COMMISSIONED PAPER (NL)

Endocrine diseases in ferrets

Nico J. Schoemaker[*1], *Yvonne R.A. van Zeeland*[1]

SUMMARY

Endocrine diseases are among the most commonly seen conditions in ferrets. Tumours of the islet cells in the pancreas, referred to as insulinomas, and tumours of the adrenal glands, referred to as hyperadrenocorticism, are more commonly described in this species than in any other species. Insulinomas are predominantly benign, insulin-producing tumours which cause hypoglycaemia and associated clinical signs, such as weakness of the hind limbs, a glazed look in the eyes and/or coma. Due to their small size, visualisation of insulinomas is difficult, rendering measurement of blood glucose as the primary diagnostic tool. The condition can be managed both surgically as well as medically. After diagnosis, the average survival is one year due to the appearance of new islet cell tumours.

Hyperadrenocorticism is even more common than insulinomas. The clinical signs, which result from increased plasma concentrations of androgens and oestrogen, are most frequently seen in neutered animals and include return of sexual behaviour, signs of oestrous in females and difficulty urinating in males due to the pathology of the prostate. Diagnosis is based on clinical signs in combination with identifying the affected gland during an ultrasonographic examination. Surgery as well as hormonal therapy are treatment options which are discussed.

Keywords: Insulinoma, hypoglycaemia, hyperadrenocorticism, adrenal gland, Mustela putorius furo, androgen

This paper was commissioned by FECAVA

Introduction

Endocrine diseases, especially neoplastic conditions, are commonly seen in ferrets. Insulinomas or islet cell tumours, and adrenocortical tumours constitute the majority of these neoplasms and are particularly common in middle-aged to older ferrets, although they may be occasionally seen in younger ferrets as well. Both of these diseases will be addressed later.

Aside from these two endocrine disorders, persistent oestrous is also a well-known endocrine condition that affects non-neutered female ferrets. Female ferrets are induced ovulators and therefore remain in oestrus until they are mated, or for as long as daylight lasts longer than 12 hours. The prolonged oestrous may subsequently result in an oestrogen-induced bone marrow suppression, and thus pancytopenia (Fig 1)[1]. Neutering is therefore recommended in any ferret which is not bred. Surgical intervention may however, potentially result in the development of adrenal neoplasms, hence explaining the high incidence of hyperadrenocorticism in pet ferrets.

[1] Division of Zoological Medicine, Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University,Yalelaan 108, NL-3584 CM, Utrecht

* Corresponding author E-Mail: N.J.Schoemaker@uu.nl;

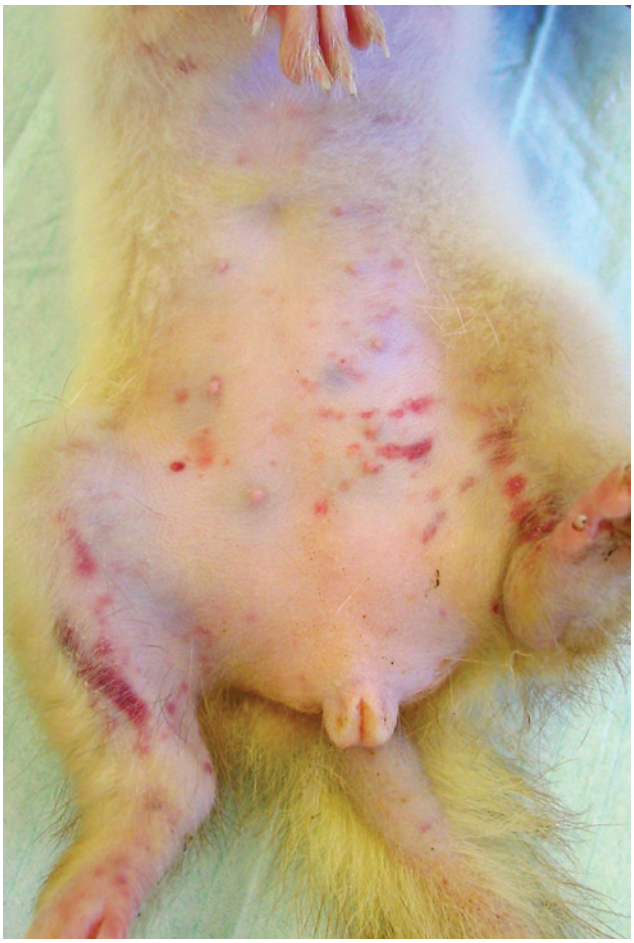

Figure 1 Petechiae due to thrombocytopaenia in a ferret with persistent oestrous

(Spontaneous) diabetes mellitus has been reported in ferrets, but is a relatively uncommon and difficult to treat disease in ferrets [2]. The clinical signs are identical to those in the more common companion animal species and include polyuria/polydipsia, lethargy and weight loss despite good appetite. Glucosuria combined with plasma glucose concentrations over 21 mmol/L are suggestive of the diagnosis, although repeated measurements are advised. A reference interval has been determined for fructosamine in ferrets (101 – 202 µmol/L [3]), but to date, no measurements have been performed in cases of (confirmed) diabetes mellitus. Although treatment with insulin is considered challenging [2], treatment with twice daily SC injections (0.5 U) of the long-acting peakless insulin glargine has been reported to be successful [4]. Since the type of diabetes mellitus is undetermined in ferrets, the use of oral hypoglycaemic drugs, such as glipizide, is questionable [5].

A few cases of hypothyroidism have been reported [6]. Clinical signs observed in these ferrets included obesity and lethargy. After finding low thyroid hormone levels, hypothyroidism was suspected, but similar to dogs and cats, confirmation of the diagnosis required the use of a TSH-stimulation test [6]. Oral treatment with 50 – 100 µg levothyroxine, twice daily has been found effective [6].
Of the endocrine diseases described in companion animals, the following have never been documented in ferrets: growth hormone deficiency or growth hormone excess, diabetes insipidus, hyperthyroidism, hypo- and hyperparathyroidism and spontaneous hypoadrenocorticism (Addison's disease). These diseases would therefore not be placed high on the differential diagnosis list. A single case report of a C-cell carcinoma [7] and a case of pseudohypothyroidism [8] have been described, however. Despite the lack of reported cases, the above mentioned differentials should not be ruled out, and further diagnostic work-up for such diseases is warranted when confronted with a ferret with clinical signs corresponding to symptoms seen in dogs and/or cats with the aforementioned endocrine diseases.

