may alleviate clinical signs, but it does not stop tumor growth. Please note that the use of these drugs for AD is up to the discretion of the veterinarian and the informed client. There is not much long-term data available on the use of many of these drugs in the ferret and for most of them, the FDA has not approved their use in this species.

GnRH Super-Agonists

Until recently, no drug was specifically approved for use in ferrets in the United States. Within the last year one product, Suprelorin® (Deslorelin acetate-Virbac) has been approved and has become available to veterinarians in the US without special import restrictions. Until this product became generally available a number of other medications were used to manage AD. The best known of these is Lupron® (Leuprolide acetate-Tap).

Lupron ®

Lupron® decreases the levels of both estrogen and testosterone through tonic stimulation of the pituitary gland resulting in down regulation of FSH and LH secretion. It is available as an injectable drug in several forms (short acting daily, 1-month depot, 3-month depot, 4-month depot). One protocol includes using a high dose of Lupron 4-month depot®. In those cases of AD which respond to this type of drug the protocol is highly 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. Other clinicians have suggested using lower dosages in the range of 100 ug to 200 ug/ferret. Do not use the short-acting daily form as it is ineffective and may even aggravate the condition.

The drug comes in the form of a powder and diluents which are mixed together prior to administration. Many veterinarians will reconstitute and divide the stock bottle into separate aliquots and freeze the doses for use at a later time. No hard data exists regarding the stability of the product when frozen and the manufacturer (Tap) strongly counsels against freezing for later use.

Some compounding pharmacies will separate the dry powder of the 4-month depot formulation into vials containing individual dosages based on the veterinarian's request allowing one to mix only the amount to be given at any one time and avoiding the complications relating to freezing and storage of reconstituted material.

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 site also removes the depot drug. Anti-inflammatory medication may provide comfort and help speed resolution.

Casodex®

Casodex® (Bicalutamide) 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 of straining to urinate, aggression, and return-to-male behavior. Most ferrets start to become more active and play more within one to two weeks after starting Casodex®. The drug may be effective for males and females depending on which hormone(s) the adrenal gland is producing. Pregnant women should not handle Casodex®. Some pharmacies will compound the table into a suspension. The dose is 5 mg/kg once daily until all clinical signs resolve, then pulse therapy (one week on and one week off) for life. Do not use this drug with Arimidex. (See below)

Arimidex®

Arimidex® (Anastrozole) blocks the enzyme that converts testosterone and androstenedione 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 AD. Pregnant women should not handle Arimidex®. The dose is 0.1 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 Casodex®.

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 dominant 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.

Oral Melatonin

Oral dosing regimens of 0.5 to 1 mg per ferret daily have been used. In a limited number of published clinical studies, oral melatonin therapy resulted in consistent improvement in clinical signs including hair regrowth, reduction in vulvar or prostatic size. Hormone studies revealed interesting results with concentrations of estradiol, 17-hydroxyprogesterone (17-HP), and dihydroepiandrosterone (DHEA) decreasing over the first four months but then rising above pretreatment levels by 8 – 12 months. Further, concentrations of another steroid intermediate, androstenedione gradually increased above initial levels in every ferret at each time point throughout the one year study and adrenal tumor growth as measured by ultrasound measurement was not affected by the treatment. It is speculated that improvement in clinical signs is a result of decreases in serum prolactin levels rather than suppression of adrenal steroid production.

Additionally, the report indicated that mean width of abnormally large adrenal glands was significantly increased after the 12-month treatment period and 6 of 10 treated ferrets had recurrence of clinical signs at the 8-month evaluation.

Based on these findings, the use of oral melatonin as the sole long-term medical therapy for ferrets with AD cannot be recommended.

Melatonin Implant (Ferretonin® Melatek)

A 5.4 mg implant (similar in size and shape to a microchip) comes in a prepackaged single dose, sterilized syringe (implant device) with needle and releases melatonin for three months. Unfortunately, few large-scale and long-term studies using a melatonin implant in ferrets with AD have been published. In one article, 70 pet ferrets with clinical signs of AD were implanted and monitored over the next 3-4 months. Clinical response was excellent with 69 of 70 showing resolution of signs including swollen vulvas, alopecia, and itchiness. Several developed large external fat pads in the cervical region which could be confused by clinicians as enlarged lymph nodes and evidence of lymphoma. Hormone levels were monitored in only one ferret, a neutered male. While levels of 17-HP and androstenedione decreased, estradiol levels increased over the four month study period.

