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FERRET NEOPLASIA

FERRET ADRENAL DISEASE
The alopecia and pruritis that may occur with adrenal disease in ferrets appear clinically similar to atopy and other allergic dermatologic diseases in dogs. Even when veterinarians are aware of the prevalence of this adrenal syndrome in ferrets, the tendency is to think of this as Cushing’s disease. It is not a pituitary based disease, nor are the hormones produced in excess glucocorticoids. Estrogen, testosterone, and/or progesterone derivatives are produced in excess by the ferret adrenal glands.1

A prevalent theory is that very early orchiectomy or ovariohysterectomy as is performed on the majority of domestically raised ferrets in the United States causes the adrenal glands to compensate for the lack of circulating estrogens and/or androgens. The adrenal glands respond to the elevation of serum LH by production of gonadal hormones. (Recent work has determined that ferret adrenal tissue has LH receptors, allowing it to produce sex hormones). Therefore, clinical signs may vary according to the particular sex hormone(s) that are being produced. It is also postulated that the increased incidence of adrenal disease may be related to the abnormally prolonged photoperiods to which domestic ferrets in the U.S. are exposed. Some European ferrets are more similar to polecats in temperament and body size and their genetic make-up differs from ferrets in the US. In some European countries, ferrets are generally housed outdoors and are therefore exposed to normal seasonal photoperiods.

For a thorough explanation of the proposed pathophysiology of ferret adrenal disease and the role of endogenous and exogenous melatonin, the following excerpt from writings of Thomas Donnelly, BVSc, MS, DACLAM, is included:

"... when there is less than 12 hours of light per day, plasma melatonin concentrations are high resulting in a thick winter coat. High melatonin concentrations also suppress the release of gonadotropin releasing hormone (GnRH) from the hypothalamus. With increasing day length, this suppression is lost and GnRH is released in a pulsatile fashion, resulting in the pulsatile release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. These hormones (LH & FSH) in turn stimulate the release of estrogen and testosterone from the gonads, which in turn exert a negative feedback on the hypothalamus and pituitary gland resulting in suppression of the release of GnRH, LH and. When ferrets are neutered, this negative feedback is lost, resulting in an increased release of gonadotropins (LH & FSH), which promote (extragonadal) steroidogenesis and induce non-neoplastic and neoplastic adrenocortical enlargement. (Bielinska M et al. Gonadectomy-induced adrenocortical neoplasia in the domestic ferret (Mustela putorius furo) and laboratory mouse. Vet Path, 2006; 43(2): 97-117). Increased light exposure, when ferrets are kept indoors, has also been suggested as a contributing factor in the occurrence of hyperadrenocorticism. This hypothesis is in line with increased LH levels causing hyperadrenocorticism. During increased light exposure (think of it as >12 hours of light per day), ferrets are under the influence of LH for a longer period compared with those that are kept under natural light situations.

Treatment with melatonin ...mimics high melatonin concentrations in the blood during short days, and suppresses GnRH which in turn suppresses gonadotropins LH & FSH. During increasing photoperiod length & long days, the effects of melatonin on GnRH are overridden. But during short days and decreasing photoperiods melatonin suppresses GnRH, which suppresses LH, which stops stimulating adrenocortical adenoma. However, some adrenal tumors may no longer respond to LH and secrete sex steroids independent of gonadotropin levels. Photoperiod information is transduced neurologically by the circadian rhythm of melatonin release (i.e. daily changes in the duration of the nocturnal melatonin surge are decoded and subsequently relayed to the pars distalis to adapt gonadotropin [and prolactin] release). Although photoperiodic influences on the reproductive axis (hypothalamic-hypophysal neurosecretory system) have been well characterized, the precise mechanisms by which photoperiodic information and other seasonal cues are integrated to regulate reproductive function remain less well specified. Two recently discovered neuropeptides, kisspeptin and gonadotropin-inhibitory hormone (GnIH), have pronounced opposing influences on reproductive function. (For review read Greives TJ et al. Recent advances in reproductive neuroendocrinology: a role for RFamide peptides in seasonal reproduction? Proc Biol Sci 2008; 275(1646):1943-1951). GnIH transduces photoperiodic information via changes in the melatonin signal, thereby influencing the reproductive axis. Interestingly, the other endocrine neurosecretory system of the brain is the pineal gland, which secretes melatonin.
Although treatment with melatonin results in hair regrowth in ferrets with hyperadrenocorticism, as well as decreased pruritus, increased activity level and appetite, and decreased vulva or prostate size, in these ferrets sex-steroid concentrations still increase and the adrenal tumors continue to grow. Melatonin decreases clinical signs associated with adrenocortical disease in ferrets but not tumor growth or sex-steroid levels. ... this does not appear to be through inhibitory effects of sex-steroid production in the adrenal glands, but may be due to down-regulation of androgen receptors in peripheral organs”.