Due to the relatively infrequent occurrence of endocrine diseases other than insulinoma and hyperadrenocorticism, this review will further focus on the latter two conditions, and give an overview of the currently available information on their respective aetiology, clinical signs, diagnostic work-up, therapeutic intervention and prognosis.

Insulinoma

Insulinomas or islet cell tumours are small tumours (Fig 2) of the pancreatic beta cells which results in the production of excessive amounts of insulin and subsequent hypoglycaemia. The distribution of these adenomas, which are usually between 0.5 and 2 mm, is equal among the sexes. With a reported prevalence of 20-25% of the diagnosed neoplasms in ferrets, insulinomas are one of the most commonly diagnosed tumours in middle-aged to older ferrets, with a

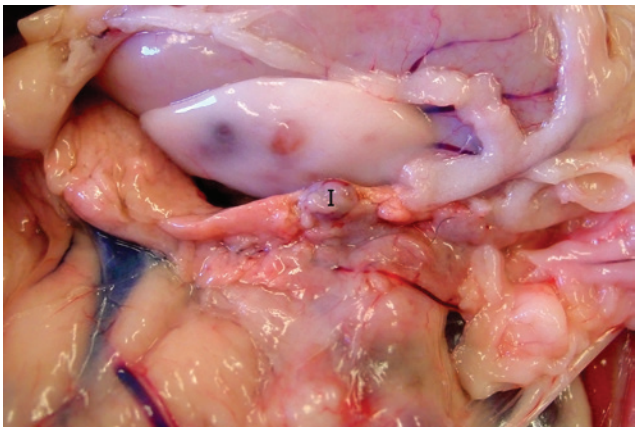

Figure 2 A relatively large tumour within the pancreas of a ferret is seen at (I). Histological examination of this tumour proved it to be of islet cell origin.

median age of 5 years (range 2 - 8 years) [2,9,10,11,12].

Aetiology

The aetiology of the development of insulinoma in ferrets is unknown. The limited genetic diversity of ferrets, which stem from a limited number of breeder farms, has led to the suggestion that a genetic component may be involved [5]. Another theory suggests that, based on the natural carnivorous diet of mustelids, diets high in carbohydrates may contribute to the development of these tumours [13]. A diet high in protein (42–55%#), high in fat (18–30%#1), low in carbohydrates (8-15%#1), and low in fibre (1–3%#1) has therefore been advised to reduce the incidence [13]. Alternatively, feeding commercial balanced diets based on entire prey animals has been recommended. No scientific evidence, however, is available to back up any claims on the aetiology of insulinoma, nor has it been proven that the incidence is reduced when ferrets are fed prey based diets or low-carbohydrate kibble.

Clinical signs

Clinical signs vary from lethargy, slight incoordination and weakness in the hind limbs to complete collapse and coma [2]. In humans, an overdose of insulin may result in stimulation of the autonomic nervous system resulting in nausea. The nausea, which is commonly seen in ferrets with an insulinoma, but not in dogs and cats, often manifests itself in the form of ptyalism and pawing at the mouth. In addition, owners may notice a glazed look in the eyes of their ferrets. Signs are most evident when the ferret has not eaten for some time, and will often resolve spontaneously after providing the ferret with some food (Fig 3) or a calorie-rich beverage. If the waxing and waning of the signs are not seen, other diseases affecting the hind limbs should also be considered [2,11].

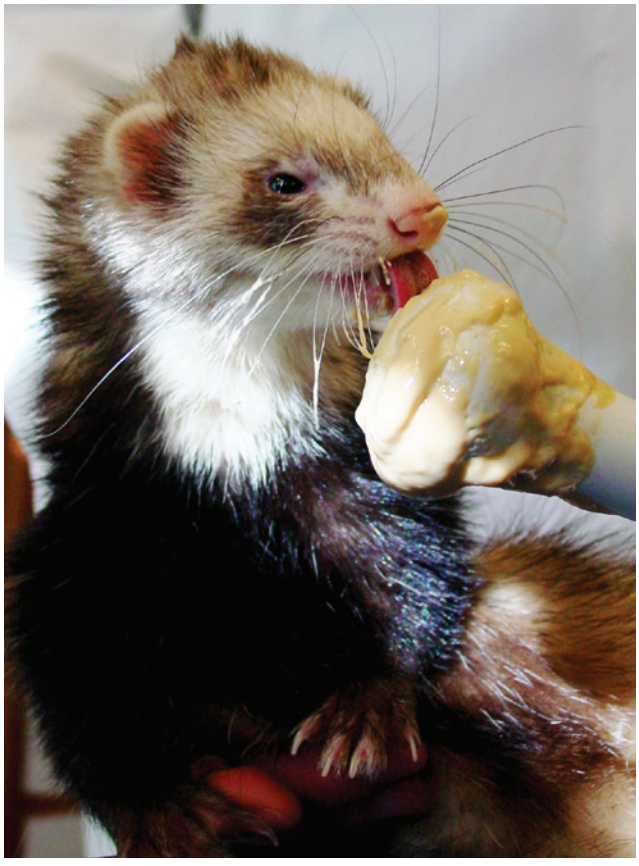

Figure 3 A ferret in a hypoglycaemic crisis may be fed a protein rich diet to quickly correct the energy balance

Differential diagnosis

The differential diagnosis of hind limb weakness consists of: neurological diseases (e.g. trauma, intervertebral disc disease, Aleutian disease), cardiac disease, generalized weakness and metabolic disorders, such as hypoglycaemia [14]. In ferrets, hypoglycaemia is considered the most commonly seen cause of hind limb weakness.
Within the differential diagnosis of hypoglycaemia, excessive glucose consuming conditions, such as rapid multiplying neoplastic cells, severe hepatic disease and sepsis should be considered#[2]. These conditions can usually be ruled out based on the results of the history, physical examination and/or the diagnostic work-up.