In another study, two female ferrets with AD were used to compare a melatonin implant with monthly Lupron® depot (100ug). Hormone levels were monitored and demonstrated slightly lower levels in the ferret with the implant. Though these findings are promising, clearly a study using a much larger number of ferrets is needed to arrive at statistically significant results and evaluation of long-term efficacy.

Trilostane

Trilostane acts by inhibiting adrenal enzymatic conversion of steroids. Inhibition of sequential synthetic steps results in an increase in pregnenolone, 17 α -OH pregnenolone, and dihydroepiandrosterone (DHEA), and a decrease in cortisol and aldosterone. Studies in dogs demonstrate that after oral administration, absorption is rapid, peak levels are seen within 2 hours and return to near base-line within six. Preliminary studies in ferrets show response with regression of signs of AD and decrease in sex steroids, estradiol, 17-OH progesterone, and androstenedione.

Deslorelin

In 2012, Virbac Corp. purchased the import and distribution rights for Suprelorin®, Deslorelin acetate from Peptec, Australia. Currently a 4.7 mg implant can be purchased individually or in lots of five implants.

Research studies performed on adult ferrets with clinical AD have demonstrated significant decreases in clinical signs and hormonal concentrations related to AD. Vulvar swelling, puritis, sexual behaviors and aggression disappeared or decreased within 14 days of implant, with hair regrowth evident by 4-6 weeks. Plasma concentrations of steroid hormones decreased within 2 months (estradiol 32%, 17-OH progesterone 91%, androstenedione 93%). Response persisted for an average of 19 months, (range 8.5-26 months). Adrenal sizes varied, with some cases showing shrinkage, a greater proportion showing progressive increase in size. In some cases progression of adrenal tumors did not seem affected by implant.

Results of these studies suggest that Deslorelin implants are best used in ferrets with AD which do not have evidence of adrenal malignancy at time of implant. Further, evaluation of adrenal size at time of implant and monitoring of size during treatment is recommended with cases having smaller glands (<1cm) followed by sequential abdominal ultrasound at yearly intervals. Those with larger glands (>1cm) would benefit from more frequent monitoring (2-3 yearly) and surgical intervention if signs of neoplastic transformation becomes evident.

Vaccination

Research is underway aimed at developing a safe and effective vaccine directed against either GnRH or FSH/LH. One GnRH vaccine (GonaCon®/AdjuVac patent pending) induces production of antibodies against endogenous GnRH. Antigen-antibody complexes are formed within the hypophysis. Due to large molecular size, these complexes cannot diffuse through pituitary stalk capillaries into the pituitary gland effectively suppressing LH and FSH production. Studies have demonstrated both response of clinical AD and a protective effect on young ferrets (1-3 years of age) significantly reducing development of AD compared to control animals.

Summary

Although many of these drugs can effectively block and/or inhibit the production of the adrenal source hormones and alleviate clinical signs, most do not decrease the size of the adrenal tumor or hyperplasia, nor arrest the advancement of the underlying disease process once it has begun. The veterinarian, in concert with a well-informed client must weigh the benefits and risks of both medical and surgical approaches to management of AD.

Perhaps the most important consideration when looking at medical and/or surgical intervention for AD in ferrets looks at the long-term efficacy of each modality. Of the therapies currently available, the approach yielding the longest disease-free interval post-initiation of therapy is one of surgical intervention followed by long-term medical suppression of GnRH release. Using only a medical or a surgical mode of therapy is less likely to provide an optimal outcome. However other factors such as intercurrent disease (heart disease, insulinoma, lymphoma, etc.) as well as the age of the patient and the ferret owner's financial constraints must be considered.

Obviously, prevention of AD is most desirable. The use of GnRH super agonists administered at strategic times in the growth periods of ferrets and then at appropriate intervals for the life of the patient may provide long-term suppression of pituitary activity and remove the single-most important factor in the initiation of AD. Similarly, vaccination before AD commences may hold promise as a safe and effective way to prevent this most common disorder of the domestic ferret.