EVERYTHING YOU WANTED TO KNOW ABOUT ADRENAL DISEASE IN FERRETS

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Adrenal disease can refer to changes to the adrenal cortex and/or to the adrenal medulla. The most common form of adrenal medulla pathology is a pheochromocytoma. These rare tumors are usually much larger than tumors of the adrenal cortex and can remain unnoticed for a long time. Although cases have been reported where pheochromocytomas have been diagnosed based on histologic characteristics of the adrenal tumor, measurement of urinary metanefrine is necessary to confirm the diagnosis. To the author's knowledge this type of confirmation has not yet been performed in ferrets. The most common form of adrenal disease in ferrets is hyperadrenocorticism, also referred to as adrenocortical disease, in which the adrenal cortex is affected. The outermost layer of the adrenal cortex is the zona glomerulosa, which produces mineralo-corticoids (primarily aldosterone). The zona fasciculata consists of an outer and inner part, and produces glucocorticoids (cortisol and corticosterone) and androgens. The most interior zone is the zona reticularis, which is extremely variable in its prominence and cellular composition. This zone contains the smallest cells of the adrenal cortex and produces primarily androgens. Thus, in principle, three distinct syndromes may arise in adrenocortical hyperfunction: hyperaldosteronism, hypercortisolism, and hyperandrogenism.

Primary hyperaldosteronism or Conn's syndrome is the most common form of hyperadrenocorticism in cats, usually due to excessive secretion of mineralocorticoids by an adrenocortical neoplasia or bilateral adrenocortical hyperplasia. The exact pathogenesis of primary hyperaldosteronism remains to be elucidated.

Hypercortisolism or Cushing's syndrome is the most common form of hyperadrenocorticism in dogs, and also occurs frequently in humans. In these species, hypercortisolism most frequently results from excessive secretion of adrenocorticotropic hormone (ACTH) by a pituitary adenoma. ACTH-independent hypercortisolism may be due to excessive secretion of glucocorticoids by a benign or malignant adrenocortical tumor. However, ACTH-independent hypercortisolism may also occur as a result of expression of aberrant or overactive eutopic hormone receptors. In humans, various membrane-bound receptors, functionally coupled to steroidogenesis, have been reported, including gastric inhibitory polypeptide, catecholamine, vasopressin, serotonin, and luteinizing hormone (LH) receptors. LH-dependent hypercortisolism has been reported in several women. In addition to LH-dependent hypercortisolism, virilizing and feminizing LH-dependent adrenal tumors have been reported in humans.

HYPERADRENOCORTICISM

In neutered pet ferrets hyperandrogenism is the most common form of hyperadrenocorticism. In ferrets, plasma androstenedione, 17-hydroxyprogesterone and estradiol concentrations are increased. It has been reported that approximately 85% of ferrets with hyperadrenocorticism have enlargement of one adrenal gland without atrophy of the contralateral adrenal gland. In the other 15% of cases bilateral enlargement is present. After surgical removal of a unilateral adrenal tumor, the disease commonly recurs due to involvement of the contralateral adrenal gland. The adrenal glands have been histologically classified as (nodular) hyperplasia, adenoma and adenocarcinoma. The histologic diagnosis, however, does not provide information on functionality of the tumor, nor does it provide any prognostic information. No relationship has been found between pituitary and adrenal tumors in ferrets. At this stage, pituitary tumors should be regarded as incidental findings.

Different etiologies have been suggested for the high occurrence of hyperadrenocorticism in ferrets. These include (early) neutering of ferrets, housing ferrets indoors, and genetic background.

In recent years, evidence has been gathered that increased concentrations of gonadotropins, which occur after neutering (due to the loss of negative feedback), stimulate the adrenal cortex, eventually leading to an adrenocortical neoplasm.