Diagnostic work-up

Blood chemistry – Blood glucose concentrations lower than 3.8 mmol/l (reference range: 5.0 – 6.9 mmol/l), after withholding food for 4 hours, are highly suggestive of an insulinoma when ferrets display the above mentioned signs [9]. In ferrets with blood glucose concentrations between 3.9 and 5.0 mmol/l, the authors advise to prolong the fast with another 2 hours. In many cases, the blood glucose will then drop to below 3.8 mmol/l confirming the tentative diagnosis. Portable blood glucose meters (PBGM) seem very practical for obtaining quick results. They only need one drop of blood which can be collected from any vein (Fig 4), but also from a puncture of a footpad. Due to the method of analysis, heparinized blood should not be used. In a comparison study evaluating the agreement between glucose concentrations measured with a laboratory analyser and 3 different PBGMs it became clear that the human PBGMs severely underestimate the actual glucose concentrations [15]. The veterinary PBGM had 2 settings in which the canine setting produced the most agreeable values. If one wants to use a PBGM in practice, it is good to realize that underestimation is possible and that accurate values can only be obtained with a laboratory analyser. Plasma insulin concentrations can also be measured and are usually

based on dry matter base

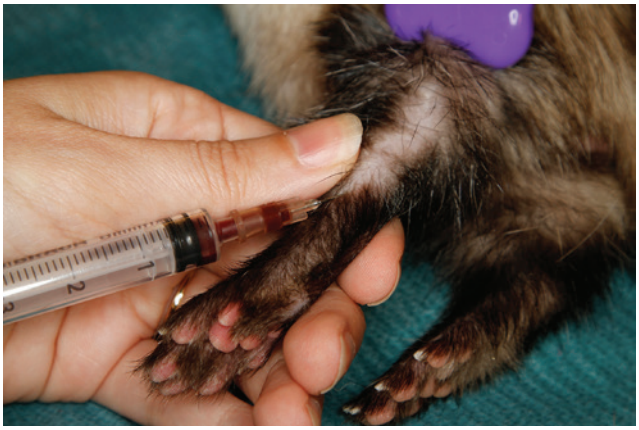

Figure 4 In ferrets suspected of having an insulinoma, blood may be collected from the lateral saphenous vein

increased, but concentrations within the reference range may also be seen [2]. The latter should still be considered increased, as insulin plasma concentrations should decrease during a hypoglycaemic event [2].

Diagnostic imaging – As insulinomas are usually very small in size (0.5–2 mm), it is extremely difficult to visualize the primary tumour by use of ultrasound [16]. In the experience of the authors, insulinomas may occasionally be visualized by ultrasound, but they are also frequently missed. In dogs, insulinomas have a poor prognosis due to the high rate of metastasis, which frequently occurs to the liver. These metastases can be visualized on ultrasound. Adenocarcinomas of the pancreas have been reported in ferrets, and metastases have been found on ultrasound [16]. The great majority of insulinomas, however, are benign and do not metastasise [11]. Diagnostic imaging in the form of radiography or ultrasound examination is therefore not routinely advised. Computed Tomography, MRI and nuclear scintigraphy with octreotide or indium-111 have, to the authors' knowledge, not been used in ferrets to diagnose insulinomas. The expense of the nuclear scanning and the lack of sensitivity in finding insulinomas in dogs and humans with CT and MRI make these advanced diagnostic imaging tools less promising for future use in practice [2].

Treatment

Insulinomas may be managed surgically and/or medically. Many factors, such as age of the ferret, desire of the owner to have an instant solution and/or financial restrictions, may play a role in the decision-making process. It is recommended by the authors that a veterinarian presents all facts, in order to allow the owner to make an informed decision based on the pros and cons of each method.

Surgical treatment – To fully eliminate the source of excess insulin production, surgical removal is seemingly the best therapeutic option. Due to the limited ability to visualize the tumours, the possibility to excise the insulinoma(s) can only be evaluated upon explorative surgery. Surgical excision may not be successful in alleviating the clinical signs as some tumours may remain undetected during surgery due to their small size. A partial pancreatectomy has therefore been recommended over pancreatic nodulectomy in order to remove as much undetectable islet cell tumours and thus increase the survival time after surgery [11]. In addition, if the neoplasm is located in the body of the pancreas, it is often difficult to remove, as resection of this part of the pancreas is not possible due to the presence of the pancreatic duct. A mean disease free state after surgery of about 1 year, and survival times of over 3 years have been reported [2,11]. Recurrence of clinical signs are mainly due to the occurrence of new insulinomas and not due to metastasis of the removed tumour. If too much of the pancreas is removed, complications such as diabetes mellitus may occur. It should be stressed that every effort should be taken to avoid this condition from occurring, since the medical management of insulinoma is far easier than that of diabetes mellitus. It could also be speculated that an exocrine pancreatic insufficiency could occur when too large a portion of the pancreas is removed. However, this has not been reported.

Medical treatment – Prednisolone and diazoxide are the most commonly used drugs for treating insulinomas. Somatostatin, which inhibits the synthesis and secretion of insulin by normal and neoplastic beta cells, has also been incidentally used in ferrets, but no clear beneficial effects were seen over the other two modes of treatment [2]. In private practice, prednisolone and other glucocorticoids, which induce gluconeogenesis, are frequently used as the drug of first choice. Although these drugs commonly induce side-effects in other species, ferrets seem relatively refractory to developing side-effects due to glucocorticoid administration, and generally respond well to the treatment protocol [2]. Weight gain and impaired hair growth (suggestive of iatrogenic Cushing's disease), however, has been reported in ferrets that have received glucocorticoids for prolonged periods of time [9]. In addition, the gluconeogenic mode of action of glucocorticoids results in an increase of glucose, which may be contraindicated in ferrets with insulinomas due to the risk of stimulating the secretion of insulin.

