Update of Ferret Adrenal Disease: Etiology, Diagnosis, and Treatment

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Abstract: Ferret adrenal disease or hyperadrenalcorticism is a common disorder in ferrets, characterized by marked sex steroidogenesis and neoplasia. Control mechanisms and etiology of the disease have established initial stimulation and mechanisms of stimulation, active LH receptors in diseased adrenal tissue, and correlation with time of gonadal removal. A genetic or familial predisposition appears to exist and is currently being studied as a possible homologous genetic disorder with the Multiple Endocrine Neoplasia (MEN) syndrome in humans. Therapeutics aimed at controlling the stimulation to the adrenals, suppressing sex steroidogenesis, blocking peripheral hormonal effects, and debulking of the tissue are currently used to manage the disease.

Introduction

Ferret adrenal disease or ferret hyperadrenalcorticism is one of the most common clinical presentations of ferrets. Unlike Cushing's disease, the primary hormones elevated are sex steroids. Within the past few years, a number of studies have been done looking at the different aspects of the disease, developing the model of what is occurring, and developing management strategies to enable affected ferrets to live out their lifespan.

Endocrine Controls and Neoplasia

It is well known that domestic ferrets are seasonal breeders, with copulatory ovulation and subject to a complex hormonal stimulation and feedback system that was studied as a model of reproductive controls in the 1970s and 1980s. Examination of these systems established a number of factors that have importance in the development of adrenal disease. It was established that in the ferret, in the absence of the gonads, the adrenal gland can respond similarly to a gonad for sex steroidogenesis. A first step in connecting the basic research and the disease was to look for active hormonal receptors that would result in sex steroid production. It had been determined that there were significant elevations of estradiol, androstenedione, and 17 OH progesterone rather than cortisol in ferrets with hyperadrenalcorticism. It was determined that the adrenal gland has lutinizing hormone (LH) receptors that are active in affected ferrets.[1]

Basic endocrine research in the ferret determined that at puberty and consequently at breeding, sex hormone levels achieve peaks then "set the gonadostat" in the brain regulation areas (hypothalamus, pituitary). Neutering at puberty or at breeding-age in adult ferrets causes an LH surge which then acts similarly to breeding itself. This LH surge followed by subsequent increased gonadotropin releasing hormone (GnRH) without gonadal response serves to downregulate sex steroid production. This action seems contradictory, but prolonged elevated levels of GnRH is a negative feedback mechanism for sex steroid production . A study was that examined the pituitary glands of intact or neutered ferrets, and 10 neutered ferrets with hyperadrenocorticism. The ferret pituitary gland

histologically was similar to the dog pituitary. In 2/10, a tumor was detected in the pituitary gland, although these had characteristics of clinically non-functional gonadotrophic tumors seen in man. In some of the ferrets, there was low pituitary immunoreactivity for gonadotrophic hormones, which was considered to be due to the feedback of autonomous steroid secretion by the neoplastic transformation of the adrenal cortex. This study concluded that the initially high concentrations of gonadotrophins resulting from castration initiated the hyperactivity of the adrenal cortex. The conclusion of this study was that because of the low incidence of pituitary tumors and the low density of gonadotropin-positive cells in non-affected pituitary tissue suggested that persistent hyperadrenocorticism was not dependent on persistent gonadotrophic stimulation.[2] This finding contradicts the clinical finding that a medication sustaining gonadotrophin releasing hormone levels with a synthetic GnRH analog, recognized by the pituitary depresses the production of sex steroids in the ferret. This finding does explain the initial stimulation to the gland, and possibly why as the tumor progresses as it is not responsive to pituitary control. It would then follow that progression of anaplasia may be under a tumor suppressor gene control, rather than continuous pituitary stimulation. Episoidic pituitary stimulation does explain why some ferrets will exhibit "rat tail" and pre-hyperadrenocorticism seasonally, before they are considered "adrenal disease." In intact animals, coitus triggers an LH surge, with subsequent ovulation or intromission. In males, the hormone feedback causes downregulation so the male goes out of season. In the female, pregnancy ensues in most cases. Hormonal feedback from the gonads is necessary to conclude the breeding season. The author noted in her study using intact ferrets, 1–2 weeks of hot weather (over 80^{o}F with no air conditioning) caused both the males and females to go out of season spontaneously. In the 3 years we followed intact ferrets, all would cycle-out of season by late August, and none of the females developed estrogen-toxicity and anemia, despite monthly blood draws of 2-3 mLs.3 (C. A. J. D., J. Oliver, unpublished data, February 2006).