- First, the initial signs of hyperadrenocorticism occur only during the breeding season, when plasma concentrations of gonadotropic hormones are high.
- Second, in the US, where the neutering of ferrets is common practice, hyperadrenocorticism is common, whereas hyperadrenocorticism is seldom diagnosed in the United Kingdom, where ferrets are usually not surgically castrated.
- Third, a significant correlation has been found between the age at neutering and age at onset of hyperadrenocorticism.
- Fourth, the depot gonadotropin-releasing hormone (GnRH)-agonists leuprolide acetate and deslorelin have been used successfully in the treatment of this disease.[6,7]
- Finally, luteinizing hormone (LH) receptors have been detected in the adrenal cortex of ferrets. These receptors are considered to be functional, because plasma concentrations of adrenal androgens increase after intravenous injection of a GnRH agonist.[4]

There remains debate, however, if the neutering has to take place at an early age for this disease to occur. In the US, ferrets are commonly neutered at an age of 6 weeks. In the Netherlands, however, most pet ferrets are neutered between 6 and 12 months of age. Since the prevalence of hyperadrenocorticism in Dutch ferrets is approximately 0.55% (95% confidence interval: 0.2–1.1%), it is likely that this disease is just as common in the Netherlands as it is in the US. The age at which

ferrets are neutered is therefore not likely to have an influence in the development of these tumors.

The hypothesis that ferrets that are being kept indoors have a higher chance of developing hyperadrenocorticism compared with ferrets housed outdoors is in line with the above mentioned hypothesis. Ferrets that are kept indoors will be more under the influence of light—and thus gonadotropins—than ferrets that are housed outdoors. This applies to neutered as well as intact ferrets. The fact that adrenal gland disease is less common in the United Kingdom can therefore be explained by the fact that many ferrets are still being kept outdoors without being neutered.

A genetic background can play a role in the etiology of this disease as well. In the US, a specific breeding facility, which provides an estimated 80% of all American ferrets, has been blamed for the high occurrence of hyperadrenocorticism in American ferrets. If this claim would be accurate, than why is the prevalence of hyperadrenocorticism so high in the Netherlands, where ferrets do not have the same genetic background as ferrets from this facility? Although the breeding facility cannot be blamed for the high incidence of hyperadrenocorticism in ferrets, this does not mean that a genetic background for the disease is not possible. In humans three different hereditary syndromes have been recognized in which multiple endocrine neoplasms are seen (MEN1, MEN2a and MEN2b). Since insulinomas and adrenal gland tumors are frequently seen simultaneously in ferrets, a condition similar to MEN in humans may exist. Research at the University of California, Davis is in progress to determine if this is indeed the case.

Clinical signs of hyperadrenocorticism in ferrets include symmetrical alopecia, vulvar swelling in neutered female ferrets, recurrence of sexual behavior after neutering, urinary blockage in males (due to peri-prostatic or peri-urethral cysts), occasional mammary gland enlargement in female ferrets, and pruritus. The skin is usually not affected, although some excoriations may be seen. Alopecia usually begins in spring, which coincides with the start of the breeding season, and may disappear without treatment. The next year the alopecia usually returns after which it usually does not resolve spontaneously at the end of the breeding season. Polyuria and polydipsia are reported in ferrets with hyperadrenocorticism. It is not clear, however, whether adrenal hormone production is responsible for these signs, or if these (elderly) ferrets have concurrent kidney disease. A case of LH-dependent hypercortisolism (Cushing's disease) has been diagnosed by the author. The major complaint in this ferret was severe PU/PD. Only a minimal amount of alopecia was found in this ferret. The diagnosis in this case was confirmed by a plasma ACTH-concentration which was below the detection limit, an increased urinary corticoid creatinine ratio, and a rise of the plasma cortisol concentration after the administration of human chorionic gonadotropin (hCG). During ultrasonographic examination an enlarged right adrenal gland was detected while the left adrenal gland could not be located. Polyuria and polydipsia resolved within 3 weeks after the administration of a deslorelin implant (see later). Plasma and urinary hormones had returned to normal 3 months after the initial diagnosis. It was striking to find that the right adrenal gland had diminished in size, while the left adrenal gland now had a normal appearance, suggesting that the left adrenal gland was initially atrophic. Two years after diagnosis the ferret is still doing fine without recurrence of symptoms.

