**Update on Adrenal Gland Disease in Ferrets**

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Likely most common disorder of pet ferrets in the United States (~25 years recognized)  
In 2003, 70% of pet ferrets in U.S. estimated to have the disease (as compared to 30% in 1993)  
Veterinarians treating ferrets in practice need a good basic knowledge of the anatomy, physiology and pathophysiology of adrenal disease

**Anatomy and Physiology**  
Bilateral glands generally located adjacent to the cranial pole of the kidneys  
Accessory adrenal tissue may be also be present in surrounding fat  
Left gland  
Smaller than right (2-3mm wide x 6-8mm long)  
Located to the left of the abdominal aorta and caudal to cranial mesenteric artery  
Typically embedded in fat  
May be able to palpate normal gland  
Right gland  
Larger than left (2-3mm wide x 8-11 mm long)  
Located more cranially than the left gland  
Ventral to the vena cava under the caudate lobe of the liver  
Curves around vena cava and often attached to and encompassing the dorsal side of the vena cava  
Difficult to palpate normal right adrenal  
The diseased right gland often enlarges and envelopes the caudal vena cava  
Vascular supply  
Blood supply to each gland may vary somewhat but generally includes the aorta cranially and the renal artery caudally. The phrenico-abdominal vein is associated with the ventral surface of the gland running from a lateral to medial direction  
Endocrine function  
Similar to other mammals the adrenal cortex contains zona glomerulosa, fasciculata and reticularis and the medullary regions zona intermedia and juxtamedullaris  
Adrenal glands of ferrets secrete cortisol similar to other mammals  
Adrenal disease in ferrets however does not result in an increase in blood cortisol levels (as seen in cushing’s disease in dogs)  
The adrenocortical zona reticularis secretes sex steroids (estradiol, 17-hydroxy-progesterone, dehydroepiandrosterone and androstenedione)and this portion of the adrenal gland is the tissue affected by adrenal disease in ferrets***  
Etiology and pathophysiology  
See more frequently in ferrets in U.S.(sterilized at a young age, smaller founder population)  
For many years thought to be related to genetics, diet, light cycles etc.  
Research has now shown that the effects of early sterilization combined with the artificial prolonged photoperiod of indoor pet ferrets in the United States predisposes them to adrenal gland disease
Shoemaker, et al., showed a correlation between the age at sterilization and age at onset of adrenal disease. Hypothalamus of the sterilized ferret continues to secrete gonadotrophic-releasing hormone (GnRH) which stimulates the pituitary gland, which in turn releases lutenizing hormone (LH) and follicle stimulating hormone (FSH). The increased LH and FSH then stimulates the zona reticularis of the adrenal gland resulting in an increase in the secretion of sex hormones. In the absence of normal gonadal secretion of estrogens and androgens there is a lack of negative feedback on the hypothalamus causing a continuous release of GnRH and a continuous stimulation resulting in adrenal disease syndrome. Early sterilization also may initiate an LH surge which may cause the initial hyperactivity of the adrenal cortex resulting in increasing the receptivity (i.e. initially early-sterilized ferrets have the same seasonal hormonal levels as intact females). One possible strategy for minimizing this receptivity is to mimic this seasonal hormonal state by administering Lupron at the same time as the ferrets first breeding season.

**Signalment**
- Ferrets of either sex affected
- Females shown higher incidence (may be biased w/increased presentation for aswollen vulva)
- Disease seen in ferrets as young as 8-9 months
- Average age for incidence of disease is 3.5 to 4.5 years

**Clinical signs (both sexes)**
- Progressive alopecia (most common consistent clinical sign seen in 90% cases)
- Poor coat quality with epilation occurring easily
- Often starts with tail progressing to rump, flanks, dorsum then ventrum
- Hair loss may have seasonal pattern (increase loss in spring, summer then return with regrowth in fall)
- Pruritis is common and can be intense resulting in skin trauma (often non-responsive to drugs)
- Lethargy
- Muscle atrophy and weight loss
- Pot belly appearance (weakened abdominal musculature)
- Strong odor (can be secondary to pruritis)
- Abnormal adrenal glands often enlarge and may be detectable on abdominal palpation (especially left)

**Females**
- Vulvar swelling is common (70%), often associated with vaginitis (mucopurulent discharge)
- Stump pyometra
- Mammary gland enlargement (nipples more prominent)
- Increased aggression (sexual)