Early spay/neutered (ES/N) animals have levels of sex steroid production seasonally similar to their intact counterparts. This was not anticipated when the longitudinal study began. The longitudinal study was comprised of 6 ES/N animals (3 males, 3 females) and age and sex-matched locally bred intact ferrets, followed with monthly hormone analysis from 4 months of age through 12 months of age, and then periodically (30 days post-neuter/spay for the intact ferrets), and twice annually for the ES/N ferrets. A number of the original study ferrets have been adopted and lost to the study, several remain available for periodic sampling. The 6 ES/N animals reside with the author. Unlike intact animals that have gonadal production of sex steroids, and breed, which then downregulates the system, the ES/N animals' adrenals respond and produce sex steroids, but no "breeding" occurs to shut the system down. The sex steroid levels continue to be produced throughout the year at a level appropriate to the breeding season level.

Post-puberty spayed/neutered ferrets have a markedly lessened hormonal cycle throughout the year, but it is still present. Sex steroids in all ferrets (altered or intact) rise at what can be considered the start of breeding season (late December/January for males; January–March for females). Levels are lowest for males in late summer, early fall, and for females September-November. Females lag behind the males' sex steroid level elevation by 1–2 months. Keeping ferrets on artificial light cycles, or supplying melatonin may suppress the sex steroid seasonal responses for awhile, but eventually the cycle continues. It may be out-of-synch with the calendar.

There is a correlation between the timing of removing the gonads and the onset of "adrenal disease."[3] A study was done that explored some of the possible endocrine pathways for control (ACTH or alpha-MSH) by examining plasma levels of the hormones in neutered animals and intact animals. It was concluded that ferrets with hyperadrenocorticism did not have detectable abnormalities in plasma concentrations of ACTH or alpha-MSH.[4]

The working hypothesis proposed by the author for the etiology of adrenal disease is that stimulation via the pineal, pituitary and secretion from the hypothalamus of GnRH and LH up-regulates sex steroid production in the adrenal tissue which then responds without a set-point for "shut-off": the tissue responds initially with hyperplasia.

Elevations of estradiol, androstenedione, and 17 OH progesterone can be measured by validated hormonal assays performed at the University of Tennessee's Clinical Endocrinology Laboratory, Knoxville, TN, USA.

The second hypothesis is that if an aberrant tumor suppressor gene is present, hyperplastic tissue with stimulation progresses to adenoma, then eventually adenocarcinoma, following models in other animals and humans. A completed study looked at tumor markers in ferrets, based on the work in gonadectomized DBA/2J mice that develop adrenocortical tumors expressing transcription factor GATA-4. 86% of the ferret adrenocortical carcinomas, particularly in areas of myxoid differentiation expressed GATA-4. Normal adrenocortical cells lacked GATA-4 expression. Two other markers of adrenocortical tumors in gonadectomized mice that are co-expressed with GATA-4 are inhibin-alpha and LH receptor. These were co-expressed in some of the ferret tumors. No GATA-4 expression was observed in 3 cases of nodular hyperplasia; however, patches of anaplastic cells expressed GATA-4 in 50% of the tumors classified as adenomas. The conclusion was that GATA-4 does function as a marker of anaplasia in ferret adrenocortical tumors.[5] The relevance of this shows that there may be a way of tracking and marking the tumors (prognostication for the practitioner when advising the client), and pathways of cancer development in the ferrets is similar to that of other species. This also is suggestive of a genetic root to the development of the disease, as GATA-4 is a protein marker.