When considering predisposing factors, age appears to be an important factor, which is in its turn linked to age at neutering (as mentioned earlier). In the US, diagnosis of hyperadrenocorticism in ferrets is already possible at an age of 2 years. In the Netherlands, however, most cases of hyperadrenocorticism are seen in ferrets older than 3 years of age. Although initial reports suggested that the majority of ferrets with adrenocortical disease were females, a Dutch study could not confirm this sex predilection. In the author's practice there is actually a tendency of seeing more male than female ferrets with hyperadrenocorticism.

The most important differential diagnoses for a ferret with signs of hyperadrenocorticism are a non-ovariectomized female or a ferret with active remnant ovaries. Severe alopecia and pruritus in a ferret, however, has also been seen due to a food allergy. Hormone analysis in blood and urine, as well as an abdominal ultrasound could not confirm the presence of a hyperfunctioning adrenal gland in this case. All signs in this ferret resolved after it had been converted to a different brand of ferret food.

Although many advanced techniques can be used in diagnosing hyperadrenocorticism in ferrets, the clinical signs remain the most important. Further confirmation can sometimes be obtained by palpating a (tiny) firm mass craniomedial to the cranial pole of the kidneys, representing the enlarged adrenal gland(s). The right adrenal gland is more difficult to palpate due to the overlying right caudate process of the caudate liver lobe. Hormones that are commonly elevated are androstenedione, estradiol, and 17-hydroxy-progesterone. Blood can be sent to the University of Tennessee for analysis of these hormones. Dehydroepiandrosterone sulfate used to be included in this panel, but is currently no longer incorporated. Elevation of one or more of these hormones is considered to be diagnostic for hyperadrenocorticism. However, plasma concentrations of androstenedione, estradiol, and 17-hydroxyprogesterone in intact female ferrets are identical to those in hyperadrenocorticoid ferrets. It is therefore likely that this hormone panel does not aid in differentiating between a ferret with hyperadrenocorticism and one with an active ovarian remnant. The author therefore does not routinely measure these hormones in the diagnosis of this disease. He does, however, measure plasma concentrations of androstenedione (the only androgen in the panel and precursor of estradiol) for the evaluation of hormonal treatment.

ACTH stimulation tests and dexamethasone suppression tests—as commonly used in dogs with

Cushing's syndrome—are not considered diagnostic in ferrets. In addition, plasma concentrations of ACTH and α-MSH in hyperadrenocorticoid ferrets were found to be identical to those from healthy neutered ferrets. It was concluded that these hormones, therefore, could not aid in diagnosing hyperadrenocorticism in ferrets.

Plasma cortisol concentrations have, just as in dogs, been found to be of no use for the diagnosis of hyperadrenocorticism in ferrets. In dogs, it has become standard to measure the urinary corticoid-creatinine ratio (UCCR), in combination with a high dose dexamethasone suppression test (HDDST). An increased UCCR has also been found in ferrets with adrenocortical disease. The HDDST demonstrated that the hyperadrenocorticism is of adrenal and not pituitary origin. This is in agreement with the fact that no functional pituitary tumors have been found in hyperadrenocorticoid ferrets. Although the UCCR is elevated in ferrets with adrenocortical tumors, the UCCR is considered to be of no diagnostic value because this ratio is also increased in intact ferrets during the breeding season, and in ferrets with an active ovarian remnant.

The most useful tool in diagnosing hyperadrenocorticism in ferrets is abdominal ultrasonography. One has to remember, however, that with this technique only the size of abdominal organs is visualized. This technique does not provide any information on hormone release. It is therefore possible that only one adrenal gland is enlarged, while both adrenal glands contribute to the androgen release. Ultrasound is especially of great value prior to surgery, if you want to determine which adrenal gland is affected, or if an ovarian remnant is present. In this way the owner can be informed about the potential surgical risks that may be encountered. Another advantage of this technique is that other abdominal organs can be evaluated during the same procedure.