Diazoxide, which is registered for treating human insulinoma patients, inhibits insulin release [2]. The authors therefore prefer this drug over the use of glucocorticoids. The drug, however, is more expensive than prednisolone, which may also explain why prednisolone is frequently chosen over diazoxide. Although this is a factor to be considered in dogs (especially larger breeds), the ferret's low body weight results in limited daily requirements of the drug, thereby making diazoxide an affordable alternative for ferrets. Compounding the drug is, however, necessary to allow accurate dosing. Treatment is started at an oral dose of twice daily 5 mg/kg diazoxide. Based on the response to treatment (as judged by disappearance or continuation of clinical signs), the dose may need to be increased gradually. When using plasma glucose concentrations to monitor the effect of treatment, blood should always be collected 4 hours after giving the diazoxide. During this period food should be withheld from the ferret. Once the dose of diazoxide has been increased to 15 – 20 mg/kg q12h and clinical signs still have not resolved, prednisolone may be added to the treatment protocol in a concentration of 0.2 – 1 mg/kg PO, q24h. For both drugs, doses may be increased further if necessary, with no real upper limits existent. The only limiting factor may therefore be the development of side-effects such as vomiting and anorexia [2]. Medical management based on the aforementioned protocol is usually sufficient to control hypoglycaemia for a period up to 18 months, with some ferrets in the authors' clinic even surviving up to 2 years on medical treatment.

Prognosis

In ferrets, the prognosis is better compared to dogs, in which metastases are very common. Although metastases are rare in ferrets, multiple tumours and recurrent signs are common. Recurrent signs are probably due to the development of new tumours rather than metastasis of the earlier tumour [2].

Hyperadrenocorticism

Hyperadrenocorticism is most commonly seen in neutered pet ferrets that are older than 3 years of age. An exact incidence of the disease is not known, but some have reported that up to 95% of ferrets presented for post mortem examination have adrenal pathology [9]. In the United States, however, some ferrets are already diagnosed with the disease at the age of 2 years. The disease affects males and females equally [17].

In contrast to dogs (in which excessive production of glucocorticoids [hypercortisolism or Cushings' syndrome] is most common) and cats (in which excessive production of mineralocorticoids [hyperaldosteronism or Conn's syndrome] is most common), hyperadrenocorticism in ferrets most commonly results in hyperandrogenism. In rare cases, hypercortisolism [18] or hyperaldosteronism [19] may be seen in ferrets as well.

Hyperadrenocorticism in ferrets is characterized by elevation of plasma levels of plasma androstenedione, 17∝-hydroxyprogesterone and/or oestradiol concentrations [18]. In ferrets with hyperadrenocorticism, a unilateral or bilateral enlargement of the adrenal glands may be present. A unilateral enlargement (without atrophy of the contralateral adrenal gland) appears to be most common (present in approximately 85% of ferrets) [20]. In these cases, however, disease may develop in the contralateral adrenal gland after surgical removal of the initially affected gland, thereby leading to recurrence of the disease [21]. Bilateral enlargement may be found in a small percentage of cases (approximately 15% of ferrets with adrenal gland disease) [20]. The adrenal tumours have been histologically classified as (nodular) hyperplasia, adenoma and adenocarcinoma [20]. This histological diagnosis, however, does not provide any prognostic information, nor does it say anything about functionality of the tumour. In contrast to dogs with Cushing's disease, no relationship has been found between pituitary and adrenal tumours in ferrets [22].

Aetiology

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

(Early) neutering – In previous years, it has been hypothesized that a castration-related increase of gonadotrophins, which develops as a result of a loss of negative feedback from the gonads, stimulates the adrenal cortex, eventually leading to the development of an adrenocortical neoplasm (Fig 5) [17,20]. Findings in support of this hypothesis include 1) initial signs of hyperadrenocorticism occur only during the breeding season, when plasma concentrations of gonadotrophic hormones are high [23]; 2) adrenal tumours are more frequently seen in countries where ferrets are routinely neutered (USA), compared to countries where ferrets were not routinely surgically castrated in the past (UK) [24]; 3) a significant correlation has been found between the age at neutering and age at onset of hyperadrenocorticism [17]; 4) the successful use of the depot gonadotrophin-