**Males**
- Prostatic enlargement
- Periurethral cysts
- Resulting in urethral narrowing and associated dysuria, strangury and blockage (True blockage may be life threatening and require emergency treatment)
- Secondary tenesmus and diarrhea (likely related to involuntary defecation with strangury)
- Mammary gland enlargement (less common than females)
Increased aggression (sexual) when seen in males may be association with adrenocortical carcinoma

**Diagnostics**
History, signalment, clinical signs and physical examination valuable****
**CBC/ chemistry profile/cortisol levels**
- Often normal
- Help assess general health
- Mild anemia (profound anemia from severe estrogen suppression of bone marrow rare )
- Pancytopenia may occur
- Plasma cortisol, corticotropin normal (stim tests not useful)

**Hormone panel**
- University of Tennessee
- Testing for elevations of all three sex hormones (estradiol, androstenedione and 17-hydroxyprogesterone)
- Elevations in 2 out of 3 sex hormones usually confirms active adrenal disease
- Expensive (processing/shipping)
- Confirmation of active disease

**Radiology**
- Not useful unless adrenal tissue considerably enlarged
- Abnormal adrenal tissue rarely mineralizes
- Helpful in looking for concurrent disease and preoperative information (cardiac ds., etc)

**Ultrasound (US)**
- Useful to determine which gland is affected (important for surgical consideration)
- Size and architecture of gland
- Assess other organs for concurrent issues
- Also useful to look for prostatic disease in males or uterine stump in females
- Abnormal adrenal tissue more “round” appearance and enlarged often more so at one end (>3.9mm)
- Changes in the gland such as hyperplasia or adrenal adenomas may appear normal on US

**Differential diagnosis**
Intact female (persistent estrus)
Ovarian remnant
- Spayed young female ferrets (swollen vulva)
- Surgeries typically done at ferret farm at a very young age, tissue accidently left behind
- Hormones (panel)
  - Estradiol elevated w/ovarian remnant and adrenal disease
  - Only androgens elevated in adrenal disease
- Ultrasound (ovarian tissue)
- Exploratory surgery
- Treatment with human chorionic gonadotropin (1000 IU 2 weeks apart) reduces vulva size with remnant not adrenal disease
Treatment

Surgery
Still an appropriate treatment in certain cases
Allows evaluation of both adrenal glands and an opportunity to remove diseased tissue
Surgical biopsy of adrenal tissue also allows histopathological diagnosis
Histopathology provides important clinical information for management
Surgery provides evaluation of other abdominal organs such as pancreas (insulinoma), liver, abdominal lymph nodes etc.
Age (3-5 years surgery good option), health of the patient and economics are all factors for deciding on surgical or medical approach
Pre-surgical work up is recommended to rule out concurrent disease (insulinoma, heart disease) and includes CBC/Chemistry and full body radiographs
Ultrasound may be performed to determine which gland is affected (right gland 15-20% of cases) but not necessary if surgeon is prepared to deal with either
Surgery usually indicated with prostatic disease
After abdomen is explored, both adrenal glands are identified to determine which gland(s) is abnormal
Left adrenalectomy is routine, use of hemoclips helpful
Right adrenalectomy more complicated with close association of gland with vena cava
Debulking of right adrenal gland may be only safe option without the use of vascular clamps
Ligation of the vena cava for removal of right gland is not recommended (30% ferrets develop acute renal failure with ligation)
Hemoclips necessary to remove or debulk right adrenal gland
Use of laser, cryosurgery, radio surgery have all been utilized for right adrenal gland manipulation, it is important to use caution not to damage wall of vena cava with these modalities
If right gland is, debulked but not removed adrenal gland disease may return
Post surgical supportive care important (pain management, hydration, alimentation, keep in hospital several days postop)
Recurrence after unilateral adrenalectomy about 17% (usually 11-24 months post surgery)
Improvement in clinical signs seen as early 3-4 weeks (up to 8 weeks or longer) after surgery
Medical management may be initiated after surgery especially if a subtotal right adrenalectomy was performed

Medical
Palliative
Improve clinical signs but does not inhibit the growth or progression of adrenal tumor/pathology
Often an option for
- Older ferrets
- Ferrets with concurrent disease making them poor surgical candidates
- Owners averse to surgery
- Economic issues