It has been reported that adrenal glands may remain undetected during an ultrasonographic exam. It is especially difficult to distinguish an adrenal gland from an abdominal lymph node. By using specific landmarks, however, the adrenal glands can fairly easily be detected in nearly 100% of the cases. The left adrenal gland is located lateral to the aorta, at the level of the origin of the cranial mesenteric and celiac arteries. The right adrenal gland is more difficult to locate. Since this adrenal gland lies adjacent to the caudomedial aspect of the caudate process of the caudate liver lobe, the liver may be used as an acoustic window. The three major vessels (aorta, portal vein and caudal vena cava) in that area are located. The vena cava is the most lateral and dorsal of the three. In addition, the portal vein has a much wider diameter compared to the caudal vena cava. The right adrenal gland is attached to the dorsolateral surface of the caudal vena cava, at the level of and/or immediately cranial to the origin of the cranial mesenteric artery. The adrenal glands of ferrets with hyperadrenocorticism have a significantly increased thickness, have a rounded appearance, a heterogeneous structure, an increased echogenicity, and sometimes contain signs of mineralization.

When attempting to treat a ferret with hyperadrenocorticism, the most ideal treatment would probably be a combination of surgery and placement of an implant containing deslorelin (a depot GnRH analogue). Many different factors influence the eventual choice of treatment. An owner may decline surgery based on criteria such as the age of the ferret, presence of concurrent disease (cardiomyopathy), risk of surgery when the right or both adrenal glands are involved, and financial limitations. When an owner chooses for only surgery, gonadotropin release will persist, resulting in continued stimulation of the remaining adrenal gland. Disadvantage of hormonal therapy (use of a depot GnRH agonist such as leuprolide acetate) may be the price of this drug and the fact that it needs to be repeated on a regular basis. Once the deslorelin implants become registered for use in animals the latter disadvantage will be diminished. Autonomous production of steroids by the adrenal gland may result in loss of response to treatment with a depot GnRH agonist.

Surgical removal of the left adrenal gland is fairly easy. The adrenal gland is dissected out of the retroperitoneal fat and the *Vena phrenicoabdominalis* is ligated. The location of the right adrenal gland makes it much more difficult to remove. The close proximity to the liver and the dorsolateral attachment to the caudal *Vena cava* would make a dorsal approach more logical. This is in fact the surgical approach to the adrenal glands in humans. In ferrets, however, an abdominal approach is most commonly used. During resection of the right adrenal gland, either a part of the adrenal needs to be left attached to the *Vena cava*, or part of the wall of the vein has to be removed. Ligation of the caudal *Vena cava* is only possible if this vein is already occluded for a major portion of its diameter and collateral veins have opened up. If this is not the case there is a great risk of hypertension distal to ligation which may lead to acute kidney failure. Although the author is not in favor of removing bilateral adrenocortical tumors, different surgical protocols have been proposed. Many advise to leave part of an adrenal gland behind, while others advise to remove both adrenal glands. It would seem likely that hypoadrenocorticism would occur after removing both glands, but this seems to occur only in a minority of cases. Accurate diagnosis of an Addisonian crisis, including an ACTH stimulation test to confirm the diagnosis, has not been published. It appears, however, that short-term treatment with cortisone and fludrocortisone seems to be sufficient in most cases.

The most effective drugs at this moment are the depot GnRH-agonists of which leuprolide acetate (Lupron Depot, TAP Pharmaceutical Products) is the most well known. Deslorelin is another pharmaceutical GnRH-analogue. This drug is commercially available as implant for chemical castration of male dogs in Australia (Suprelorin®, Peptech Animal Health, Australia). Advantages of these implants over leuprolide acetate are that the drug does not need to be reconstituted, lasts much longer than the depot injections, will be registered

for use in animals, and will probably be cheaper. These implants have already been used in ferrets with hyperadrenocorticism and seem to be very effective. Once this drug becomes commercially available in Europe and the US, it is likely that this will become the drug of choice. Approximately 10% of ferrets seem to develop adrenal carcinomas after 1.5 to 2 years of treatment. More research will be necessary to determine why these tumors are seen, and how high the frequency actually is.