A point of management of the disease is to depress or suppress the stimulation to the adrenal gland, thereby stopping sex steroid production. Blocking sex steroids from affecting other tissues can also be done, thereby decreasing clinical signs, but none of these medical therapeutic agents may halt the progression of hyperplasia to adenoma to adenocarcinoma, if the possibility of an aberrant tumor suppressor gene is involved. Central (brain level) suppressive drugs such as leuprolide acetate depot formulations (Lupron 3.75 mg, 7.5 mg 30 day Depot; TAP Pharmaceuticals, Lake Forest, IL, USA) have been proven to down-regulate sex steroid production and decrease clinical symptoms. Melatonin implants (Ferretonin, Melatek, LLC, Fort Collins, CO, USA) in some ferrets have short-term suppressive effects. There are additional medications used for humans that work in ferrets for either central or peripheral sex steroid downregulation, blocking peripheral hormone receptor sites or interruption in the enzymatic pathways of sex steroidogenesis.[6–9]

Genetic Research

Because of the high incidence of neoplasia in ferrets, the search for the possibility of genetic or chromosomal aberrations is being studied in domestic ferrets. In humans, the appearance of benign or malignant proliferations within 2 or more endocrine glands is nearly always genetically determined and is termed multiple endocrine neoplasia (MEN) syndromes. There are 3 currently accepted human familial syndromes in which there is a progression from hyperplasia to neoplasia in endocrine tissues; these include MEN types 1 (MEN1), 2a (MEN2a), and 2b (MEN2b). MEN1 syndrome usually is characterized by parathyroid hyperplasia, pancreatic islet cell, and/or pituitary tumors. Up to 40% of MEN1 patients also develop adrenal, thyroid, or thymic tissue tumors. MEN2a and MEN2b syndromes are characterized primarily as medullary thyroid cancer (MTC) with or without pheochromocytomas and parathyroid adenomas. MEN1 and MEN2 are inherited as autosomal-dominant genetic traits. The MEN1 gene is ubiquitously expressed and is not limited to organs affected by the syndrome. A number of different mutations have been described for the MEN1 gene in humans. As there seems to be a similarity between the endocrine neoplasm patterns in the ferret and the human MEN1 syndrome, research being conducted by Dr. Michelle Hawkins at the University of California at Davis is first looking for a homologous gene in the ferret to the human MEN1 gene. At this time, a homologue has been identified. The sequence of the normal ferret MEN1 gene must be completed, then it can be determined in which tissues the normal gene is expressed. The next step will be to test neoplastic tissues from affected animals for mutations within these genes to determine whether an association can be made with the human MEN syndromes. (M. Hawkins, written communication, January 2006).

Therapeutic Regimens

Lupron 30 day depot formulation (TAP Pharmaceuticals) was effective in downregulating sex steroid production in intact ferrets in-season. Effects lasted 30 days. Lupron 3 month depot formulation (TAP Pharmaceuticals) was effective in the intact males for 75–90 days (January through April); but 2 females in one study returned to estrus by 60–75 days, so it is doubtful that the 3-month formulation will truly last for the full 3 months (C. A. J. D., J. Oliver, unpublished data, February 2006).

Melatonin implants (Melatek LLC) in one controlled study in intact males in season did not effectively decrease sex steroids.[10] Others have reported clinical effects of regression of outward signs.[9]

Surgery to debulk the glands may slow the progress by decreasing the tissue producing the sex steroids. A clinical study has shown that without additional suppression of the hormone stimulation, ferrets who have surgery as the only treatment did not live as long as those that had lupron 30-day treatment alone. Surgery to debulk along with hormone suppression appears to have a slight edge over Lupron 30 day depot (TAP Pharmaceuticals) alone (C. A. J. D., J. Oliver, unpublished data, February 2006).