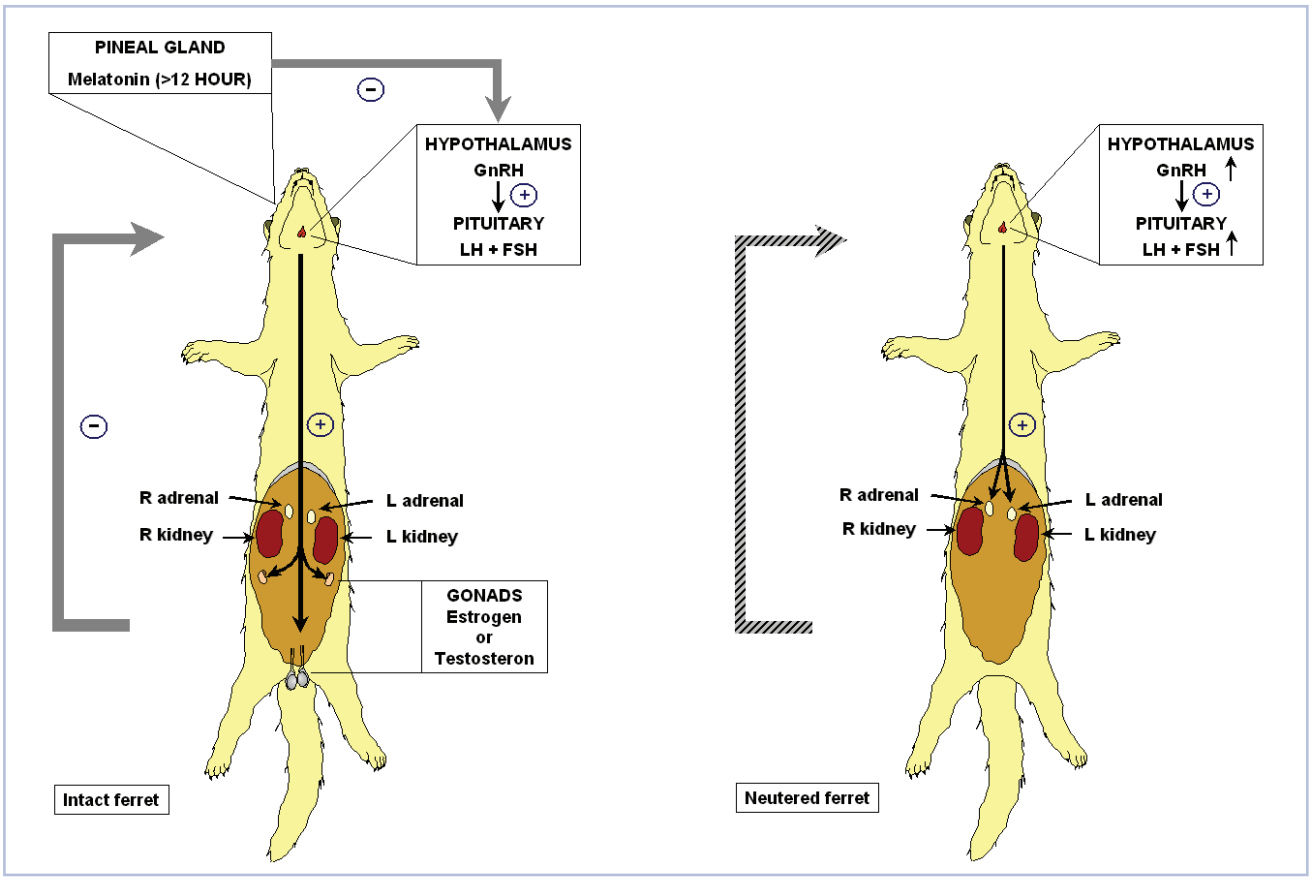

Figure 5 Diagram illustrating the regulation of reproductive endocrinology in intact ferrets, the consequences of neutering on this process, and the possible role it plays in the development of hyperadrenocorticism in this species. In short; high melatonin concentrations for more than 12 hours per day suppress the release of GnRH. When this suppression is lost, GnRH is released in a pulsatile fashion, resulting in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate the release of estrogen and testosterone. This exerts a negative feedback on the hypothalamus and pituitary gland. When ferrets are neutered this negative feedback is lost, resulting in an increased release of the gonadotrophins, which may activate their respective receptors in ferret adrenal glands if they are present.

releasing hormone (GnRH)-analogues leuprolide acetate and deslorelin, which lead to a decrease in gonadotrophins, in the treatment of hyperadrenocorticism [25,26]; and 5) the increased plasma androgen concentrations seen after an intravenous injection of a GnRH-agonist, as a result of the presence of functional luteinizing hormone (LH) receptors in the adrenal cortex of ferrets [24]. Although a correlation has been found between neutering and occurrence of adrenal tumours in ferrets, it is questionable whether the age of neutering is of influence as the prevalence of hyperadrenocorticism in Dutch ferrets (which are usually neutered between 6 and 12 months of age) appears to be more or less similar to the prevalence in the USA ferrets (which are commonly neutered at an age of 6 weeks) [17]. The age of neutering may thus be of less importance for the development of adrenocortical tumours in ferrets than neutering itself.

Housing ferrets indoors – Similar to the hypothesis that increased gonadotrophin levels induced by neutering pose an increased risk for developing adrenal gland tumours, indoor housing may also pose as a risk factor for developing increased gonadotrophins and subsequent hyperadrenocorticism [27]. As ferrets that are kept indoors will be exposed to longer daylight periods (i.e. owners will have lights on inside when it is already dark outside), melatonin will be longer suppressed, resulting in prolonged periods of elevated gonadotrophin plasma concentrations in comparison to ferrets that are housed outdoors. This hypothesis is further supported by the lower incidence of adrenal gland disease in the UK, where many ferrets are kept outdoors [28]. Lack of neutering in these ferrets may, however, (partially) bias these findings [28].

Genetic background – In addition to the previous two hypotheses regarding the aetiology of hyperadrenocorticism in ferrets, a genetic background has also been suggested. As ferrets have a high incidence of both insulinomas and adrenal gland tumours, it has been hypothesized that the hereditary changes causing multiple endocrine neoplasms

in humans (MEN1, MEN2a and MEN2b), could also play a role in the aetiology of the formation of adrenal tumours in ferrets [29]. Since many of the ferrets in the USA come from the same breeding facility, thereby sharing a similar genetic background, it is possible that in the USA the limited genetic variation of ferrets poses an explanation for the high incidence of the disease. Ferrets in the Netherlands, however, do not share this similar background. It therefore remains questionable if the MEN genes are involved. Further research is needed to identify whether genetic abnormalities are involved.

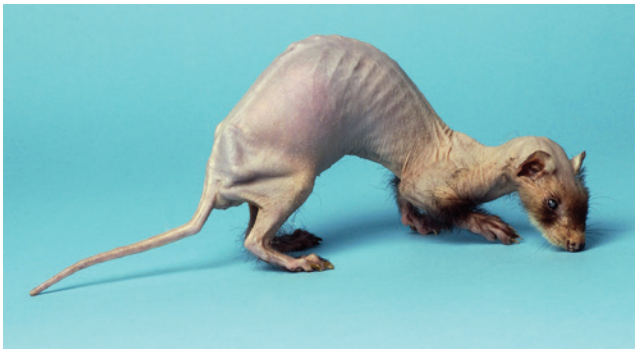

Figure 6 Severe alopecia seen in a 7-year-old, neutered female ferret with hyperadrenocorticism

Clinical signs

The most common clinical signs in ferrets with hyperadrenocorticism include symmetrical alopecia (Fig 6), recurrence of sexual behaviour after neutering, and pruritus [17,20,21]. Skin lesions are usually absent, unless scratching results in excoriations. In (neutered) female ferrets, vulvar swelling and occasional mammary gland enlargement may furthermore be noted [17,20,21], whereas in the male ferrets dysuria, pollakisuria and/or anuria may be encountered due to the development of secondary peri-prostatic or peri-urethral cysts causing urethral obstruction [30,31].
Polyuria and polydipsia has also been documented in ferrets with hyperadrenocorticism [20,21]. Whether this is due to concurrent kidney disease occurring in (elderly) ferrets, or the adrenal hormone production is not known. In a case of LH-dependent hypercortisolism (Cushing's disease) in a ferret, PU/PD was the primary clinical sign, while the other common signs of hyperadrenocorticism in ferrets, such as alopecia, were only minimally present [18].