Melatonin
Ferrets as pets often have unnatural exposure to light throughout the year affecting (lowering) melatonin levels which has been shown to have an effect on sex hormones
Melatonin supplementation appears to result in short term suppression of sex hormones and improvement in clinical signs over 4-8 months
However long term results (after 12 months of oral treatment) showed a return of elevated hormone levels and clinical signs. If oral melatonin is given (0.5-1.0mg/day given approximately 8 hours after sunrise) Melatonin implants also available (Ferratonin, Melatek, Fort Collins, Colorado) More research and clinical study is needed to determine usefulness of melatonin in adrenal disease

**GnRH agonists**

GnRH agonist work by down-regulating gonadotropin receptors in the pituitary gland Initially the agonist hyperstimulates GnRH receptors resulting in a negative feedback that then down regulates GnRH receptors which then reduces the production of gonadotropin which is responsible for stimulating the adrenal glands production of steroids

Ferrets will usually show improvement in clinical signs in 6-8 weeks

Use of GnRH agonist does result in the suppression of estradiol, androstenedione, dihydroepiandrosterone and 17-hydroxyprogesterone

Clinical signs may worsen in the first few weeks of administration of GnRH agonist due to this initial surge of hormone (owners should be informed of this)

**Leuprolide acetate** (Lupron 30-day formula) at 100-150 micrograms/kg monthly is the most common GnRH agonist used

Lupron 30-day formula found to consistently suppress production of sex steroids for 30 days (as compared to Lupron 4-month which did not consistently suppress sex steroids for a full 4 months)

Monthly veterinary visits for repeat injections of the Lupron 30-day formula has worked well for medical management of ferrets with adrenal disease

Problems with 30 day injections include

- Inconvenience to owner with monthly visits
- Economics
- Discomfort at injection site
- If initiated in younger ferrets (2-3 years) owners returning monthly for years
- Veterinary clinics handling of drug, expense and need to separate drug to freeze to make economically viable

Some ferrets with adrenal disease do not show improvement in clinical signs with leuprolide acetate treatment and this may be related to dosing, individual variation, or most likely to the pathology of adrenal disease (i.e. adenocarcinomas poor or no response)

**Deslorelin acetate 4.7 mg (Suprelorin) Virbac Ferrets USA**

Synthetic GnRH agonist placed in a slow release implant

Works same as other GnRH agonist with benefit of a much longer action due to its slow-release

Research by Wagner, et al, 2005 showed a 3mg slow-release deslorelin implant improved clinical signs and suppressed sex hormone plasma concentrations in ferrets for 8-12 months

No side effects were found in the study however (as with other GnRH agonist) deslorelin does not inhibit tumor growth

Previously only available by importation from Australia, difficult and expensive

Now FDA approved for use in the United States and commercially available now! (www.virbacferretsusa.com)

Implant is placed subcutaneously with needle delivery system (similar to placement of microchip)

Implant is about the same size as a microchip and can be palpated after placing

Recommend sedating with gas anesthesia to place implant (large needle), skin prep, inject, use surgical glue to seal injection site (problems at site rare)
Looks promising for medical management
Still uncertain as to how long may last in patient and there will likely be individual variation as for lupron
At this time (once initiated) annual replacement for life once is recommended
Ongoing debate about when to initiate treatment
  • wait for clinical signs of adrenal disease before implanting
  • or implant healthy ferret at a certain age and then annually for life
More research and clinical experience needed however this medical option looks promising

**Prevention/Treatment**

**GnRH vaccine**

GonaCon™ is an immunocontraceptive vaccine

Developed by the USDA to reduce fertility in wildlife species (reducing the spread of disease)

The vaccine contains GnRH peptides (from mollusks) that stimulate the production of antibodies that neutralize GnRH released from the hypothalamus thus reducing available endogenous GnRH

Reduced GnRH results in the lower production of LH and FSH from the anterior pituitary gland

Clinical studies in ferrets revealed:
  - Vaccine was well tolerated (SQ recommended over IM administration) and effective in preventing the onset of ACD in ferrets
  - The vaccine was not as effective in the treatment of ACD as GnRH agonist
  - The vaccine did not eliminate all clinical symptoms of ACD
  - Better use as a preventative given to younger ferrets post sterilization but prior to clinical signs of ACD

**References**