Until the deslorelin implants are commercially available leuprolide acetate provides a suitable alternative. The Lupron 30-day Depot formulation is given in a dose of 100 µg IM for ferrets less than 1 kg and 200 µg IM for ferrets over 1 kg. This drug will suppress adrenocortical hormone release for at least 1 month in ferrets and may even last up to 3 months. Some veterinarians use a 3-month formulation (which is 3 times as expensive), but this drug does not seem to work 3 times longer than the 30-day formulation.

It may seem strange that a depot GnRH-agonist is used in ferrets with hyperadrenocorticism, when the increased release of GnRH and gonadotropins, which occur after neutering, are responsible for the disease in the first place. To understand the mechanism behind this treatment, it is important to know that pituitary and hypothalamic hormones are released in a pulsatile fashion. Gonadotropins are only released when GnRH is secreted in pulses. The depot GnRH-agonist overrides the pulsatile release, thereby blocking the release of gonadotropins. The administration of a depot GnRH agonist therefore results in an initial single release of gonadotropins followed by baseline concentrations.

Melatonin has also been proposed as therapeutic option for hyperadrenocorticoid ferrets. Mink which receive such an implant develop appealing thick furs. This has also been reported in ferrets. Melatonin supposedly suppresses the release of GnRH. Researchers showed in the early eighties of the last century that ferrets, which were kept under 8 h light : 16 h darkness (8L : 16D), would come into estrus only 7 weeks later than ferrets exposed to long photoperiods (14L : 10D). It is therefore debatable if melatonin is indeed capable of suppressing the release of gonadotropins. Clinical improvement, however, is seen in hyperadrenocorticoid ferrets either receiving 0.5 mg melatonin daily PO or an implant containing 5.4 mg melatonin. In the study in which melatonin was given orally, however, hormone concentrations, in general, rose and the tumors continued to grow. This treatment may therefore pose a risk to the ferrets as their condition deteriorates, which remains unnoticed by the owner. Another point to consider is that melatonin can be purchased in drugstores in the US. Home-medication with melatonin may therefore delay the initial presentation of ferrets with hyperadrenocorticism to veterinarians.

As described above, the most common medical treatment option for ferrets with hyperadrenocorticism is the use of a depot GnRH agonist. Ketoconazole and mitotane (o,p'-DDD) are well known drugs for treating hypercortisolism in dogs and humans. These drugs have also been tried in ferrets, but both were not considered very effective and should be considered obsolete.

In recent years Trilostane (Vetoryl®, Arnolds Veterinary Products/Dechra Veterinary Products), a 3β-hydroxysteroid dehydrogenase (3β-HSD) blocker, has become an important drug for treating pituitary-dependent hyperadrenocorticism in dogs. Since 3β-HSD is necessary for the synthesis of androstenedione and 17-hydroxyprogesterone it is tempting to speculate that this drug would be very effective in treating ferrets with hyperadrenocorticism. In a pilot study 5 mg trilostane was given orally once daily to a ferret with hyperadrenocorticism. Within a month the owner complained that the alopecia and vulvar swelling in the ferret increased. Plasma hormone analysis showed a decreased 17-hydroxyprogesterone concentration, but increased concentrations of androstenedione, estradiol, and dehydroepiandrosterone sulfate. These results can be explained by the fact that a decrease of 3β-HSD may lead to an activation of 17,20-lyase, and thus the androgen pathway. In another hyperadrenocorticoid ferret in which the depot GnRH agonist did not seem to work anymore, no improvement was seen after a month of treatment with trilostane. The hormone concentrations in this ferret did not decrease or increase in this ferret during the treatment with trilostane. More research is necessary before this drug can be safely used in ferrets.

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ADDITIONAL READING

1. Nico Schoemaker's PhD thesis on hyperadreno-corticism in ferrets can be found online at: http://igitur-archive.library.uu.nl/dissertations/2003-1128-094343/inhoud.htm.