Differential diagnoses

The most important differential diagnoses for the female ferrets with signs of hyperadrenocorticism is the presence of an active ovary, either due to a remnant of the removed ovary, or an animal which was not ovariectomized at all [2]. Food intolerance should be considered in both sexes which show signs of severe alopecia and pruritus. Infectious skin diseases should also be considered in those cases. In the latter cases, however, the skin itself will be affected. Seasonal alopecia is also commonly mentioned as a differential diagnosis. As indicated by its name, this condition is characterized by a seasonal occurrence of alopecia, with hair loss predominantly occurring on the tail. Although the actual cause for this condition is not known, the authors suspect that it may be an early sign of hyperadrenocorticism as well [2].

Diagnostic work-up

Physical examination – The diagnosis of hyperadrenocorticism can be made based on the presence of the typical signs of hyperadrenocorticism combined with the exclusion of the other differential diagnoses. During abdominal palpation, a (tiny) firm mass, representing the (enlarged) adrenal tumour, may be palpated craniomedial to the cranial pole of the kidneys [2]. The left adrenal tumour is more easy to palpate compared to a tumour located in the right adrenal gland. The right adrenal gland, on the other hand, is located more cranial, with the caudal part of the caudate liver lobe located ventral to the gland, thereby obscuring it from palpation [2].

Blood chemistry – Hormone analysis is most commonly recommended in the diagnostic work-up of ferrets suspected of hyperadrenocorticism [2,32]. For this purpose, EDTA plasma may be collected and sent to an external laboratory for analysis of androstenedione, oestradiol, and 17α-hydroxyprogesterone. This laboratory should have established reference values for these hormones in ferrets, as laboratories may use different methods to analyse these hormones, which may greatly influence the concentrations that are measured. Elevated plasma levels of one or more of the aforementioned hormones have been considered as diagnostic for hyperadrenocorticism in ferrets [32]. Plasma concentrations of androstenedione, oestradiol, and 17 α -hydroxyprogesterone in intact female ferrets, however, are identical to those in hyperadrenocorticoid ferrets [2]. The authors therefore do not consider the analysis of these hormones to help differentiate between the differential diagnoses. The measurement of these hormones may, however, be useful for monitoring the effect of treatment.

Urine analysis – The urinary corticoid-creatinine ratio (UCCR), in combination with a high dose dexamethasone suppression test (HDDST), is a common diagnostic test

for Cushing's disease in dogs [33]. This test has also been performed in ferrets and resulted in the finding of increased urinary cortisol concentrations in ferrets with hyperadrenocorticism [34,35]. As the test does not distinguish between the ferret with an adrenal tumour and an intact ferret, it is however, not considered diagnostic [35].

Diagnostic imaging – Abdominal ultrasonography is considered the most useful tool in diagnosing hyperadrenocorticism in ferrets by the authors [36]. It should be emphasized, however, that ultrasound only allows establishment of the size and morphology of the organs and does not provide any information on the functionality of the tumour. Ultrasound is, however, useful when surgical intervention is considered as it allows identification of a ovarian remnant and/or the affected adrenal gland(s). During the ultrasonographic exam, adrenal glands have a similar appearance as (abdominal) lymph nodes. Specific landmarks are therefore needed to accurately detect the adrenal glands [36]. For the left adrenal gland, which is located lateral to the aorta, the cranial mesenteric and celiac arteries branch of the aorta may be used as landmarks (Fig 7). The right adrenal gland, in contrast, is more difficult to locate as it is located dorsally to the caudomedial aspect of the caudate process of the caudate liver lobe, and attached to the dorsolateral surface of the caudal vena cava (Fig 8A). To locate this gland, the aorta, portal vein and caudal vena cava may be used as landmarks. First, these vessels are located in the region of the caudate process of the liver, of which the portal vein is the most ventral of the three, and the one with the widest diameter. The aorta is the most dorsal of the three, and pulsates. After identifying the different vessels, the right adrenal gland may be located at the level of and/or immediately cranial to the origin of the cranial mesenteric artery (Fig 8B). The ultrasonographic changes of a healthy adrenal gland to that of an adrenal tumour are the significantly increased thickness, rounded appearance, heterogeneous structure, increased echogenicity, and/or the presence of signs of mineralization [36]. Finding an extremely large adrenal gland may be suggestive of an adrenal carcinoma, which usually does not respond (well) to hormone therapy. Establishing the size of the adrenal gland may thus also be of use in non-surgical cases.

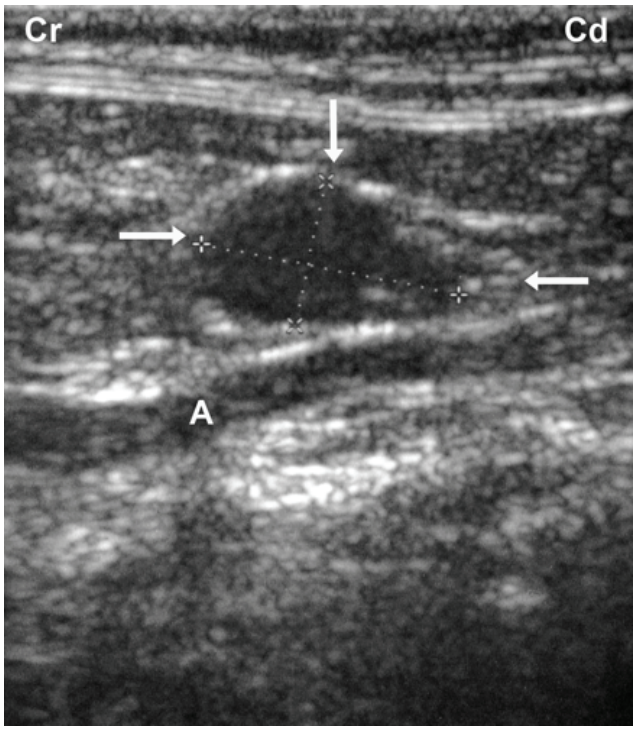

Figure 7 A longitudinal sonogram of a left adrenal gland (between the arrows) of a 3.5-year-old spayed female ferret with hyperadrenocorticism. The cranial pole is enlarged. Adrenal length is 10.4 mm and thickness is 6.4 mm. Histopathological diagnosis was adrenocortical hyperplasia. Note the location of the adrenal gland ventrolateral to the aorta (A). The top of the image is ventral, Cr= cranial, Cd= caudal (previously published [36]).