Data suggests that ES/N is detrimental for at least 2 reasons: 1) the set point in the sex steroid production feedback loop is not set–the ferret comes into puberty and its first breeding season similarly to intact ferrets, but the system does not shut down and 2) time for onset of adrenal disease is shortened so that younger ferrets are affected. Adrenal disease has been documented by hormone level, ultrasound, and histopathology in ES/N ferrets as young as 8 months of age (C. A. J. D., J. Oliver, unpublished data, February 2006).

Clinical Recommendations 2006

Until Dr. Hawkin's genetic work to seek a tumor suppressor gene is completed, as clinicians we may consider the following based on data collected so far:

1. ES/N is not advantageous to the ferret as the hormonal feedback system responds similarly to intact ferrets at puberty and into the breeding season.

2. In ES/N ferrets, the author is trying a "chemical breeding" at the time of puberty or their first breeding season. There may be a specific window of opportunity, but without weekly hormone panels, the author is using the calendar and the weather/light levels for timing: January for the males, mid-February to mid March for the females: males receive 200 µg of Lupron 30 day (TAP Pharmaceuticals); females 100 µg. Data from the longitudinal study of ES/N and intact, age-matched counterparts supports this. (C. A. J. D., J. Oliver, unpublished data, February 2006).

3. All ES/N ferrets should probably be given a "chemical breeding" every breeding season annually to cause the LH surge, then maintain a plateau long enough to keep them out of cycle for the whole season. It may be advantageous to use the 3-month formulation for subsequent years. As this longitudinal study is on-going, this is still a hypothesis based on the data collected to date. This should block that "initiating stimulation."

4. If ferrets are to be spayed or neutered, as late in life as possible, and towards the end of breeding season their first year (puberty) is likely ideal. The question that has not been answered for these is should they

be “chemically bred” each subsequent year like the ES/N ferrets. Preliminary data shows that the following year, these ferrets have hormonal rises to match the onset of breeding season, just not as elevated as intact ferrets. (C. A. J. D., J. Oliver, unpublished data, February 2006).

5. The goal of all therapy is to enable the ferret to have a good life for the 5–7 years of its lifespan. A management program, like vaccination programs as annual visits, can be formulated. Owners then need to be educated about the importance of annual veterinary attention for their ferrets, and perhaps twice a year for ferrets as they age. With further data analysis and publication of the data gathered, a goal may be to stop the early spay/neuter practice in this seasonal, copulatory ovulator animal.

And in conclusion, if an aberrant tumor suppressor gene or genes are discovered and a commercial assay developed to enable screening of all ferrets, we as veterinarians need to give considerable thought now to issues this will cause. The first group of ferrets to be tested by an assay would be the breeders.

1. If we try to eliminate the gene through a breeding program, will we create further genetic problems?

2. What will happen to all the breeder ferrets that test positive, yet may never have the disease? (Phenotype expression is not an absolute.) If baby ferrets are tested at the breeding facility and show positive, will these all be killed?

3. In all pet ferrets that are screened, what will happen to any that test positive?

4. This could lead to very large numbers of euthanasias of perfectly healthy ferrets that may or may/not ever show a neoplastic disease. Ferrets already owned and then tested and shown to be positive: what do you tell the owner? The author anticipates that many ferrets will be killed or dumped at shelters.

We need to consider the implications on the ferret population and the animal’s desirability as a pet. I believe that based on the data and pathophysiology of this disease, a first step would be to halt the early spay/neuter practice. Second would be to consider essentially a “chemical breeding” for all ES/N ferrets annually for life, starting at puberty. Thirdly, we need to get this information out to pet shops, veterinarians, and the owners. Most veterinarians are conditioned to think about an annual vaccine – not much different than an annual anti-hormone shot, but it may be a better preventative injection for the ferret than that vaccination.

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