It is also likely that there is a genetic component to adrenal disease in ferrets. One proposed theory for the high incidence of adrenal (and pancreatic) neoplasia is that ferrets in the U.S. may possess a chromosomal abnormality similar to the MEN (Multiple Endocrine Neoplasias) syndrome in people. In this syndrome in humans, pancreatic, adrenal, pituitary and thyroid neoplasias are manifested in individuals possessing an abnormal tumor-suppressor gene on chromosome 11. In people, this syndrome may be exacerbated in individuals with decreased gonadal hormone production. The ferret chromosomes have been mapped for their use in numerous human medical research applications.2 However, identification of specific chromosomal abnormalities related to adrenal disease in ferrets has not been accomplished.

The University of Tennessee has a commercially available assay for gonadal hormones. This assay includes levels of the following gonadal hormones, which have been found to be most consistently elevated in ferret adrenal disease: androstenedione, 17-OH progesterone and estriol. Male ferrets with an increase in serum androstenedione levels may exhibit aggression, sexual behavior, and prostatic enlargement (which may lead to leading to dysuria). These clinical signs in the male ferret may occur with or without the more common finding of progressive alopecia. Female ferrets generally present with alopecia and may have concurrent vulvar swelling. Clinical signs (alopecia, vulvar swelling) ultrasound identification of enlarged adrenal gland(s) and gonad hormone assays are used for diagnosis. However, a normal size adrenal may still be abnormal in function (i.e. be producing gonadal hormones).

Surgical removal of the affected adrenal gland(s) may be curative, although not both glands are completely removed (which is indicated if both are pathologic), recurrence of clinical signs may occur when the residual normal adrenal tissue proliferates. Dr. Avery Bennett will discuss adrenalectomy techniques in his lecture. Ectopic adrenal tissue in the abdomen is not uncommon.

On the positive side, even with total resection of both glands, mineralocorticoid deprivation does not cause life threatening clinical signs in most ferrets.1,3,4,7 Serum electrolytes should be monitored post-operatively, and mineralocorticoid and glucocorticoid therapy administered as indicated. In this author’s experience, a small percentage of ferrets undergoing bilateral adrenalectomy require prolonged administration of mineralocorticoids (i.e. fludrocortisones = Florinefr @ 0.05-0.1 mg/kg PO q 24 hrs).

Medical Therapy for Adrenal Disease

Melatonin
can be administered either orally or via a depository injection. The recommendation for oral melatonin is 0.5 mg/ferret (per kg) once daily. This has been demonstrated in one clinical trial to be efficacious for at least 8 months when given orally.9 Commercially prepared implants are available in 2.7 and 5.4 mg concentrations by the US manufacturer (www.melatek.net ). These can be repeated q 4-12 months prn.

Depo-LupronR,
(leuprolide acetate) is a GnRH receptor agonist. By blocking the stimulation of LH, it suppresses adrenal production of gonadal hormones and may be used in conjunction with or in lieu of surgical resection of the affected gland(s).10 Injections are given @ 100-200 ug/kg and last about 1

Mitotane
(LysodrenR) therapy is not a reliable therapy for ferret adrenal disease. Some ferrets tolerate the medication (although those with insulinomas should not be given this drug, due to the potential for developing a severe hypoglycemic episode). The clinical signs, however, are usually only partially and temporarily improved. Recommended dose is 50 mg/kg q 24 hrs.