In addition to ultrasonography, computed tomography may be useful when evaluating the adrenal glands in ferrets. When using this technique, intravenous contrast medium will be needed to delineate the adrenal gland better from the caudal vena cava and enable better visualisation of the size of this gland (Fig 9).

Treatment

The most commonly used modalities for treating ferrets with hyperadrenocorticism are surgery and/or the use of long-acting GnRH analogues. The choice of treatment is influenced by many factors. Criteria such as the age of the ferret, presence of concurrent disease (e.g., renal failure, lymphoma and/or cardiomyopathy), risk of surgery (which is higher when the right or both adrenal glands are involved), and/or financial limitations may lead an owner to decline surgery. When surgery is chosen, however, it is important to realise that gonadotrophin release will persist, thereby resulting in a continued stimulation of the remaining adrenal gland. This gland may subsequently become affected at a later stage. The use of hormonal therapy (the placement of a long-acting implant containing deslorelin) may therefore also be recommended when a surgical intervention has been performed. The extra costs for the medication, may, however result in an owner opting for surgery alone.

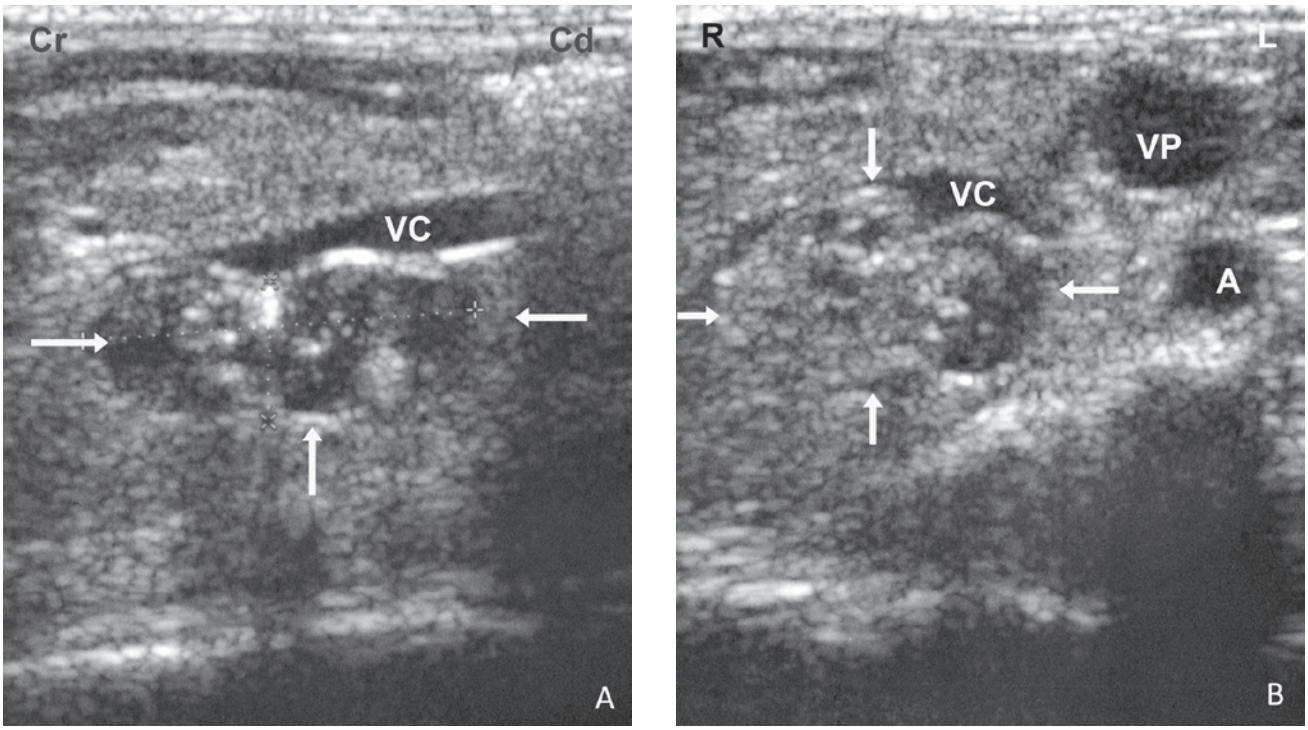

Figure 8 A longitudinal (A) and transverse (B) sonogram of the right adrenal gland (between the arrows) of a 6.5-year-old castrated male ferret with hyperadrenocorticism. The adrenal gland is hyperechoic, heterogeneous, and contains mineralizations (hyperechoic spots). The adrenal gland length is 15.6 mm and thickness is 5.5 mm. The right adrenal gland is located dorsolateral of the Vena cava (VC). The top of the image is ventral. A=aorta, VP= Vena porta, R=right, L=left, Cr=cranial, Cd=caudal (previously published [36]).

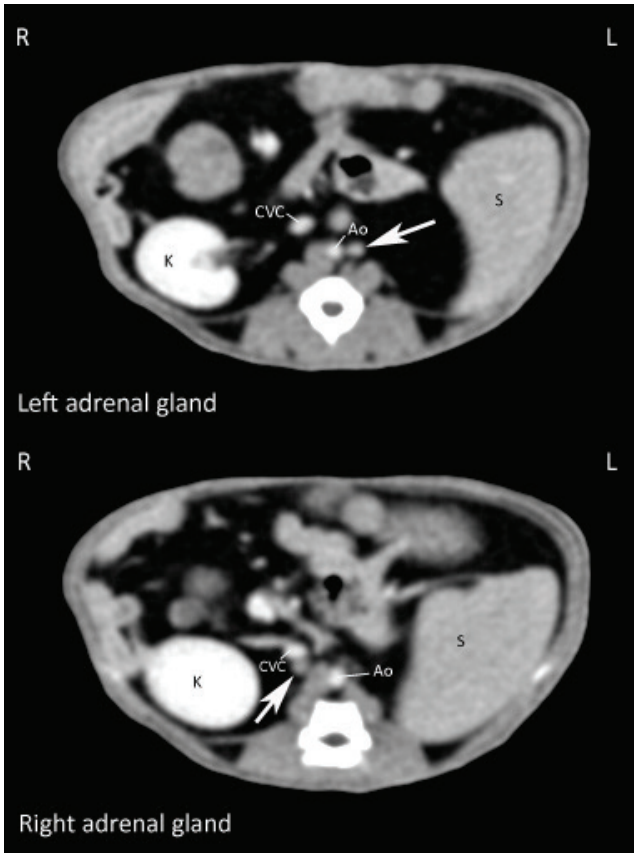

Figure 9 Computed Tomography images of a 3-year-old female ferret after IV administration of 2 ml contrast medium. The left adrenal gland (top arrow) is located in close proximity of the aorta (Ao). The right adrenal gland (bottom arrow) is located dorsal of the caudal vena cava (CVC), medial to the right kidney (K). The spleen (S) in this ferret is large, which is not uncommon in ferrets.

Surgical treatment – Compared to removal of the right adrenal gland, surgical removal of the left adrenal gland is considered fairly easy and straightforward [2,37]. The anatomical location of the right adrenal gland, however, hinders its accessibility during a standard ventral abdominal approach. In addition, surgery may be complicated further as complete removal of the adrenal gland involves removal of part of the wall of the caudal vena cava. Due to the difficulty of this procedure, many surgeons prefer to remove only part of the adrenal gland, thereby posing a risk for recurrence of the problems. Upon removal of both adrenal glands, one should also be aware of the risk for developing hypoadrenocorticism (Addison's disease). This complication, however, is rarely seen, most likely due to the fact that the right adrenal is seldom removed completely, with the remnant tissue preserving sufficient function, thereby minimizing the chance of the development of iatrogenic Addison's disease.

Medical treatment – The most effective drugs currently used for the hormonal treatment of hyperadrenocorticism are the depot GnRH-agonists leuprolide acetate and deslorelin [38,39,40,41].

Depot GnRH-agonists suppress the release of gonadotrophins by continuously releasing GnRH into the circulation, which

overrides the pulsatile release of GnRH that is needed for the release of gonadotrophins (LH and FSH). Thus, initially the administration of a depot GnRH agonist will result in short-lived release of gonadotrophins (due to the initial increase of GnRH in the circulation), which is soon followed by a drop in gonadotrophin concentrations to baseline levels (due to the reaching of a plateau phase which lacks a pulsatile release of GnRH). Initially leuprolide acetate, which is registered for use in people, was the only drug available. Since deslorelin, which is now registered for use in dogs and ferrets, has become available on the market leuprolide acetate is no longer the drug of first choice. The deslorelin containing implants can be given subcutaneously (Fig 10). The implant containing 4.7 mg deslorelin will generally be effective for approximately 8 to 30 months [40]. In a study in which a 3 mg containing implant was used in 15 ferrets with hyperadrenocorticism, five developed adrenal tumours greater than 2 cm in size within 2 months after the activity of the implant had worn off [39]. Since this publication, however, this high incidence has not been seen in practice. More research will therefore be necessary to determine why these tumours developed, and how high the actual frequency is. In addition, it should be considered that autonomous production of steroids by the adrenal gland may occur, leading to a lack of or loss of response to the hormonal treatment [40,41].

Other medical treatment options – Other medications have been proposed for the treatment of hyperadrenocorticism in ferrets. These include melatonin, mitotane (o,p'-DDD) combined with ketoconazole, and trilostane (a 3β-hydroxysteroid dehydrogenase blocker [HSD]). Although the treatment with mitotane and/or ketoconazole is well-known for treating hypercortisolism in dogs and humans, this combination was found to be insufficiently effective in ferrets [2]. Melatonin, given in a dose of 0.5 mg/kg daily PO or in the form of an implant (containing 5.4 mg melatonin), did result in clinical improvement [27,42]. However, upon receiving melatonin, tumours continued to grow, thereby posing a risk for deterioration of the ferret's condition without the owner noticing it [27]. Trilostane, a 3β-HSD-blocker that is commonly used to treat pituitary-dependent hyperadrenocorticism in dogs [33], has been used only incidentally in ferrets. Although the drug theoretically may be effective for treatment of hyperadrenocorticism in ferrets (as 3β-HSD is necessary for the synthesis of androstenedione and 17α-hydroxyprogesterone), a pilot study in ferrets with hyperadrenocorticism given 5 mg trilostane PO once daily showed deterioration or no effect rather than improvement of the clinical symptoms. More research is therefore necessary to determine whether this drug is effective and safe for use in ferrets with hyperadrenocorticism.

Figure 10 A deslorelin containing implant is placed subcutaneously in an awake ferret. The ferret is so distracted by the food provided that is does not mind the placement of the implant.

Prognosis

The prognosis of a ferret with hyperadrenocorticism in general is good. An average disease free period of 16.5 months and 13.6 months has been reported in ferrets treated with a deslorelin implant or ferrets that were surgically treated, respectively [41]. In another study, 1- and 2-year survival rates after surgery were 98% and 88% [43]. Since metastases rarely occur, this hardly influences the overall prognosis [2]. In male ferrets, however, prostate involvement may result in a life threatening urinary blockage, thereby influencing chances of survival if not treated promptly [2].

Future perspectives

Despite the frequent occurrence of insulinomas and adrenal neoplasms in ferrets, the exact aetiological cause for this high incidence has yet to be determined. If the incidence of adrenal tumours indeed is related to increased gonadotrophin release induced by surgical castration, the incidence of adrenal gland tumours should decrease when using deslorelin containing implants as alternative for surgical castration. Currently, a study is ongoing with ferrets to determine whether this indeed is the case.
In addition, molecular studies are being performed to identify the potential genes and pathways involved in the development of adrenal gland tumours [44] and (ab)normal adrenal steroid synthesis. Similarly, molecular studies may be helpful to unravel the pathophysiology of insulinomas in ferrets. Recently, a cell-line of a ferret insulinoma

was established in the endocrine laboratory at Utrecht University, which is currently being characterized and may help to determine which cellular-molecular processes and/or mutations play a role in the development of this tumour. In addition to gaining further insight into the aetiology and pathophysiology of the conditions, these molecular studies may also be useful to help identify potential new targets for preventive and therapeutic intervention.

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