Deslorelin
is available in the EU but not in the US. Deslorelin is a GnRH receptor agonist as is Depo-Lupron. It is used as an implant and is reported to be effective for up to one year.11

Another useful medication in male ferrets with concurrent prostatic cystic disease is finasteride (Proscar®) designed for the treatment of prostatic hypertrophy in human males. Dosages used are 0.5-2.5 mg/day. It prevents the conversion of testosterone to 5-a-dihydrotestosterone, the active form of testosterone. It will generally decrease the size of the prostate and prostatic cysts prior to or in lieu of surgery. Flutamide works in the same manner and can be given at 10 mg/kg PO q 12 – 24 hrs for prostatic
FERRET INSULINOMA

Insulinomas are pancreatic islet cell tumors of the insulin-secreting beta cells. Insulinomas are one of the most common tumors found in middle-aged to older ferrets in the United States. Clinical signs may include intermittent lethargy, mental dullness, irritability, hypersalivation, pawing at the mouth, weight loss, weakness in the hind limbs, and in severe cases, hypothermia, seizures, coma or death. These signs may occur acutely or have a gradual onset with increasing severity over several weeks to months. Blood glucose measurements of less than 70 mg/dL (3.9 mmol/L) suggest insulinoma. Normal blood glucose values for ferrets are reported to range from 90 to 120 mg/dL (5.0 – 6.6 mmol/L). In this author’s experience, young, healthy ferrets will exhibit blood glucose levels (when venipuncture is accomplished without anesthesia), of over 110 mg/dL (6.1 mmol/L).

Ferrets with insulinoma often have blood glucose levels that fluctuate. Drawing blood after a four to six hour fast or using serial blood glucose measurements will be more accurate diagnostically. Fasting is contraindicated if clinical signs of hypoglycemia are apparent. Blood insulin levels may also help in making a presumptive diagnosis. Ferrets with insulinomas are reported to have insulin values from 107.7 to 1738 µU/mL. Normal values are reported to be 15 to 35 µU/mL. Abnormally high insulin concentrations in association with low blood glucose levels are indicative of insulinoma. A normal insulin concentration with an abnormally low blood glucose level does not rule out insulinoma – the insulin/glucose ration may still be abnormal.

Exploratory laparotomy is the definitive diagnostic approach. Micro-metastasis throughout the pancreas has usually occurred by the time a diagnosis is made. The incidental finding of insulinomas during gastric foreign body removal in ferrets less than two years of age indicates that these neoplasias may be present for prolonged periods prior to the onset of clinical disease. Surgery is rarely curative but functions to debulk the visible tumor tissue in an attempt to slow the progression of the disease. Partial pancreatotomy rather than simple removal of the nodule(s) carries a better prognosis. Medical treatment will usually be required at some future point as the disease progresses. The owner should be forewarned that management of this disease will be required for the rest of the patient’s life. Medical treatment is aimed at maintaining a blood sugar level that provides for the ferret’s comfortable existence. Prednisonone at 0.25 to 1.0 mg/kg orally every 12 hours will serve to increase the blood sugar via several physiologic mechanisms. Ferrets on prednisonone therapy often do better clinically than their blood glucose levels would suggest, probably also due to the multiple effects of glucocorticoid administration. As the disease progresses, the dose is increased as needed, often to levels as high as 2- 3.0 mg/kg to approximate euglycemia, maintain the ferret’s weight and control clinical signs. When prednisonone alone fails to control the hypoglycemia, diazoxide at 5 to 30 mg/kg orally twice a day can be added to the treatment protocol. The recommended diet is a high quality ferret food ad lib. Sugary snacks should be avoided, as they tend to cause a rebound increase in insulin. Eventually, the hypoglycemia may no longer be controllable medically or surgically.

Concurrent problems are extremely common in ferrets 3 years of age and older. Adrenal gland disease, lymphoma, cardiomyopathy and skin tumors are present in many ferrets with insulinoma. A thorough physical exam is important. A complete blood count and serum chemistry panel should be performed to ensure general health and to rule out concurrent illness. Insulinomas are often presumptively diagnosed during the presurgical workup for another disease when the blood glucose is revealed to be less than 70 mg/dL (3.9 mmol/L).

Ultrasoundography, when available, may be used to screen for concurrent diseases (i.e. adrenal gland disease and lymphoma) and may occasionally detect large insulinomas, although most are too small to be detected via ultrasound.

Pre-surgical fasting is generally recommended for ferrets. Ferrets believed to have insulinoma will be particularly prone to hypoglycemia and should be fasted for only 2 to 4 hours under observation. An IV drip of 2.5 to 5% dextrose with a balanced electrolyte solution is indicated. Ferrets are excellent surgical candidates and tend to do well with many anesthetic protocols. Isoflurane or sevofoflurane are currently the anesthetics of choice in the United States.

The surgical procedure for insulinoma resection will be discussed in the lecture by Dr. Avery Bennett. One point that bears emphasizing is that insulinomas are often not grossly visible. Palpation of the pancreas is needed to detect the insulinoma nodules, which are firmer in texture than the surrounding pancreas. Ectopic nodules in may also occur in the omentum or on the serosal surface of adjacent organs. The blood glucose level should be checked immediately post-surgery and repeated several times during the first 24 hours after the IV dextrose has been discontinued. The ferret should be encouraged to eat as soon as it has recovered from anesthesia. Most ferrets will be euglycemic or hyperglycemic after surgery.

Fasting blood glucose levels should be rechecked 7 to 10 days post-surgery and then every 2 to 4 months as long as the ferret remains subclinical. Occasionally ferrets will remain hypoglycemic post-operatively. These
LYMPHOMA

Lymphoma is common in ferrets of two age groups, juveniles and older individuals, much as in cats. The young ferret is often affected with mediastinal lymphoma and may present with dyspnea, lethargy, and coughing. Peripheral lymphadenopathy is not usually noted in this group. Abdominal (lymph nodes, spleen and liver involvement) lymphoma is also seen in this age group.

Older ferrets with lymphoma have more variable presentations. Peripheral lymphadenopathy does occur, but is uncommon. The practitioner should be cautious when palpating peripheral lymph nodes to differentiate between the pronounced accumulation of fat that commonly surrounds these lymph nodes (especially the pre-scapular and submandibular nodes) and the actual nodes lying within the fat. Lymph node excision and submission for histopathology is usually conclusive, whereas aspirates are difficult due to the surrounding fat and the relatively small size of even enlarged nodes. The popliteal lymph node in ferrets is easily accessible for resection and not as vascular as in dogs and cats. Splenic lymphoma may occur, but without biopsy and histopathology it is difficult to diagnose due to the nearly universal splenic enlargement (usually benign extra-medullary hematopoiesis) that occurs as ferrets of the U.S. gene pool as they age.

Abdominal lymphadenopathy is common in ferrets with lymphoma, however, reactive lymph nodes are also common in older ferrets for a variety of reasons. Ultrasound identification of enlargement of abdominal lymph nodes does not confirm lymphoma – fine needle aspirates (FNA) or a biopsy must be obtained. Peripheral lymphocytosis may occasionally occur with lymphoma. The finding of peripheral lymphoma cells on a blood smear is rare. Hepatic involvement is also common, requiring FNA or biopsy for diagnosis.

Chemotherapy for ferrets with lymphoma is commonly employed. Chemotherapy protocols vary and include: 1) Full multimodal regimes that include vincristine, cyclophosphamide and doxorubicin (such as those used in dogs), 2) Lomustine (CCNU) 3) L-asparaginase, and 4) Prednisolone in conjunction with one of the preceding. The prognosis for a remission of 3-12 months with a good quality of life is much higher than the older literature indicates. The option of treatment with prednisolone alone exists, with generally the same positive (good initial remission, low cost, few side effects) and negative (very short term remission–often only weeks) qualities that are noted with prednisolone use for lymphoma in dogs and cats.

Reverse transcriptase activity and retrovirus-like particles have been isolated from tissue of affected ferrets in at least one "cluster" diagnosis of this neoplasia. Horizontal transmission was then experimentally induced from affected ferrets via both cell culture and cell free inoculation. Both clinical and pathologic findings indicate that a virally induced lymphoma is present in some cases of lymphoma in ferrets, but further research is needed to confirm a viral etiology.

An acute presentation of lymphoma in young adult ferrets is seen with some frequency. Specific clinical signs other than severe depression and fever are not documented. Diagnosis in these cases is usually determined at necropsy.

OTHER NEOPLASIAS

Ferrets have a high incidence of neoplasia, including the previously discussed adrenal cell tumors, insulinomas, and lymphoma. Chordomas of the vertebral column occur with some frequency, most commonly on the tail tip, and amputation is warranted. These are very slow growing but also highly invasive, so delayed recurrence is common. Cutaneous neoplasia is also common, including but not limited to mast cell tumors, basal cell adenomas, adenocarcinomas and squamous cell carcinomas. Mast cell tumors are non-invasive, so delayed recurrence is common. Cutaneous neoplasia is also common, including but not limited to mast cell tumors, basal cell adenomas, adenocarcinomas and squamous cell carcinomas. Mast cell tumors in ferrets may be recurrent and multi-focal but they do not tend to metastasize to distant organs. Resection as needed, with the general health of the patient, concurrent disease, and quality of life all considered, is a prudent course of action.

Bibliografia

